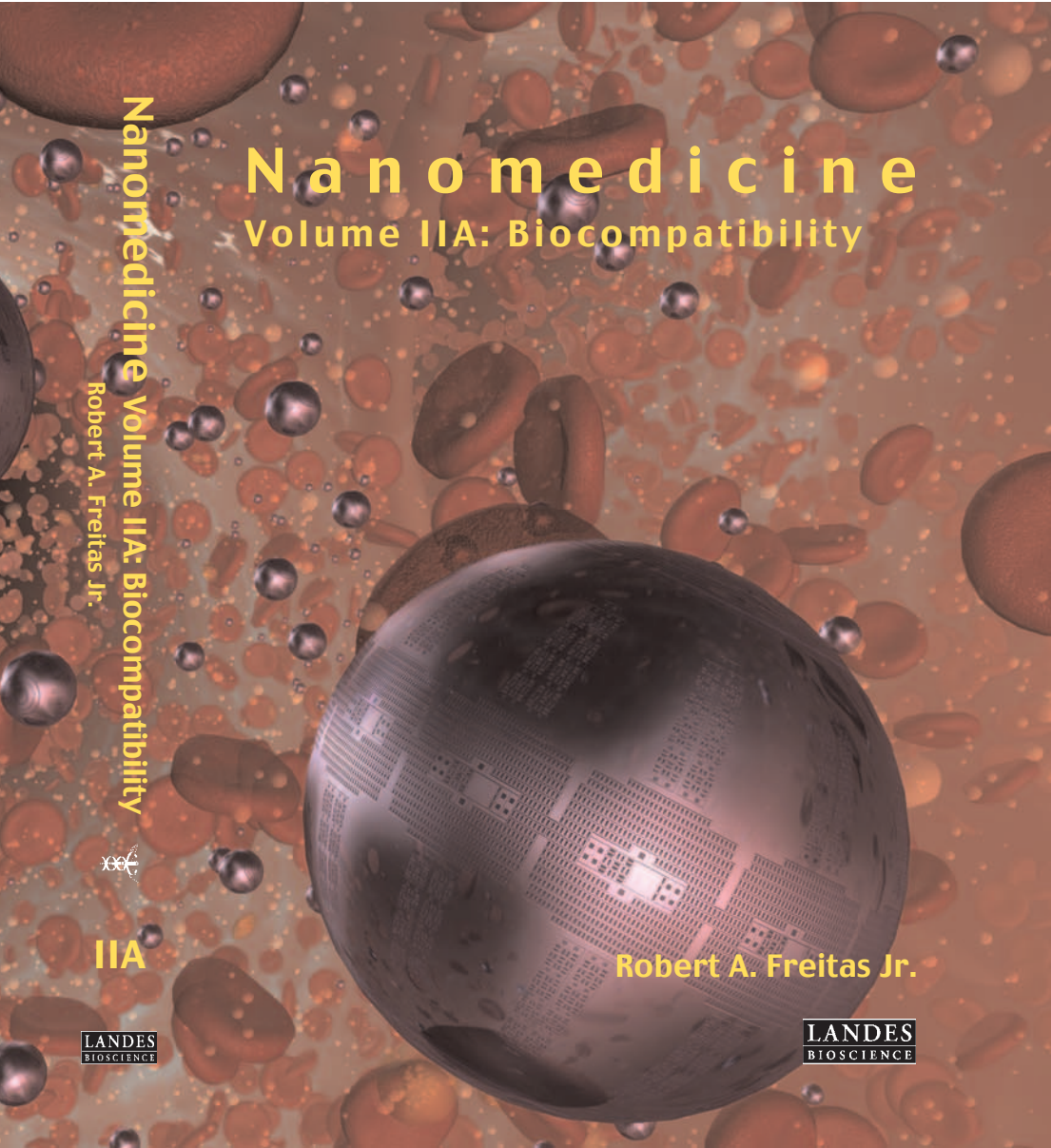
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Volume IIA: Biocompatibility
Robert A. Freitas Jr.
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To those who persevere

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PREFACE & ACKNOWLEDGMENTS

"Compatibility" most broadly refers to the suitability of two distinct systems or classes of things to be mixed or taken together without unfavorable results.[2004] More specifically, the safety, effectiveness, and utility of medical nanorobotic devices will critically depend upon their biocompatibility with human organs, tissues, cells, and biochemical systems. Classical biocompatibility[234-243,260,6030-6048] has often focused on the immunological and thrombogenic reactions of the body to foreign substances placed within it. In this Volume, we broaden the definition of nanomedical biocompatibility to include all of the mechanical, physiological, immunological, cytological, and biochemical responses of the human body to the introduction of medical nanodevices, whether "particulate" or "bulk" in form. That is, medical nanodevices may include large doses of independent micron-sized individual nanorobots, or alternatively may include macroscale nanoorgans (nanorobotic organs) assembled either as solid objects or built up from trillions of smaller artificial cells or docked nanorobots inside the body. We also discuss the effects on the nanorobot of being placed inside the human body.

In most cases, the biocompatibility of nanomedical devices may be regarded as a problem of equivalent difficulty to finding biocompatible surfaces for implants and prostheses that will only be present in vivo for a relatively short time. That's because fast-acting medical nanorobots will usually be removed from the body after their diagnostic or therapeutic purpose is complete. In these instances, special surface coatings along with arrays of active presentation semaphores may suffice. At the other extreme, very long-lived prostheses are already feasible with macroscale implants such as artificial knee joints, pins, and metal plates that are embedded in bone. As our control of material properties extends more completely into the molecular realm, surface characteristics can be modulated and reprogrammed, hopefully permitting long-term biocompatibility to be achieved. In some cases, nanoorgans may be coated with an adherent layer of immune-compatible natural or engineered cells in order to blend in and integrate thoroughly with their surroundings. Today (in 2002), the broad outlines of the general solutions to nanodevice biocompatibility are already apparent. However, data on the long-term effects of implants is at best incomplete and many important aspects of nanomedical biocompatibility are still unresolved — and will remain unresolved until an active experimental program is undertaken to systematically investigate them.

Since a common building material for medical nanorobots is likely to be diamond or diamondoid substances, the first and most obvious question is whether diamondoid devices or their components are likely to be hazardous to the human body. **Chapter 15.1** briefly explores the potential for crude mechanical damage to human tissues caused by the ingestion or inhalation of diamond or related particles. There are varying degrees of potential mechanical injury and these are probably dose-dependent. It will be part of any medical nanorobot research project to determine the actual amount of diamondoid particulate matter necessary to cause clinically significant injury.

Classical biocompatibility refers to the assessment of the totality of nanorobot surface material-tissue/fluid interactions, both local and systemic. These interactions may include cellular adhesion, local biological effects, systemic and remote effects, and the effects of the host on the implant. **Chapter 15.2** summarizes the current status of medical implant biocompatibility and then discusses the important future nanomedical issues of protein interactions with nanorobot surfaces, immunoreactivity, inflammation, coagulation and thrombosis, allergic reactions and shock, fever, mutagenicity and carcinogenicity.

A great deal of preliminary information is already available on the biocompatibility of various materials that are likely to find extensive use in medical nanorobots. **Chapter 15.3** includes a review of the experimental literature describing the known overall biocompatibility of diamond, carbon fullerenes and nanotubes, nondiamondoid carbon, fluorinated carbon (e.g., Teflon), sapphire and alumina, and a few other possible nanomedical materials such as DNA and dendrimers — in both bulk and particulate forms.

The purposeful movement of solid bodies and particulate matter through the various systems of the human body is also of particular interest in nanomedicine. **Chapter 15.4** examines the requirements for intact motile nanorobots that can locomote inside the human body while avoiding geometrical trapping, phagocytosis, and granulomatization, thus achieving controlled or indefinite persistence without clearance by the natural immune system. The analysis extends to the fate of free-floating nanorobots and their material ejecta, or fragments, as well as the fate of motile nanorobots that have malfunctioned and lost their mobility, or which are moving passively through the body, or are being driven by cell-mediated processes.

Unlike pharmaceutical agents whose interactions with biology are largely chemical in nature, medical nanorobots may interact both chemically and mechanically with human tissues and cells. Similarly, while traditional biomedical implants produce both chemical and bulk mechanical effects, nanoorgans and nanoaggregates may possess active nanoscale features and moving parts that can apply spatially heterogeneous mechanical forces at the molecular and microscopic scale. Thus any study of nanomedical biocompatibility must necessarily include an analysis of the mechanical biocompatibility, or mechanocompatibility, of nanorobotic systems as they interact with the tissues and cells of the human body. Accordingly, **Chapter 15.5** describes the mechanical interactions of nanorobotic systems with human skin and other epithelial tissues, including mechanical tissue penetration and perforation leakage, as

well as mechanical interactions with vascular systems, extracellular matrix and tissue cells, and nontissue cells such as erythrocytes, platelets, and leukocytes. The Chapter ends with a detailed review of cytomembrane and intracellular mechanocompatibility, and a brief consideration of electrocompatibility and nanorobot-nanorobot mechanocompatibility.

Finally, otherwise biocompatible medical nanodevices might provoke unwanted reactions by simple physical displacement of critical biological systems or fluids. **Chapter 15.6** examines issues of volumetric intrusiveness — the degree to which artificial systems can safely displace natural systems volumetrically. The brief discussion includes a look at the acceptable limits of volumetric intrusiveness of macroscopic objects placed inside the human body (or its various organs), the bloodstream, and in individual human cells.

The discussion of nanorobot biocompatibility was originally intended to include just a single chapter, Chapter 15, in the Nanomedicine book series. However, during the course of this research it became clear that biocompatibility is a central issue in determining the feasibility, limitations, and technical requirements of medical nanorobotics. This recognition demanded additional investigations that resulted in the present book-length "Chapter 15."

The primary intended audience of this Volume is biomedical engineers, biocompatibility engineers, medical systems engineers, research physiologists, clinical laboratory analysts, and other technical and professional people who are seriously interested in the future of medical technology. Readers wishing to keep abreast of the latest developments can visit the author's Nanomedicine Page website (http://www.foresight.org/Nanomedicine), hosted by the Foresight Institute; or may read the author's most recent (2002) popular[23,28] and technical[25,30-32] summaries of the emerging field of nanomedicine; or may visit http://www.nanomedicine.com, the first commercial Internet domain exclusively devoted to nanomedicine and the online home of this document and related materials. Since 1994, the author has expended on the Nanomedicine project ~27,000 man-hours in total, including ~8000 man-hours on the present Volume IIA, a total of ~13 man-years of effort to date. Volume I[1] has been favorably reviewed.[2-5] The author's Nanomedicine Art Gallery (http://www.foresight.org/Nanomedicine/Gallery/index.html), hosted by the Foresight Institute, also provides the largest online collection of original and previously-published nanomedicine-related images, graphics, artwork, animations, and relevant links.

References [####] are used in this book to denote the source of: (1) a direct quotation (enclosed in quotes), (2) a paraphrased passage (footnoted but not enclosed in quotes), or (3) a specific datum. Citations are also employed to indicate sources of additional information on a given topic, especially collections of literature review papers that would provide a suitable introduction to a given field of study. The author apologizes in advance for any inadvertent instances of unattributed usage of previously published material. Such events should be few but should be brought to the author's immediate attention for correction in a future edition of this work. An attempt was made to cite primary sources whenever possible, but some references are made to secondary sources believed by the author to be reliable. Unreferenced in-text attributions to specific named people generally refer to comments made by a technical reviewer of the manuscript, usually as a personal communication.

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6 December 2002

To understand the very large we must understand the very small.

– Democritus, 470-380 BC

The human understanding, when it has once adopted an opinion (either as being the received opinion or as being agreeable to itself) draws all things else to support and agree with it. And though there be a greater number and weight of instances to be found on the other side, yet these it either neglects and despises, or else by some distinction sets aside and rejects, in order that by this great and pernicious predetermination the authority of its former conclusions may remain inviolate.

– Francis Bacon, Novum Organum: Aphorisms on the Interpretation of Nature and the Empire of Man, 1620

The future belongs to those who prepare for it.

– Ralph Waldo Emerson (1803-1882)

CHAPTER 15.1

Are Diamondoid Nanorobots Hazardous?

It is believed that one of the most common building materials for medical nanorobots will ultimately be **diamond** or **diamondoid** substances (Chapters 2 and 11). The first and most obvious question regarding biocompatibility thus must be: What health risks, if any, are associated with the in vivo use of **diamondoid** devices or their detached parts, components, or detritus? There may be billions or trillions of nanorobots employed during a nanomedical procedure, and conservatively it must be presumed that some small unavoidable amount of in vivo nanorobot detritus (e.g., detached nanorobot manipulators, tool tips, or sensor elements, fragmented devices, or even nonfunctional whole nanorobots) might be generated during this activity.

Leaving aside the question of the chemical inertness of nanorobot components until later (e.g., Sections 15.3.1.5, 15.4.4, etc.), other possible avenues for mischief are conceivable. Using information ranging from historical anecdotes to modern clinical reports, Chapter 15.1 briefly explores two of these avenues: the potential for crude mechanical damage to human tissues caused by the ingestion (Section 15.1.1) or inhalation (Section 15.1.2) of **diamond** or related particles. Similar mechanical damage to vascular, membrane, and organ systems likewise cannot be ruled out (Chapter 15.5). A study to rigorously assess the mechanical toxicity in human tissues of **diamond** dust and fractured **diamond** particles, as crude proxies for medical nanorobotic **diamondoid** detritus, appears warranted.

15.1.1 Mechanical Damage from Ingested Diamond

One informal anecdotal modern source[100] has described **diamond** dust as "perhaps the most terrible poison in existence. Every other poison has a principle behind its action — cyanides attack, alkaloids destroy, barbiturates deaden, glycosides deteriorate, ricin and abrin phytotoxins agglutinate. **Diamond** dust abrades."

Hutchkinson*[100] continues: "If one ingests **diamond** dust, the natural peristaltic motion of the digestive tract causes these tiny splinters of the world's hardest substance to imbed themselves along the alimentary canal, the natural motions of the inner body causing them to work deeper and deeper until your internal organs are perforated and ripped apart. This goes on from anywhere between 2-6 months, until the victim is dead. The pain accompanying this can only be imagined by the few. A large amount of **diamond** dust would probably feel similar to having a Portuguese Man-O-War living inside of you. Even in its earliest stages, the difficulties behind diagnosis can well be imagined. The only way to extricate the tiny **diamond** splinters is surgery, wherein each particle would have to be located and removed individually, an impossible feat."

In ancient times, **diamonds** were regarded as having magical curative powers. According to Pliny the Elder (23-79 AD) in his Natural History, **diamond** "prevails over all poisons and renders them powerless, dispels attacks of wild distraction and drives groundless fears from the mind." It was once thought that **diamond** powder, taken orally, possessed curative abilities.[101] Physicians in the Middle Ages debated this subject at great length and were of divided opinion, though the proponents of such treatment met with many notable failures. Apparently, wealthy people were still being dosed with ground **diamonds** to cure them of stomach disorders well into the 16th century.[102] For example, Pope Clement VII (Giulio de' Medici) died on 25 September 1534 when his doctors failed to cure his ailments — the bill for the fourteen spoonfuls of precious stones he had been administered is said to have been 40,000 ducats.[103] As late as the 19th century, some of the wealthy citizens of India had **diamond** powder applied to their teeth in an attempt to repair decay.[104] (The powder supposedly also provided protection from lightning.) Even today, **diamonds** are found in the "precious pills" of traditional Tibetan medicine.[99]

More commonly, though, **diamond** was regarded as a potential poison. Up until the 18th century, rumor had it that even uncrushed **diamonds** were poisonous, a fantasy that those who owned or mined the stones no doubt wished to promote.[104] This is because a favorite and effective means of stealing a **diamond** was to swallow it whole and wait a few days for it to pass through the digestive system. The myth that stones were poisonous presumably deterred many would-be gem thieves from the attempt.[102,104] We now know that uncrushed **diamond** is a neutral contributor to the human diet, doing neither good nor harm — a swallowed **diamond** gemstone "re-emerges in due course".[102]

Other stories suggested that fragmented **diamonds** were even more hazardous. The splinters produced by shattering a **diamond**, which Pliny knew could "make hollows in the hardest materials," are easily capable of cutting the stomach and intestines of anyone who swallows them.[102] One writer[96] reports that Paracelsus was poisoned by **diamonds**. Sultan Bejazet II, leader of the Ottoman Empire (Turkey), was reportedly assassinated in 1512 by his son Selim, who fed the Sultan a fatal dose of pulverized **diamond** mixed in with his food.[97,98] Some claim that Frederick II, emperor of the Holy Roman Empire, also died after imbibing a fatal dose of **diamond** powder,[98] and that the Countess of Essex poisoned Sir Thomas Overbury with mercury and **diamond** dust in 1613 while he was imprisoned in the Tower of London.[97] **Diamond** splinters have been used as a murder weapon through the ages and in different

** It is important to note that Hutchkinson is writing informally and in a historical context. He is neither a surgeon nor a pathologist and evidently has no experience in the diagnosis or characterization of the pathophysiology of **diamond** dust ingestion. M. Sprintz notes that **diamond** would be visible radiographically, and a modern pathologist would definitely identify the particles after exploratory surgery was performed in a modern case of **diamond** poisoning. Death might also be caused by a peritoneal infection with subsequent sepsis secondary to the bowel perforation.*

societies.[102] For example, a member of the Bengal Civil Service, William Crooke,[105] writing at the beginning of the 20th century, tells us that in India "as an irritant poison, pounded glass has been often used. But **diamond** dust enjoyed a still higher reputation...it is believed in South India to be at once the least painful, the most active and infallible of all poisons. It was kept as a last resort in times of danger."

During the Renaissance, it was widely believed that **diamond** powder had pernicious properties, for by then it was realized that the powder rarely cured and apparently often killed.[101] The poisoner became an integral part of the political scene.[106] Catherine de Medici (1519-1589) reportedly used **diamond** powder to eliminate certain people who were acting against her. Her enemies called the mixture she prepared "the powder of succession," though one observer averred that the principal toxic component of the powder might have been added arsenic.[104] According to another account, the methods of Catherine de Medici depended on developing direct evidence to arrive at the most effective compounds for her purposes. Under guise of delivering provender to the sick and the poor, Catherine reportedly tested toxic concoctions, carefully noting the rapidity of the toxic response (onset of action), the effectiveness of the compound (potency), the degree of response of the parts of the body (specificity, site of action), and the complaints of the victim (clinical signs and symptoms).[106]

Diamond dust became a rather popular means of assassination during the Renaissance. One classical discussion of this technique may be found in the autobiography of Benvenuto Cellini,[107] the famous Italian goldsmith and sculptor, who described a botched attempt on his life by his enemy, the powerful Pierluigi Farnese, son of Pope Paul II, which took place in 1539 while Cellini was imprisoned in Rome by the Pope. Cellini writes:

> *"Messer Durante of Brescia engaged the soldier (formerly druggist of Prato) to administer some deadly liquor in my food. The poison was to work slowly, producing its effect at the end of four or five months. They resolved on mixing pounded diamond with my victuals."*
>
> *"Now, the **diamond** is not a poison in any true sense of the word, but its incomparable hardness enables it, unlike ordinary stones, to retain very acute angles. When every other stone is pounded, that extreme sharpness of edge is lost; their fragments become blunt and rounded. The **diamond** alone preserves its trenchant qualities. Wherefore, if it chances to enter the stomach together with food, the peristaltic motion needful to digestion brings it into contact with the coats of the stomach and the bowels, where it sticks, and by the action of fresh food forcing it farther inwards, after some time perforates the organs. This eventually causes death. Any other sort of stone or glass mingled with the food has not the power to attach itself, but passes onward with the victuals."*
>
> *"Now Messer Durante entrusted a **diamond** to one of the guards, and it is said that a certain Lione, a goldsmith of Arezzo, my great enemy, was commissioned to pound it. The man happened to be very poor, and the **diamond** was worth some scores of crowns. He told the guard that the dust he gave him back was the **diamond** in question, properly ground down. The morning when I took it, they mixed it with all I had to eat. It was a Friday, and I had it in salad, sauce, and pottage. That morning I ate heartily. It is true that I felt the victuals scrunch beneath my teeth, but I was not thinking about knaveries of this sort. When I had finished, some scraps of salad remained upon my plate, and certain very fine and glittering splinters caught my eye among those remnants. I collected them, and took them to the window, which let a flood of light into the room, and while I was examining them, I remembered that the food I ate that morning had scrunched more than usual. On applying my senses strictly to the matter, the verdict of my eyesight was that they were certainly fragments of pounded **diamond**. Upon this I gave myself up without doubt as dead...."*
>
> *"Now, hope is immortal in the human breast. Lured onward by a gleam of idle expectation, I took up a little knife and a few of these particles, and placed them on an iron bar of my prison. Then I brought the knife's point with a slow strong grinding pressure to bear upon the stone, and felt it crumble. Examining the substance with my eyes, I saw that it was so. In a moment new hope took possession of my soul. Messer Durante, my enemy, or whoever it was, gave a **diamond** to Lione to pound for me of the worth of more than a hundred crowns. Poverty induced him to keep this for himself, and to pound for me a greenish beryl of the value of two carlins, thinking perhaps, because it also a stone, that it would work the same effect as the **diamond**...."*

In 1995, the author undertook a modest informal experiment to confirm the potentially dangerous shardlike quality of pounded **diamonds**, as claimed by Cellini. **Diamond** grit was acquired and pounded using a simple apparatus, then carefully cleaned and visually examined using a scanning electron microscope (SEM).* Even a single hammer blow produced numerous particles of a wide variety of sizes (0.1-100 micron), many possessing sharp ragged "fishhook" edges, deep angular concavities, serrations, irregular holes, and other interesting features on the order of a few microns in size (Figures 15.1 and 15.2), which is in stark contrast with the relatively smooth-looking (unpounded) **diamond** particle microphotographs reproduced in McCrone's Particle Atlas.[109] Figure 15.3 shows a pound-particle that is star-shaped with several jagged edges at a magnification of 300X. At 8000X, the uppermost tip of the star (Figure 15.4) reveals even smaller-scale serrations with several concave "fishhook" features measuring ~250 nanometers in diameter (a plausible size for a detached nanorobot manipulator arm). Some grit particles appear to be aggregates of much smaller particles, so it is possible that the pounding allows crystal fragments to dislodge irregularly, leaving behind concave holes. However, there also appear to be many concave fracture features present in each of the samples. Under the microscope, unpounded grit particles generally appear smoother and more rounded. The author also observed that the pounded grit tended to cling to human skin, especially in the narrowest creases of the fingers, producing a slight itching sensation, whereas unpounded grit generally does not.

The author is unaware of any direct study of the mobility of fractured **diamond** shard in human tissues, that might confirm or disprove the historical and anecdotal evidence reported above. Crystalite Corp.[108] confirms that there are no major health warnings associated with the normal use of commercial **diamond** grit in jewelry-related grinding operations.** Classic toxicology textbooks

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** **Diamond** grit of 250-micron mesh size was obtained from Crystalite Corp.;[108] the cost was $3-$4/carat, depending on mesh size which can range from 100 mesh (~250-micron particles) down to 100,000 mesh (~250 nanometer particles). The grit was pounded between a steel anvil and a steel rod using a single blow from a 600-gm hammer dropped through a ~3-inch vertical fall. The crush was washed with 31% HCl to dissolve any metal fragments, then rinsed in distilled water several times and finished with an acetone drying rinse. Crushed samples were examined using a Zeiss Ultraphot II optical microscope at 125X and a JEOL JSM-35C SEM (kindly made available to the author by Dr. Elizabeth Mathews at San Joaquin Delta College, California) at various magnifications from 180X up to 12,000X, and were subjectively compared to uncrushed powder.*

*** One Material Safety Data Sheet (MSDS) for **diamond** grit[2392] describes the primary acute and chronic health hazard as "inhalation: pneumoconiosis and mucous membrane irritation," recommends that spills may be cleaned up the same way as "for handling unregulated dust and sand," notes that there is no known carcinogenicity, but warns that workers should "minimize inhalation and direct skin contact." Another MSDS for pure **diamond** powder[2393] warns that grinding may produce dust that is "potentially hazardous when inhaled, swallowed, or comes into contact with eyes — may irritate eyes." Yet another **diamond** powder MSDS[2394] warns of acute/chronic tissue irritation if the material is inhaled or ingested, or if it comes into contact with skin or eyes.*

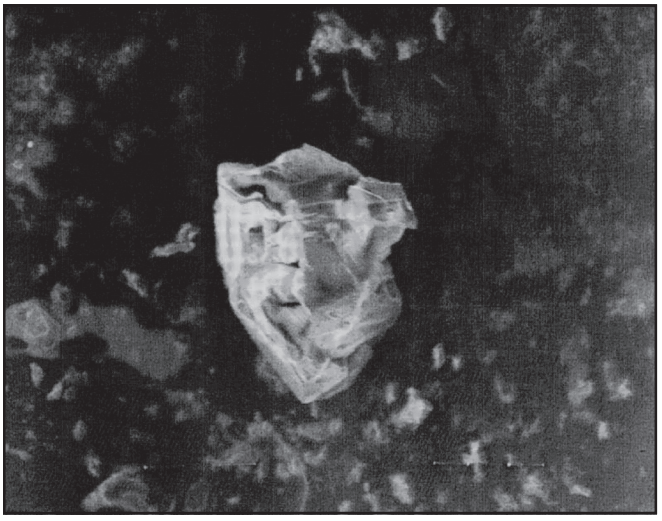

Fig. 15.1. Arrowhead-shaped particle of pounded **diamond**; SEM 200X. (©1995 Robert A. Freitas Jr.)

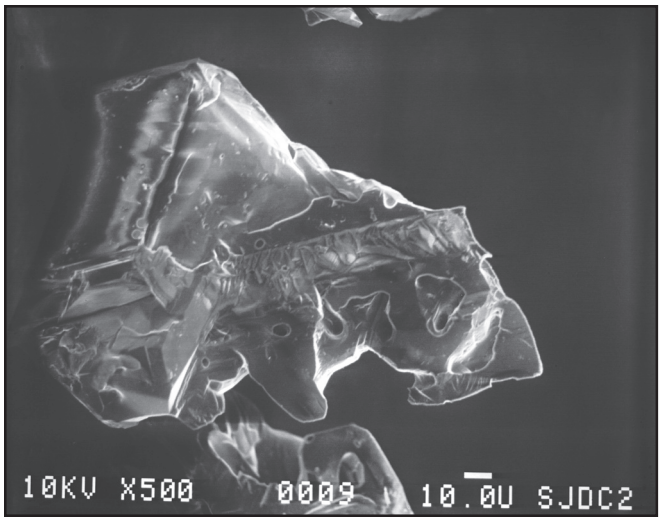

Fig. 15.2. Fishhook-shaped particle of pounded **diamond**; SEM 500X. (©1995 Robert A. Freitas Jr.)

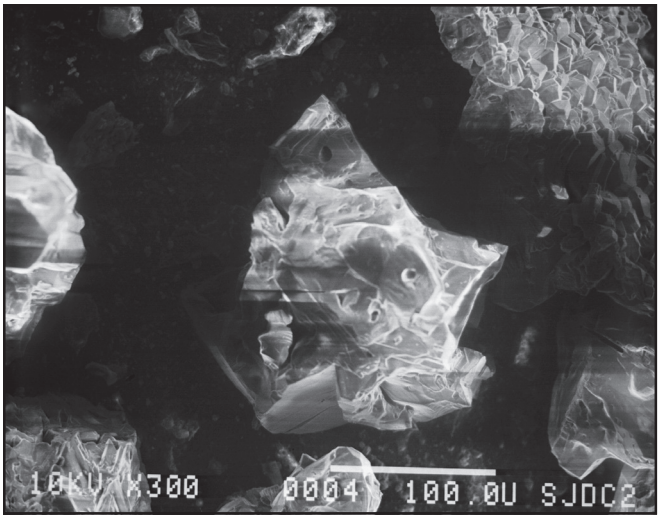

Fig. 15.3. Star-shaped jagged particle of pounded **diamond**; SEM 300X. (©1995 Robert A. Freitas Jr.)

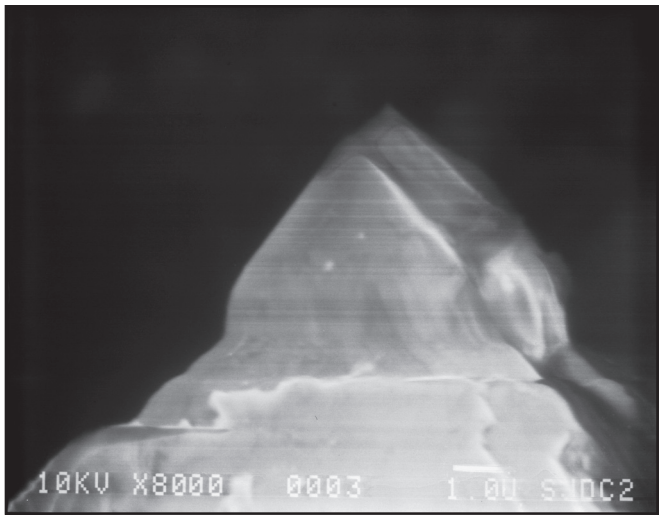

Fig. 15.4. Tip closeup of star-shaped jaffed particle of pounded **diamond** showing ~250 nm fishhook features; SEM 8000X. (©1995 Robert A. Freitas Jr.)

make no mention of **diamond** as a poison,[174] and this author could find no mention of powdered or pounded **diamond** in any of dozens of well-known standard modern reference works on medical toxicology, poisons, or forensic toxicology, or in the journal literature, although this would not be entirely unexpected given the likely rare incidence of accidental **diamond** shard ingestion or attempted homicide by **diamond**, especially in the 20th century. The **diamond** content of waste particles abraded into the mouth from **diamond** burs[111-114] on dental drills during clinical use is apparently considered relatively nonhazardous in comparison with the accompanying release of metallic ions such as Ni^{++} into the body fluids during these procedures.[115]

Broadening the search only yields additional conflicting data. For example, it is well known in veterinary medicine that ingested string can loop around epithelial folds and cut through a dog's digestive tract,[116] and similar cases have been reported in humans.[122] On the other hand, a weighted gelatin capsule trailing a 140-cm length of absorbent nylon line that is swallowed by a human patient, then safely pulled back out through the mouth 3.5 hours later, is sometimes used to test bile composition and bacterial content of the gut, and is commonly known as the "string test".[117-119]

Similarly, gastric and colon perforation with peritonitis has been reported[120-124] in cases of pica,[125-133] with mixed pica (especially involving ingested paper, plastic bags, cloth and string) more likely to require surgery and to cause perforation.[122] Abrasive household cleaners largely composed of pumice or silica can cause gastrointestinal irritation but have a low order of toxicity,[174] as with lithophagy,[126] although massive ingestion of sand can cause intestinal blockage,[134] diarrhea,[135] or tooth wear.[136] Cases of foreign body ingestion including broken glass,[137,138] glass splinters,[139-141] bent hypodermic needles and pins,[142-144] fishhooks,[145] razor blades,[146-149] wires,[150] wire springs,[147] coins,[132,144,151-153] screwdrivers,[154] dentures[153] or knocked-out teeth[155] have produced esophageal perforation but generally are not regarded as life-threatening except in cases of complete obstruction of the intestine or colon[148,156] or concurrent metal poisoning.[157,158] Most (80-90%)[159-162] ingested

foreign bodies that reach the stomach can be eliminated uneventfully through the gastrointestinal tract,[163] but perforation may occur with ingestion of long, sharp pointed objects[164] or animal bones,[148,153] and is more frequent among those who have had previous abdominal surgery or intestinal diseases.[148] In one unusual case,[165] an ingested plastic bag clip was found by radiography to have clipped itself to the small bowel mucosa.

The author concludes that there is sufficient uncertainty and necessity to warrant a study to rigorously assess the mechanical toxicity in human tissues of **diamond** dust and fractured **diamond** particles, as crude proxies for medical nanorobotic **diamondoid** detritus.

15.1.2 Mechanical Damage from Inhaled Diamond

As with ingested **diamond** dust, inhaled microscopic nanorobots (Section 15.4.3.3.3) or other **diamondoid** particulates might do serious mechanical damage to lung tissues. (MEMS researchers such as Kaigham Gabriel at AT&T Bell Laboratories have already reported the accidental inhalation — evidently harmless — of silicon micromachines.[110]) It has long been known that abrasive dusts can increase the incidence of upper respiratory tract diseases, and fibrosis-inducing dusts can lead to chronic lung ailments.[167] Fiber health science commonly focuses on particle dose, dimension, and durability.[6061] World Health Organization (WHO) antipollution guidelines specify a maximum allowable exposure of 0.23 mg/m^3 of total suspended particulate matter (SPM) for no more than 7 days per year,[168] consistent with human health. The Swiss national standard is an annual mean SPM of 0.07 mg/m^3, though an increase in respiratory symptoms and some decrease in lung function has been observed[770] for chronic exposures as low as 0.014-0.053 mg/m^3. In the 1990s, most Western cities were measured at ~0.05 mg/m^3, while most major third world cities were measured at ~0.20 mg/m^3.[169,515] In 1996, the U.S. EPA proposed new particulate matter standards for ≤2.5-micron particles ($PM_{2.5}$) of 0.015 mg/m^3 for the annual mean and 0.050 mg/m^3 over a 24-hour period.[170] (A Health Effects Institute study in 2000 found 0.5% increase in death rates per 0.010 mg/m^3 increase in $PM_{2.5}$.[2172])

An SPM of 0.10 mg/m^3 consisting entirely of 1-micron^3 **diamondoid** flying nanorobots (Section 9.5.3) of mass density ~1000 kg/m^3 would represent a number density of ~10 million particles/m^3. By comparison, quiet country air (absent any local mining activities) has ~20 million particles/m,[167] residential city air perhaps 60 million/m^3,[167] the worst congested downtown city air ~150 million/m^3,[167] and a room with smokers present ~270 million/m^3[896] or more. In 1999, laminar flow clean rooms in a Class One semiconductor fab plant had air with only ~10 particles/m^3 of size 0.5 microns or larger.[896] Experimental data suggests that a condition of lung overload occurs when the retained lung particle burden reaches a particle volume of ~10^9 micron^3 per gram of lung tissue (e.g., ~0.1% by volume).[781]

A resident of an industrialized Western country typically inhales ~30 billion particles per day.[6061] A cubic meter of ordinary air likely contains ~10,000 grains of pollen and fungal spores, as well as carbon monoxide, radon gas, scent molecules, spider legs, fragments of soil, fur, a bit of carbon from a faraway fire, dust mites from the carpet, flakes of skin, hair and lint particles, bacteria and viruses, up to 10^{11}/m^3 nanometer-sized particles in urban air,[6197] sea spray wave-produced ultrafine salt particles near the coasts,[6179] and even wisps of 15-micron-wide droplets from when someone last sneezed[896] — often with a thin coating of hydrocarbon molecules (esp. fossil fuel combustion products). It is universally recognized that continued inhalation of certain dusts is detrimental to health and may lead to reticulation of the lungs and eventually to fatal diseases included under the general term pneumoconiosis.[171,172] Coal and silica dusts are particularly harmful. Chronic inhalation of crystalline silicon dioxide particles measuring 0.5-5 microns in size can lead to silicosis,[173,174] a chronic inflammatory lung disease that can ultimately destroy the ability to breathe.

Fine particles in the micron size range, typical for dust inhalation hazard, can bypass the mucociliary (e.g., cilia in the respiratory epithelium; Sections 8.2.2 and 15.4.3.3.3) and cellular defense mechanisms, invading the lung parenchyma and causing an inflammatory response. Nasal turbulence ensures that almost no particles larger than 2-5 microns reach the lower airway[2495] (Section 8.2.2); these larger particles are deposited by inertial compaction at airway bifurcations, hence are easily flushed out via bronchial mucus flow. (The airstream turns abruptly, and particle inertia carries it straight on against the airway wall.[173]) However, these large particles can be inhaled orally, with experimentally-determined[5023] retention rates of 46-56% after 24 hours, and 25-31% after 21 days, for 6-micron Teflon particles inhaled rapidly or very slowly, respectively.*

Particles smaller than 0.5 microns generally remain airborne and are exhaled, though a few may be deposited in the alveoli.** [173] There also is much evidence that some particles which are nontoxic in micron sizes may be toxic in the nanometer range.[761,769,929-933,4846,4858] For instance, the intensity of neutrophil alveolitis is lowest for 260 nm carbon particles, higher for 50 nm particles, and highest for 14 nm particles at low doses up to 0.5 mg/kg where particle reaction is governed by surface area effects.[769] However, at larger doses sufficient to induce lung overload, the larger particles become more inflammogenic per unit mass or volume.[769]

In the mining, quarrying, ceramic and abrasive industries, the acute danger limit (e.g., the minimum toxic dose) is reached when ~200 million particles/m^3 of free silica are present in air, with sizes below 5 microns. Of these, as many as 25% are retained in the respiratory tract.[167] Unfiltered 20th century airborne industrial dusts typically would consist of ~20% of particles below 1 micron, ~70% between 1-3 microns, and ~10% over 3 microns in diameter.[167]

Like **diamond**, pure silica has a tetrahedral crystalline lattice that cleaves similarly, potentially making hard shards (Table 9.3) of comparable sharpness, and thus possibly displaying similar mechanical effects on human lung parenchyma. Particles 0.5-5 microns in size that reach the lower respiratory tract are deposited in small airways and along the surfaces of alveoli deep inside the

** In hamster lungs, inhaled 5.5-micron Teflon microspheres show maximum retention after 21 minutes in alveoli (72.4%), less in intrapulmonary conducting airways (22.9%), and the least in extrapulmonary mainstem bronchi (0.3%) and trachea (4.4%).[5027] The Teflon particles were found submerged in the aqueous lining layer and in close vicinity to epithelial cells. In intrapulmonary conducting airways, 21.5% of the microspheres had been phagocytized by macrophages, a fate made possible by the displacement of particles into the aqueous phase by surfactant.[5027]*

*** Certain very small submicron particles may be trapped in the alveoli. For example, technegas[661-668] is an argon gas-suspended Tc^{99m} labeled 5-200 nanometer[661] carbon-particle radioaerosol developed for diagnostic lung imaging that is well tolerated by patients,[662,663] with over 100,000 clinical studies by 1993.[664] It was once suggested that technegas particles might be C_{60} molecules each containing a single endohedrally-trapped technetium atom,[665] but TEM, SEM, and AFM imaging found that this radiopharmaceutical consisted of hexagonal mostly 30-60 nm platelets of metallic Tc^{99m} encapsulated within a thin layer of graphitic carbon.[666] Traditional dry insoluble technegas particles adhere well to alveolar walls upon inhalation (after a single-breath diagnostic dose[667]), whereas pertechnegas particles, which have no carbon coating, rapidly disappear from the lungs via exhalation.[668]*

lungs.[173] Many silica crystals penetrate the respiratory epithelium, lodging in the interstitium between cells (Figure 8.15), and eventually worm their way into the lymphatic channels and progress into the lymph nodes.[173] About 20% of these insoluble crystals are never cleared from the body (Section 15.4.3.3.3). At the site of each intrusion, a lesion develops, probably due in part to the chronic mechanical irritation, leading to tissue inflammation, the formation of "silicotic nodules," fibrosis and scarring.[175] (Inhaled insoluble tungsten particles have also been found in mediastinal lymph nodes (Section 8.2.1.3) of workers with hard metal lung disease.[176])

Alveolar macrophages engulf and ingest silica crystals that reach the alveoli. Once inside the cell, the crystal sets in motion a sequence of biochemical reactions (especially involving reactive oxygen molecular species) that ultimately destroys the cell, causing it to rupture and release its intracellular enzymes and the silica crystal back into the surrounding lung tissue. (See also footnote, Section 15.6.3.4.) The enzymes damage the lung tissue, which subsequently heals by fibrosis. This silica particle is re-phagocytized by another macrophage, and the cycle repeats; the end result of this process is respiratory failure.[177] (Neutrophils are also present, typically ~6 x 10^4 cells per gram of wet tissue in mammalian lungs.[763]) One study suggested that as little as 1 milligram of 5-micron silica crystals inhaled per 100 grams of body weight is enough to kill a rat by producing a severe alveolitis and fatal pulmonary edema. Indeed, within 24 hours of the lethal exposure researchers observed "gasping, cyanosis, and discharge of a pinkish and frothy fluid from the mouth and the nostrils" among the rodents prior to death.[175] The equivalent exposure at a 70-kg human body weight, all else equal, would require the inhalation of ~0.7 gm of 5-micron silica dust — roughly the same volume as ~3 billion inhaled 5-micron airborne silica crystals.

Pneumoconiosis from exposure to artificial graphite made from coke has not been reported and probably occurs only rarely.[670] A survey of over 600 cases of graphite pneumoconiosis[673] yielded just one case in which nearly pure graphite might cause graphite pneumoconiosis. The majority of the evidence indicates that pneumoconiosis is a mixed-dust lung reaction, and that analytically pure graphite probably does not cause pneumoconiosis.[673,674,675] Silicographitosis has been documented following excessive exposure to natural graphite (plumbago) in graphite mines,[671] which is a crystalline form of carbon containing free silica.[174] Carborundum fibers, a synthetic abrasive made by fusing silica and carbon, also produce fibrosing alveolitis.[672] The most common carbonaceous-hazard diseases include anthracosis and emphysema (coal),[178] graphitosis (natural graphite), and smog lung (carbon plus photochemicals). Federal regulatory limits on coal mine dust (predominantly elemental carbon with a maximum of 5% silica[179]) are 2 mg/m^3. Subchronic inhalation of 1.1 mg/m^3 of carbon black dust is not mutagenic or genotoxic for rat alveolar epithelial cells and elicits no detectable adverse lung effects.[761]* Subchronic inhalation of carbon fibers at 20 mg/m^3 also has no injurious effect on rats.[765] Bronchiolar (large-particle) coal dust is quickly cleared via the mucociliary escalator (Section 8.2.2). Smaller alveolar-resident particles are mostly taken up by macrophages, which migrate over the airspace surface to the terminal bronchioles, then enter the mucociliary stream.[179] Within ~2 hours post-exposure, ~2% of these particles penetrate the airway lining and enter the interstitium (Figure 8.15) and the phagocytic vacuoles of lymphatic endothelial cells; at 24 hours, the particles are detected in the peribronchial lymphatics and lymph nodes.[180] Pure carbon particles can also insinuate themselves permanently into the skin.[181]

More than 3000 naturally occurring minerals are known to present a respiratory hazard,[167] including aluminum,[182,958] asbestos,[183] barium,[184] beryllium,[185,186] germanium,[187] iron,[188] molybdenum,[189] talc,[190-192] and tin.[193] Even the aspiration of common table pepper particles has proven fatal in children.[194,195] Exposure to 9- to 24-micron diameter glass fibers (e.g., synthetic vitreous fibers or SVFs) such as are found in fiberglass insulation[196] can produce a transient irritation of the mucous membranes of the eyes, nose, and throat[197] though no long-term adverse effects such as lung fibrosis, lung cancer, or mesothelioma has been shown.[198,199] However, very long[758,759] and thin glass fibers (diameter < 1.5 micron) are cytotoxic in vitro[757] and highly carcinogenic after intrapleural implantation[200] inducing malignant mesothelioma and fibrosis in rats.[2493] Fiberglass dermatitis is well known.[201] Adverse pulmonary effects are a function of dose, dimensions, and durability of fibrous particles.[2494] Interestingly, even "healthy" human lungs are loaded with inorganic microfibers — a lung tissue biopsy of 10 normal subjects found 1.5 x 10^6 fibers/gm, as compared to 141.9 x 10^6 fibers/gm in the lungs of 11 asbestos-exposed individuals, with fiber length most commonly 3-5 microns in both groups.[202]

But what about **diamonds**? A recent (2002) review of the modern medical literature revealed no explicit reports of **diamond** dust inhalation toxicity, nor was this possibility even mentioned in any of the standard reference works. Potential risks from the airborne release of inhalable **diamond** dust into the oral cavity from dental drills during common clinical use appears not to have been widely investigated, despite data showing that particles can be thrown up to 90 cm from the patient's mouth and may remain suspended in the air for hours.[203] (Minor risks to dental personnel due to simultaneous metals exposure[115] or silica[204] have been considered.)

However, there is at least one suspicious case study[205] involving five Belgian **diamond** polishers that could possibly represent an instance of undiagnosed respiratory **diamond** poisoning. In the Belgian gem-finishing occupations, workers use high-speed **diamond**-cobalt grinding tools to polish **diamonds** that have already been cut. The grinding surface is a spinning wheel consisting of 20- to 40-micron **diamonds** cemented onto a layer of fine 400-mesh ~64-micron cobalt metal grit. During grinding and polishing, cobalt grit and **microdiamonds** are abraded from the wheel and are thrown into the air, then inhaled by the workers.

In 1984, eight physicians at the Clinic of Medicine of the Catholic University in Leuven, Belgium, treated five individuals (non-smokers) for interstitial lung disease or fibrosing alveolitis. This condition is normally reversible with proper treatment. Symptoms included painful breathing, crackling noises coming from the lungs, coughing and wheezing, chest tightness, runny nose, and weight loss. But the condition was puzzling because no case of lung fibrosis had ever been attributed to cobalt powder exposure alone.

Could the disease have been caused by respiration of airborne abraded **microdiamonds**? The physicians did not investigate this possibility and concentrated instead on the more familiar cobalt culprit — "intoxications by cobalt alone [would] be enlisted as a compensatable industrial lung disease." Lung tissue biopsies showed no "massive tissue necrosis," and the journal report is silent as to whether or not there was any search for evidence of **microdiamonds** in lung tissue — despite the clue, perhaps more clear in retrospect, that fume hoods over the work stations were reported to contain large amounts of "amorphous carbon" besides the cobalt particles. The physicians finally ascribed the disease to cobalt, even though, according to the case histories, 3 of their 5 patients were clearly not healed,

** The American College of Governmental Industrial Hygienists has set a threshold limit value of 10 mg/m^3 for nuisance dusts and 3.5 mg/m^3 for pure carbon black dust, but this is based on avoidance of excessive workplace dirtiness and not on the toxicity of carbon black per se.[764]*

years later, despite having received the correct treatment for cobalt poisoning. Could this be a case of undiagnosed **diamond** dust injury?

First, over the last two decades numerous studies have conclusively proven that pure cobalt is at worst a mild irritant and does not appear to cause lung fibrosis by itself.[175,206-209,212,213] Gennart and Lauwerys[210] question the role of cobalt alone in producing lung fibrosis and note that "the possible interference of other components of the dust inhaled by the workers who developed the disease remains to be elucidated....There is suggestive evidence that other components of the inhaled particles interfere with the biological reactivity of cobalt on the lung." Lauwerys and Lison[211] note that industrial exposures to cobalt commonly include "other substances such as tungsten carbide, iron, *and* **diamond**, which may modulate the biological reactivity of cobalt [emphasis added]." Others,[212] including the lead author of the Belgian study,[213] now implicitly acknowledge that **microdiamonds** could be medically relevant.

Second, other studies have suggested that the presence of carbides, particularly tungsten carbide, can interact with cobalt to produce the observed fibrosis,[175,208,214,215] but in the case under discussion the investigators specifically reported that "no measurable amounts of carbides of tungsten or other metals were present....Cobalt was, besides the **microdiamonds**, the almost exclusive component of the grinding surface of the disks."[205] Limited studies in hamsters show that intratracheally-instilled cobalt (5 mg/kg) and **diamond** particles (50 mg/kg) caused more acute lung damage then when these particles are administered alone.[213] So the original conclusion of the Belgian **diamond**-polishers alveolitis study — i.e., that cobalt alone caused the problems — might well be invalid. The specific possibility that **diamond** dust could have been involved remains unaddressed.

A related study of three additional **diamond**-polisher patients (including two smokers) who presented with bronchial asthma alone[216] probably was correctly attributed to the cobalt,[209] and there are other similar cases.[4739] But another case involving a single **diamond**-polisher patient (a smoker) who presented with both bronchial asthma and alveolitis,[217] also attributed to the cobalt, is of uncertain validity — as yet, no studies have focused on **diamond** as a possible contributory factor. An autopsy of lungs of hard-metal grinders revealed the frequent presence of corundum but no specific search for **diamond** particles was reported.[218] Vital capacity was found to be significantly impaired among young workers who were exposed to "carbon dust" during **diamond** cutting and polishing in India,[219] and in 2002 increased lipid peroxidation was reported in miners working in the **diamond** extraction industry in Yakutia, Russia.[4737] A 62-year-old Japanese patient who had been a **diamond**-grinder for 20 years showed numerous unusual well-circumscribed tumors on the parietal pleura, diagnosed as pleural plaques,[220] and 0.1- to 0.6-micron spherical carbon-black particles (in the virtual absence of quartz) are known to have caused fatal carbon pneumoconiosis in at least one other case.[181]

On the positive side, Schmidt et al[221] specifically assert that **diamond** dust is nonfibrogenic in human monocyte-macrophages ("dust cells") found in the lungs. Hedenborg and Klockars[222] used **diamond** dust as an "inert control" in their experimental work, and found that **diamond** dust did not stimulate the production of reactive oxygen metabolites by polymorphonuclear leukocytes — a proposed pathway for chronic inflammation and tissue injury of the lung. Inhalation experiments with rats and guinea pigs indicate that dust from carbon fibers produces no systemic toxicity or pathological changes in the lungs,[223,224,765] and medical examination of carbon fiber production workers has revealed no adverse effects on the lungs,[225] though one Russian animal study found slight pulmonary fibrosis and respiratory tract irritation from carbon fiber dust[226] and a Japanese study found morphological changes in rat lungs due to some kinds of carbon fibers.[762] But none of these results allow us to rule out the possibility of mechanical damage to lung tissues by ragged **diamond** shards (Section 15.1.1).

Although there is no direct evidence of any harm, a conservative appraisal would appear to warrant a careful study of the lung toxicity of fractured **diamondoid** detritus. Because of the likely importance of **sapphire** in nanodevice design, crystalline corundum and emery[227-229] (e.g., grinding grits) probably should also be investigated for both ingestion and inhalation mechanical toxicity. (See also Section 15.3.5.5.)

CHAPTER 15.2

Classical Biocompatibility

The question of biocompatibility[234-237] arises whenever any foreign substance — be it natural materials,[6054] therapeutic cells, a transplanted organ, an artificial implant, or a medical nanorobot — is placed inside the human body for medical purposes. The most general definition of biocompatibility is: "the ability of a material to perform with an appropriate host response in a specific application",[230] or, alternatively: "the exploitation by materials of the proteins and cells of the body to meet a specific performance goal",[231] but neither of these really tells the whole story. The term "biocompatibility," as used in this book, will refer to an assessment of the totality of nanorobot surface material-tissue interactions, both local and systemic. These interactions classically may include:[231-234]

1. *Cellular Adhesion Effects* — including (A) weak interactions with a nonadhesive surface, (B) strong nonspecific interactions leading to attachment and de-differentiation* of highly specialized cell types (e.g., leading to the attachment of monocytes, conversion to macrophages, the formation of giant cells, the recruitment of fibroblasts, and, at later stages, fibrosis), (C) strong specific interactions with surfaces containing appropriate receptor sites arrayed at the appropriate density (e.g., cells attach, do not de-differentiate, and perform highly specific functions), and (D) encasement in a gel or matrix either containing active receptor sites or a matrix that is noninteracting, wherein the 3D cell-matrix contact permits the cell to function in a physiologically normal manner;
2. *Local Biological Effects* — such as cell viability and mitotic function (cell proliferation, cell cycle phases), cell metabolic activity (cell protein content), and plasma membrane integrity; blood-material interactions (e.g., blood platelet adhesion and activation, leading to thrombogenesis, complement activation, or hemolysis); toxicity (e.g., the leaching of cytoreactive substances from biomaterials), modification of normal healing (e.g., encapsulation, foreign body reaction and pannus overgrowth), infection, and tumorigenesis;
3. *Systemic and Remote Effects* — such as embolization of clots or biomaterial hypersensitivity, elevation of usual components in blood, systemic toxicological response, lymphatic particle transport, systemic distribution and excretion, effects of degradation products on remote organ functions (including interactions of degradation products with therapeutic agents or devices), and allergic, pyrogenic, carcinogenic, and teratogenic responses; and
4. *Effects of the Host on the Implant* — such as physical or mechanical effects, stability and biological degradation processes (e.g., absorption of substances from tissues, enzymatic damage, or calcification), immune responses such as inflammation, fibrosis or granuloma formation around the implant, or co-option of implant structure or function.

Chapter 15.2 opens with a brief summary of the current (2002) status of medical implant biocompatibility (Section 15.2.1), followed by a general discussion of protein interactions with implant surfaces (Section 15.2.2), immunoreactivity (Section 15.2.3), inflammation (Section 15.2.4), coagulation and thrombosis (Section 15.2.5), allergic reactions and shock (Section 15.2.6), fever (Section 15.2.7), and finally mutagenicity and carcinogenicity (Section 15.2.8), especially as applied to medical nanorobots.

15.2.1 Biocompatibility of Traditional Medical Implants

During the 20th century, artificial materials and devices were developed to the point at which they could be used successfully to replace parts of living systems in the human body.[238] These special materials — able to function in intimate contact with biological fluids or living tissue, with minimal adverse reaction or rejection by the body — are called biomaterials.[239-243] Devices engineered from biomaterials and designed to perform specific functions in the body are generally known as biomedical devices or implants. By the mid-1990s, biomaterials were found in ~2700 different kinds of medical devices, ~2500 separate diagnostic products, and ~39,000 different pharmaceutical preparations.[233]

The earliest successful medical implants were bone plates,[244] first introduced in the early 1900s to stabilize bone fractures and assist in the healing of skeletal fractures. (The plate was often removed once the bone had healed and the bone could support loads without refracturing,[245] or else the plate was designed to be bioabsorbable.[246-248]) Advances in materials engineering and surgical techniques led to blood vessel replacement experiments in the 1950s. Artificial heart valves and hip joints were under development in the 1960s.[239] By the end of the 20th century, biomaterials came to play a major role in replacing or improving the function of every major human body system, and became important in extracorporeal systems such as oxygenators, dialyzers, and apheresis systems. Some common implants[233,238] include: (1) orthopedic prostheses such as total knee and hip joint replacements, spinal implants, bone fixators, and tendon and ligament prostheses;[305] (2) cardiovascular implants[241] such as artificial heart valves, vascular grafts and stents, pacemakers, and implantable defibrillators; (3) neural

** De-differentiation is the loss by mature cells of some of their specialized properties and reversion to a less developed state.[5484] De-differentiation is a normal part of healing and regeneration,[5485] can be induced mechanically,[5486] and is often a part of early tumor development.[5487]*

implants (e.g., cochlear implants) and cerebrospinal fluid drainage systems (e.g., hydrocephalus shunts); (4) plastic and reconstructive implants such as breast augmentation or reconstruction, maxillofacial reconstruction, artificial larynx, penile implants, and injectable collagen for soft tissue augmentation; (5) dental implants to replace teeth/root systems and bony tissue in the oral cavity; (6) ophthalmic systems including contact and intraocular lenses; (7) catheters and bladder stimulators; (8) drug-dispensing implants such as insulin pumps; and (9) general surgical systems such as sutures, staples, adhesives, and blood substitutes. It has been estimated that 674,000 adults in the U.S. were using 811,000 artificial hips (Section 15.2.1.1) by 1988.[249] About 170,000 people worldwide (60,000/year in the U.S.) received artificial heart valves (Section 15.2.1.2) in 1994,[238,1147] and ~1 million joint replacement prostheses were installed worldwide in 1996.[594] About 100,000 external insulin pumps (in U.S.) and ~1100 internal (implanted) insulin pumps (worldwide) had been placed in patients by 2001.[5925]

15.2.1.1 Orthopedic Biomaterials

In cases of joint injury or degenerative arthritis, when improvement cannot be gained through physical therapy, nonsurgical treatments, or surgical repairs, orthopedic surgeons often advise joint replacement surgery in which the deteriorated joint is removed and replaced with a man-made device.[250-252] Artificial joints consist of a plastic cup made of ultrahigh molecular weight polyethylene, placed in the joint socket, and a metal (titanium or cobalt chromium alloy) or ceramic (aluminum oxide or zirconium oxide) ball affixed to a metal stem. This type of artificial joint is used to replace hip, knee, shoulder, wrist, finger, or toe joints. Joint replacement surgery is performed on an estimated 300,000 patients per year in the U.S.[238] In most cases, it brings welcome relief and mobility after years of pain.

Artificial knee joints are used to alleviate pain and restore function in patients who have a diseased joint. Materials and design engineers must consider the physiologic loads to be placed on the implants and must design for sufficient structural integrity. Material choices also must consider implant biocompatibility with surrounding tissues, the environment and corrosion issues, friction and wear of the articulating surfaces, and implant fixation either through osseointegration (the degree to which bone will grow next to or integrate into the implant) or bone cement.[238]

One of the major problems plaguing orthopedic implant devices is purely materials-related: wear and fatigue-induced delamination of the polymer cup in total joint replacements.[253] Any use of the joint, such as walking in the case of knees or hips, results in cyclic articulation of the polymer cup against the metal or ceramic ball. Due to significant localized contact stresses at the ball/socket interface, small regions of polyethylene tend to adhere to the metal or ceramic ball.[238] During the reciprocating motion of normal joint use, fibrils are drawn from the adherent regions on the polymer surface and break off to form submicrometer-sized wear debris.[6051] This adhesive wear mechanism, coupled with fatigue-related delamination of the polyethylene (most prevalent in knee joints), results in billions of tiny polymer particles being shed into the surrounding synovial fluid and tissues. The biological interaction with small particles in the body then becomes critical. The body's immune system attempts, unsuccessfully, to digest the wear particles much as it would a bacterium or virus.[254] Enzymes are released that eventually result in osteolysis, the death of adjacent bone cells.[255] Over time, sufficient bone is resorbed around the implant to cause mechanical loosening, which necessitates a costly and painful implant replacement, or "revision." Since the loosening is not caused by an associated infection, it is termed "aseptic loosening".[253] The average life of a total joint replacement is 8-12 years,[256] or even less in more active or younger patients. Because it is necessary to remove some bone surrounding the implant, generally only one revision surgery is possible, thus limiting current orthopedic implant technology to older, less active individuals.[238]

Studies of wear debris extracted from actual tissue samples of patients whose implants failed as a result of aseptic loosening generated significant information regarding wear particles size, shape, and surface morphology.[257] Interestingly, investigators at the Southwest Research Institute used the atomic force microscope (AFM; Section 2.3.3) to produce detailed, high resolution images of polyethylene wear particles measuring a few hundred nanometers in size and sometimes exhibiting a cauliflower-like surface morphology.[238] By combining wear debris and cellular response studies, engineers and biologists are trying to better understand implant failure and to re-engineer implants to avoid future problems.[255,258] Experiments with diamond-coated hip-replacement implants are in progress.[609]

G.M. Fahy notes that inflammatory cells lack receptors for ultrahigh-density polyethylene or fragments thereof, yet are able to recognize these utterly foreign objects as such and attack them. This might, in part, be accomplished by "recognition" not of specific topological features or chemical groups but instead by "recognition" of a surface with a higher surface energy than the surface energy of the immune cell. The immune cell tries to reduce the free energy of the combined cell-polymer interface by coating the high energy interface — i.e., by adhering to, and if possible engulfing, the particle. This phenomenon would then provide a general guideline as to how to reduce unwanted adhesion: avoid high surface energy interfaces. Surface energy is briefly mentioned elsewhere in connection with diamond (Sections 15.3.1.1 and 15.3.1.2), Teflon (Section 15.3.4.2), and sapphire (Section 15.3.5.4) surfaces, and previously in Sections 9.2.1 and 9.2.3.

15.2.1.2 Heart Valve Biomaterials

An example of the successful development of a critical implant technology is the artificial heart valve.[260,6050] Although poor heart valve designs resulted in clinical failures in the past, by 2002 the limiting factor for long-term success had become the materials themselves. Two types of materials (hard man-made and soft bioprosthetic) were commonly used for artificial heart valves,[232,1147-1152] though a third type — polymer valves[1143] — were also being investigated.

First and most popular (~60% of implants) are the hard man-made materials used in mechanical heart valves. The principal problems with mechanical heart valves are thrombosis,[238] which may be revealed as a thromboembolism, with the formation of a stationary (thrombus) or free (embolus) clot, or hemorrhaging as a result of inappropriately elevated levels of anticoagulation. Graphite coated with pyrolytic carbon (Section 15.3.3.2) has become the material of choice for mechanical heart valves because of its excellent resistance to thrombosis (thromboresistance).[261,955,4839] During 1969-1994, an estimated 2 million components were successfully implanted, resulting in at least ~10 million patient-years of additional life.[262] It has been suggested that the service lives of pyrolytic carbon heart valves may be limited both by cyclical fatigue[263,940] and by cavitation stress* due to turbulent flow,[264]

** Lin et al[4838] used a high-speed video camera and an ultrasonic monitoring system to observe cavitation and gas bubble release on the inflow valve surfaces of a Medtronic-Hall pyrolytic carbon disk valve in a mock circulatory loop. In the absence of cavitation, no stable gas bubbles were formed, but when gas bubbles were formed, they were first seen a few milliseconds after and in the vicinity of a cavitation collapse. Bubble volume increased with both increased cavitation intensity and increased concentration of CO_2 (the most soluble blood gas), which is believed to be the major component of stable gas bubbles because no correlation was observed between O_2 concentration and bubble volume.*

because cyclic crack growth[265] is possible in this material.[238] However, double-leaflet pyrolytic carbon valves subjected to accelerated ex vivo wear testing have demonstrated up to 2.1 billion cycles (~52.5 human years) without mechanical failure or loss of functionality,[266] and recent experiments[4837] suggest that isotropic pyrolytic carbons may be fatigue-free in the physiologically relevant stress regimes encountered in contemporary bi-leaflet artificial heart-valve designs, for ~10^9 cycles.* Other drawbacks include excessive noise, catastrophic failure modes, and the need for lifelong anticoagulant therapy to prevent incidence of embolism (stroke) due to clot formation.[267] A blood pump with diamond-like carbon on all blood-contacting surfaces has been developed as an implantable left ventricular assist system.[612]

The second most common heart valve materials are the soft bioprosthetic materials (~40% of implants) or tissue valves,[267,1147] such as denatured porcine aortic valves,[268] bovine[269] or autologous[270,271] pericardium, human aortic valve homografts,[272,273] or tissue engineered biovalves.[274] It is believed that autologous pericardium, being still alive, should not degrade as fast as fixed porcine valves. Bioprosthetic valves,[268] the only option for children, often fail due to calcification[275,276] (bloodstream calcium forms deposits on the implant), which can result in mechanical dysfunction, vascular obstruction, or embolization of calcific deposits.[277,278] Bioprosthetic valves may have low thrombogenicity and immunoreactivity but are also susceptible to mechanical fatigue — cyclical valve loading can facilitate fatigue crack growth, often resulting in catastrophic failure.[279] The major unresolved problem with tissue-based heart valves is their limited durability, generally 5-15 years.[267]

A review of several large comparative studies on clinical valve performance finds that valve infection (prosthetic valve endocarditis), nonstructural dysfunction, and overall results after 10 years were about equal for tissue and mechanical valves.[1147,1152]

15.2.1.3 Bioactive Materials

When an artificial material is placed in the human body, tissue reacts to the implant in a variety of ways depending on the material type.[241] The mechanism of tissue attachment (if any) depends on the tissue response to the implant surface. Materials can generally be placed into three classes representing the type of tissue response they elicit: chemically inert, bioresorbable, or bioactive.[238]

Chemically inert materials such as titanium,[280-282] tantalum,[282,283] polyethylene,[280,284] and alumina (Al_2O_3)[285-289] exhibit minimal chemical interaction with adjacent tissue. However, even these substances are not entirely physically inert, as a "defensive" fibrous tissue capsule will normally form around chemically inert implants[238] in a reaction analogous to that of the body controlling tuberculosis by encapsulating the invading microorganisms. Tissue may also physically attach to these inert materials by tissue growth into surface irregularities, by bone cement, or by press-fitting into a defect. This morphological fixation is not ideal for the long-term stability of permanent implants and often becomes a problem with orthopedic and dental implant applications[238] in part due to a lack of strength. Nevertheless, many polymeric implant devices are generally regarded as safe and effective for periods of months to years. Biological attack occurs, but is compensated for in the design specifications.[2538]

Bioresorbable materials such as tricalcium phosphate,[289-292] polylactic-polyglycolic acid copolymers,[292-294] and even some metals,[4886,4888] are designed to be slowly replaced by tissue (such as bone or skin). They are used in drug-delivery applications[246-248,295,296] or in biodegradable implantable structures such as sutures,[4876-4880] suture anchors,[4881-4883] meniscus arrows,[4884] stents[4886-4891] and other devices.[4885] STAR Inc., a startup founded in the year 2000 by Benjamin Chu and others at the State University of New York, Stony Brook, manufactures an electrospun nanofiber polymer-mesh membrane designed to prevent body tissues from sticking together as they heal, and to break down in the body over time like biodegradable sutures. Anti-adhesion materials made of cellulose or hyaluronan are already available from Johnson & Johnson and Genzyme Corp., but doctors are unsatisfied with these materials because they tend to stick to a surgeon's wet glove and don't always work well inside a patient. Chu claims that STAR's nanomesh, using ~150 nm-diameter nanofibers, is more flexible, easier to hold, and may also be able to deliver antibiotics, painkillers or other medicines directly, and in smaller quantities, to internal tissues.[4874] eSpin Technologies[4875] is also commercializing nanofibers made of organic and biological polymers.[4874]

Bioactive materials include certain glasses,[297] ceramics, glass-ceramics,[297] and plasma-sprayed hydroxyapatites[288] that contain oxides of silicon, sodium, calcium, and phosphorus (SiO_2, Na_2O, CaO, and P_2O_5) and that constitute the only materials known to form a chemical bond with bone, resulting in a strong mechanical implant-bone bond.[298] These materials are referred to as bioactive[299-301] because they bond to bone (and in some cases to soft tissue) through a time-dependent, kinetic modification of the surface triggered by their implantation within living bone. In particular, an ion-exchange reaction takes place between the bioactive implant and surrounding body fluids during which chemical species from the ceramic diffuse into the fluid and vice versa, resulting, over time, in the formation of chemically graded layers that become a biologically active hydrocarbonate apatite (calcium phosphate) layer on the implant that is chemically and crystallographically equivalent to the mineral phase in bone, producing a relatively strong interfacial bonding.[238] Although bioactive materials would appear to be the answer to biomedical implant fixation problems, available bioactive glasses (i.e., Bioglass[302-304]) are not suitable for load-bearing applications, and so are not used in orthopedic implants. In fact, their use for other implants, even some dental applications, is limited because they have a low resistance to crack growth.

However, there are stronger ceramic materials, crystalline in structure, that are not as bioactive. Ion beam surface modification has been used to alter the atomic structure and chemistry at the surface of these crystalline ceramics to improve bioactivity, allowing ion-exchange in the modified material upon implantation.[238] For example, Richard France at the University of Sheffield has studied the effect of surface chemistry on the attachment of human skin cells (keratinocytes) from the epidermis. He uses a technique known as plasma polymerization to make surfaces containing specific concentrations of a particular functional group.[897] France finds that keratinocytes prefer a specific concentration (about 3%) of carboxylic acid functional groups. Such a surface promotes cell attachment as well as collagen deposition, and collagen is the keratinocytes' natural substratum at the dermal-epidermal junction. The cells also prefer high concentrations of amine or alcohol groups, although on these surfaces the attachment rarely matches that obtained on collagen. These plasma polymers support cell growth over a number of days and in the year 2000 were being developed as a transfer dressing to allow cells to be cultured and subsequently applied to wound beds such as burns or ulcers, promoting healing.[897]

** Medtronics' and CarboMedics' pyrolytic carbon valves have a projected wear-related half-life of 570 years.[752]*

Adam Curtis and colleagues at the University of Edinburgh have studied the effects of implant surface topography using various etched substrata. Cells align themselves to micron-scale features on a titanium surface, and the size and shape of features can control the behavior of different cells (Section 15.2.2.3). For instance, fibroblasts (responsible for new collagen fiber deposition during wound healing) migrate along the micron-sized grooves, while macrophages (white blood cells responsible for digesting foreign matter) can become trapped within these features.[897] Biomaterial scientists can exploit such topographical controls to provide new ways to guide regeneration and healing.[897]

Note that in many nanomedical applications, tissue integration with the implant is desirable (Section 15.2.2.2), and may involve chemical interaction and host cell adhesion with a bioactive implant surface. For other applications such as hemodynamic systems, a nonadhesive inert nanodevice surface is desirable (Section 15.2.2.1) to prevent thrombus formation or nidus of infection.[306] In other words, appropriate biocompatibility is very application-specific.

15.2.1.4 Implant Infection and Biofilms

In the late 20th century, millions of patients who received tissue and organ replacement worldwide experienced biomaterial-associated infection as one of the most destructive complications. Infections occurred in <1% of total hip replacements but in 2-4% of total knee replacements and in 7% of total elbow replacements,[306] while *Pseudomonas aeruginosa* was the most frequent cause of bacterial keratitis in extended-wear contact lenses.[309] Vascular grafts became infected in 6% of specific risk groups, and intravascular catheters almost always became infected if not changed at regular intervals.[306] Ventricular assist devices developed infections 20% of the time in use under 31 days,[307] and the Total Artificial Heart (TAH) of the late 1980s was at risk for infection 100% of the time if left in place for more than 1 month.[308] The formation of a biomaterial-associated biofilm (durable infection) usually led to removal or revision of the affected device or implant,[238] with obvious devastating results for the patient.

Biofilms consist of bacteria embedded in a film of adhesive polymer, especially on implanted devices; bacteria within the film are protected from the action of antibiotics. As is well known in the industrial world, bacterial biofilms routinely foul many surfaces including ship hulls, submerged oil platforms, and the interiors of pipeworks and cooling towers, causing corrosion and metal component failure. Biofilms may infest gas biofilters,[323] plastic mineral water bottles[324] and food processing systems.[325] But biofilm formation is also a serious medical problem that manifests itself as biomaterial-associated infections of devices (e.g., endotracheal tubes, sutures, intravenous catheters, urinary catheters, IUDs, and contact lenses), and as infections of prosthetic implants (e.g., mechanical heart valves, arteriovenous shunts and vascular grafts, joint replacements, biliary stents, dental implants, penile prostheses, and spinal implants),[313,326-328] with *Staphylococcus epidermis* as the most common cause.[310] Depending on the organism involved, these infections can be either acute, with symptoms appearing relatively soon after material insertion, or chronic, with symptoms taking up to months to appear.[238] Electron microscopy of the surfaces of infected medical devices shows the presence of large numbers of slime-encased bacteria.[331] Biofilms may vary widely in thickness, limited more by nutrient transport than by surface roughness. For example, aerobic *Pseudomonas aeruginosa* biofilms can grow to 30-40 microns in depth as monocultures, but these biofilms can increase in depth to 130 microns when the culture is amended with anaerobic bacteria.[2523]

Regular bacterial growth can sometimes be eradicated by cleaning implant surfaces with disinfectant or by systemic antibiotic administration. But bacteria may irreversibly adhere to artificial or natural surfaces that are surrounded by fluids. Unfortunately, adherent bacterial cells form biofilms preferentially on chemically inert surfaces,[328] which possibly could include diamondoid materials useful in nanorobotics. For example, fungal biofilms are known to adhere to polystyrene plates.[2553] Once adhered, the bacteria can multiply, forming complex multilayered microcolonies and producing a slimy matrix material (usually a glycocalyx film) that encases the bacterial cells. This bacterial biofilm has been described as "a structured community of bacterial cells enclosed in a self-produced polymeric matrix and adherent to an inert or living surface".[328] Sessile biofilm communities are resistant to antibodies, phagocytes, and antibiotics[328] because the extracellular sulfated 20-kD acidic polysaccharide[332] slime matrix acts as a physical and chemical barrier to protect the bacteria from attack. Confocal optical sectioning shows that biofilms are highly hydrated open structures composed of 73-98% extracellular materials and void spaces.[320] AFM images of the surface structure of a hydrated biofilm[238] reveal numerous ~0.25-micron pores and ~0.50-micron channels. These discontinuous channels are believed to serve as nutrient-carrying passageways to all layers of the biofilm,[319-323] thereby maintaining bacterial viability and capacity to proliferate. Atomic force microscopy has also been used to analyze the initial events in bacterial adhesion.[333,334] Cells in different regions of a biofilm exhibit different patterns of gene expression[335] as well as functional heterogeneity.

All biomaterial surfaces, regardless of preparation, acquire patterns of organic and ionic contaminants whose distribution is directed by specificities of the outer atomic layers of the implant.[306] Glycoproteinaceous conditioning films — derived from fluid or matrix phases containing plasma protein such as fibrinogen, fibronectin, collagen, and other proteins — immediately coat a biomaterial or tissue implant[315] and act as receptor sites for bacterial or tissue adhesion.* [310] The role of each constituent of this coating differs for each bacteria or tissue cell type. For instance, *Staphylococcus aureus* has discrete binding sites for collagen and fibronectin.[311,312] Predicts Gristina et al:[306] "Modifications to biomaterial surfaces at an atomic level will allow the programming of cell-to-substratum surface events." (See Section 15.2.2.)

Nanorobotic material surface characteristics and properties including roughness and surface area, fractal dimensionality, compactness or porosity, hydrophobicity, and chemistry may play a significant role in host cellular adhesion and in the ability of bacteria or cells to colonize nanorobotic surfaces.[238,316-318,2587,2588] When tissue cells colonize a metal or polymer surface and integrate with the implant surface — whether via direct chemical interaction or host-derived macromolecules — then late-arriving bacterial cells are confronted by a living integrated tissue surface which resists bacterial colonization due to its viability, intact cell membranes, exopolysaccharides and functioning host defense mechanisms, and decreased availability of binding sites due to occupation of those sites by tissue cells. However, if bacterial adhesion occurs first and a stabilized microcolony has developed, late-arriving tissue cells cannot easily displace the primary colonizers to occupy and integrate the surface.[306]

Once established, biofilm infections are rarely resolved by host defense mechanisms, even in strong hosts.[331] Antibiotic therapy

** Proteins generally stick well to glass, less well to Teflon (Section 15.3.4.1), and least of all to mica.*

typically reverses the symptoms caused by planktonic (individual) cells released from the biofilm, but fails to kill the biofilm itself.[328-330,1115-1117] It is variously estimated that bacteria within biofilms are effectively from 20-1000 times[326] to 500-5000 times[1115] less sensitive to antibiotics than planktonic microorganisms. This reduced sensitivity appears to depend on physiological changes associated with slow growth in biofilm populations,[1118-1120] possibly including gene derepression[5488] effects triggered by bacterial adhesion.[1121] Antibiotic-impregnated surfaces have enjoyed only limited success in resisting biofilm formation,[2497-2512,5291] in part because the supply of impregnating agent is nonrenewable. Nanorobotic devices capable of onboard resupply need not suffer this limitation.

One very successful surface treatment to combat the biofilm problem is a thin (~1-micron) ion-beam assisted deposition silver coating on PVC or polyethylene.[5792] Silver (Section 10.4.1.4(17)) and its compounds[336] have long been recognized as bactericidal. Silver-coated samples of implant material, tested in a modified Robbins device with *Staphylococcus epidermidis*, exhibited less prolific biofilm formation than did uncoated materials.[238] In 1997, Spire Corp. in collaboration with St. Jude Medical developed an ion-beam texturization process called "Silzone"[337] (originally "SPI-ARGENT"[314]) that allows the impregnation of heart valve sewing cuffs with silver metal to help prevent bacterial growth on the cuff. This reduces the incidence of postreplacement endocarditis, a life-threatening inflammation of the heart's inner lining. Spire Corp. similarly treats central venous catheters and surgical guide wires to reduce the likelihood of clot formation and to increase lubricity, thus easing the insertion process.[314] The Erlanger silver catheter[338] and other silver-impregnated catheters[339-342] have demonstrated greatly reduced bacterial adherence and biofilm formation. In vitro tests of silver-coated polyurethane biliary stent material reduce adherent bacteria by 10- to 100-fold,[343] and silver-coated Gore-Tex helps inhibit biofilm growth.[344]

Permanently hydrophobized glass and ceramic surfaces have been found to largely prevent biofilm formation in the oral cavity environment.[345] Diamond is also very hydrophobic, though tests of biofilm formation on diamond have not yet been reported in the literature. A coating of ciprofloxacin-containing liposomes sequestered in polyethylene glycol (PEG) hydrogel that completely inhibits bacterial adhesion on silicone catheters has been demonstrated.[346] Alternatively, a correlation has been found between the enthalpy of adhesion (Sections 9.2.1 and 9.2.3) of bacteria to material surfaces and the strength of adherence of biofilm bacteria to those material surfaces.[347] In particular, there seems to exist a certain minimum bacterial adhesive tendency that is independent of the nature of the polymer surface; modified polymers with negative surface charge give a bacterial adherence close to the adherence minimum.[347]

Another interesting approach from the nanomedical perspective is the application of low-power ultrasound in concert with aminoglycoside antibiotics (e.g., gentamicin) to enhance the effectiveness of antibiotic treatments and reduce the viability of sessile bacteria (e.g., *Pseudomonas aeruginosa*) by several orders of magnitude,[1122-1131] a synergy known as the bioacoustic effect.[1125,1130] In one experiment using 12 $\mu g/cm^3$ gentamicin on biofilms, a 2-hour exposure to ultrasound at 70 KHz killed ~99% of *P. aeruginosa* biofilm bacteria at 100 W/m^2 peak intensity, and ~90% at 10 W/m^2 peak intensity, as compared to controls (e.g., without ultrasound).[1130] These acoustic intensities are well below the <1000 W/m^2 limit deemed safe in typical in vivo nanomedical power-supply (Section 6.4.1) and communications (Section 7.2.2.2) applications. Anti-biofilm effectiveness declines log-linearly with increasing frequency: ~0.1 MHz acoustic waves are ~10 times more microbicidal than ~10 MHz waves, in combination with the gentamicin.[1130] It is postulated that ultrasound increases gentamicin transport through cell membranes (e.g., by high pressure, high shear stress, or cavitation), the proposed rate-determining step in microbial killing by the antibiotic.[1130] Electrical[1132-1139] and magnetic[1140] enhancement of antibiotic activity has been investigated. Pure sonication at 40 KHz also removes biofilms from food processing equipment.[5625]

15.2.1.5 Contemporary Biocompatibility Test Methods

As pointed out by Jonathan Black,[234] biological performance of an implant includes consideration of the host response and the material response to implantation. The traditional approach[237,241,6038] has been to define biological performance in terms of host response — biocompatibility — and then to observe evidence of material degradation that arises during in vitro and in vivo testing. Black[234] sets forth a 5-part strategy for materials qualification studies:

1. select material based on engineering properties and previous host response information;
2. determine experimentally if host response is acceptable for the intended application;
3. acquire evidence of unacceptable material response during host response studies;
4. verify satisfactory material response during long-term in vivo implant studies; and
5. monitor clinical reports detailing changes in material response during actual service.

There are two general classes of in vitro screening methods: tissue culture tests and blood contact tests (in blood contact applications[6052]).

According to Black,[234] tissue culture tests involve maintaining portions of living tissue in a viable state in vitro by any of three generic methods: (1) *Cell culture* — the growth of initially matrix-free, dissociated cells, usually in monolayers; cells may be grown in solution, on agar, or on other media substrates, and are exposed to biomaterials by direct contact with bulk materials, by diffusional contact through an intermediate layer, or by contact with particles or eluants from biomaterials in the culture media. (2) *Tissue Culture* — the growth of portions of intact tissue without prior cellular dissociation, usually on a substrate rather than in free suspension, with exposure to the biomaterial as in cell culture. (3) *Organ Culture* — the growth of intact organs in vitro, varying from fetal bone extracts that can survive without external support to whole adult perfused organs such as kidney or heart. Tissue culture tests are used to study various aspects of host responses including cell survival (toxicity, organelle/membrane integrity), cell reproduction (growth inhibition), metabolic activity (energetics, synthesis, catabolism), cell activities (inhibition of chemotaxis, locomotion, or phagocytosis, and alteration of cell size and shape), cell damage (chromosomal aberration, carcinogenicity,[5845] mutagenicity,[5846]), and specific immune system response (delayed hypersensitivity).[5847,5848] "Tissue culture techniques for screening materials may use one or more normal mammalian cell lines such as murine macrophages, abnormal cells such as HeLa or lymphoma cells, or bacterial cell lines such as *Staphylococcus aureus* or *Escherichia coli*." Each test that has been developed uses selected cells suitable for the particular questions posed, the utility of which depends on its correlation with in vivo host response.[5849-5851]

According to Black,[234] blood contact tests involve examining either coagulation times or hemolysis rates in either static or dynamic systems during or after contact with foreign materials. Because these responses are not only intrinsic to materials but are also influence by implant device functioning, the presence of interfaces, flow rates and turbulence conditions, etc., three sequential phases of testing of a new biomaterial are often employed: (1) in vitro static tests (e.g., clotting time relative to a reference surface[5852,5853]), (2) ex vivo dynamic tests (platelet adherence under controlled flow conditions,[5854,5855] exposure to whole blood, erythrocyte damage rates, etc.), and (3) in vivo dynamic tests. Despite their flaws, in vitro tests are widely used for screening because they are relatively inexpensive and are not known to yield false negatives (e.g., a material that tests poorly will not be a good implant in cardiovascular applications).[234]

After showing satisfactory results during in vitro screening, a new biomaterial is then tested using extended-time whole-animal studies[5856] that expose the biomaterial to systemic physiological processes, prior to human clinical testing. Initial nonfunctional testing is usually in soft tissue because cytotoxic effects "have a generality of action and because soft tissue sites can be approached in animals with relatively minor surgery."[234] The most popular sites include subcutaneous, intramuscular, intraperitoneal,[5857] transcortical (e.g., femur, cranium), and intramedullary (e.g., femur, tibia). Tests are of two types: nonfunctional and functional. In nonfunctional tests, the implant has a carefully selected and standardized shape and floats passively in the tissue site.[5858] Nonfunctional tests focus on the interaction between the implant material and the biochemical implant environment, and are of short to intermediate duration (e.g., 0.5-24 months).[234] Adequate experimental controls must be provided to include effects of relative tissue-implant motion and electrical charge density at the implant-tissue interface which can influence the observed host response. Functional tests require that the implanted material be placed in the functional mode that it would experience in actual service as a human implant.[234] This allows the study of tissue ingrowth into porous materials for fixation purposes;[5859,5860] the effects of mechanical forces during actual use;[5861] formation of neointima, degree of thrombosis and patency,[5862,5863] and effects of mechanical loading[5864] in vascular processes; and production of wear particles in load-bearing devices (and clinically relevant tissue responses to them). Functional tests are more costly (>$1000/animal) and complex than nonfunctional ones,[234] and test animals have shorter life spans and higher metabolic rates than humans,[5865] introducing additional uncertainty into the results.

"In the final analysis," notes Black,[234] "clinical testing is the only technique by which the true biological performance of any implantable biomaterials can be determined. [However,] any human clinical experiment must provide a potential benefit to the patients involved, [which] essentially prevents the use of humans as test subjects for biomaterials." Further discussion of clinical testing procedures for medical nanodevices is deferred to Chapter 17.

15.2.2 Adhesive Interactions with Implant Surfaces

As the famous physiological chemist Leo Vroman once hyperbolized:[950] "Facing a hail of miscellaneous eggs, we cannot expect to come away clean. Unless they are hard-boiled ones, we are most likely to become coated rapidly with a relatively thin film of matter from the most numerous and most fragile eggs. Similarly, no interfaces may exist that, facing blood plasma, can escape being coated with the most abundant and fragile plasma proteins."

Following the implantation of a biomaterial into a host tissue, the first event to occur at the tissue-material interface (which dictates biocompatibility) is the noncovalent adsorption of plasma proteins from blood onto the surface[517-520,936,954] if the material comes into direct contact with blood. (Osmotic minipumps delivering drugs subcutaneously would escape from this process.) Protein adsorption is much more rapid than the transport of host cells to foreign surfaces. Once proteins have adsorbed to the surface of the foreign material, host cells no longer see this underlying material, but only the protein-coated surface overlayer. This adsorbed protein overlayer — rather than the foreign material itself — then mediates the types of cells that may adhere to the surface, which ultimately can determine the type of tissue that forms in the vicinity.[517] Thus the type and state of adsorbed proteins, including their conformational changes, are critical determinants of biocompatibility,[518-523] so pretreatment of surfaces can be a control mechanism (Section 15.2.2.1). Even by the late 1960s, Vroman and Adams[950-952] and Baier and Dutton[953] had found that within 10 seconds of exposure to blood or plasma, a uniform ~6 nm layer of fibrinogen formed on surfaces of Ge, Pt, Si, and Ta; after 60 sec, the layer was less uniform and averaged ~12.5 nm thick, but was still dominated by fibrinogen. Rudee and Price[793] determined that human serum albumin (HSA) (molecular dimensions 8 nm x 3.8 nm,[1440] with a monomolecular radius of gyration in pH 5-7 solution of 3.2-3.4 nm[1441]) formed a continuous film on amorphous carbon surface in only 1.3 sec of exposure. Fibrinogen required 2.5 sec to form films. Protein adsorption on a range of hydrophobic and hydrophilic polymer surfaces is typically 0.3-12 mg/m^2 (~500-20,000 molecules/micron^2).[1322]

Black[234] notes that many molecules synthesized naturally in the cell have a "tail" portion that inactivates them. Later on, enzymatic processes strip away this small segment, releasing the molecule into an active extracellular substrate pool. Contact with foreign surfaces, along with adhesive forces, may cause premature activation. Indeed, some molecules are specifically designed to become activated in this manner. One common example is fibrinogen, a molecule that is reduced slightly in molecular weight and ultimately converted to the active protein, fibrin, after foreign surface contact during blood clotting (Section 15.2.5).

Three-dimensional images of adsorbed human fibrinogen molecules have been obtained by atomic force microscopy (AFM),[562,563] scanning force microscopy,[564] and electron microscopy.* [565] The mechanical kinetics of adsorption have also been examined by testing the adhesion strength of an individual fibrinogen molecule that is affixed to an AFM tip and is briefly touched to a silica surface.** [566]

** On hydrophobic mica, the adsorbed fibrinogen molecule has a bi- or trinodular slightly curved linear shape of mean length 65.9 nm and mean height 3.4 nm.[563] On hydrophobic silica, a trinodular 60-nm long form and a globular 40-nm diameter form are observed.[564] On quartz at low solution concentrations, fibrinogen molecules appear to form a 46-nm long multinodular rod with 6-7 nodes each 4 nm in diameter on hydrophilic surfaces, and a 40-nm long binodular or trinodular rod with node diameter 5-9 nm on hydrophobic surfaces. At high solution concentrations, the molecule forms end-to-end polymers on hydrophilic surfaces and spherical 18-24 nm diameter structures on hydrophobic surfaces.[565]*

*** The minimum interaction time for strong binding was 50-200 millisec, producing mean adhesion strengths from 300 pN for a 5 millisec contact up to 1400 pN for a 2 sec contact. Consecutive ruptures indicating the detachment of multiple adhesion sites occurred 20-25 nm apart along the length of the molecule. This is comparable to the characteristic distance between D and E globules of a single fibrinogen molecule, suggesting that fibrinogen adsorbs mainly through its D and E globules.[566]*

A clearer molecular picture of the fibrinogen adsorption event on implant surfaces (and subsequent inflammatory response) is slowly emerging.* [567,568] Similar tests need to be performed on, for example, diamond and sapphire surfaces.

Once the precise molecular mechanisms of protein adhesion are fully understood, we may hypothesize that nanodevice surfaces could be designed for maximum proteophobicity and that this might be possible because numerous partially proteophobic molecular surfaces are already known, including:

1. polyethylene glycol (PEG)[569] and other steric barrier coatings (Section 15.2.2.1);
2. surface-immobilized fibrinolytic enzymes such as lumbrokinase[570-572] or, more generally, immobilized proteolytic enzymes[755] that can cleave and detach proteins that attach;
3. hydrophilic cuprophane,[573-577] chemically-modified cuprophane,[578] polysulfone,[576,577] and polyacrylonitrile[579] hemodialysis membranes;
4. albumin-passivated surfaces[2536-2538] that reduce fibrinogen adsorption,[519] platelet adhesion and activation, and thrombogenicity[543,580,937] and accumulate very few adherent neutrophils or macrophages;[581]
5. tetraethylene glycol dimethyl ether glow-discharge plasma deposition surfaces, which can reduce fibrinogen adsorption to ~0.2 mg/m^2 (~350 molecules/micron^2) on many different substrates;[582]
6. surface-immobilized heparin,[1888,2535] a natural anticoagulant (Section 15.2.5); and
7. artificial glycocalyx-like engineered non-adhesive surfaces[753] (Section 15.2.2.1), low protein adsorbing films,[754] graft polymerized acrylamide,[5257] and other examples of biological adhesive surface engineering.[2356,2589]

More generally, nanomedical implants and instrumentalities may require surfaces of engineered bioadhesivity — for instance, diamond-like carbon coated surfaces with an additional overcoat of biological materials, perhaps including extracellular matrix proteins, laminin, fibronectin, albumin, and collagen IV, to either promote or inhibit cell growth and spreading.[629] Ratner[5293-5295] gives examples of biomaterials that inhibit nonspecific protein adsorption while simultaneously controlling the interactions of matricellular proteins at implant surfaces, thus reducing foreign body response while promoting healing. More systematic study is clearly needed. For instance, the Adhesion Dynamics model of Chang et al[2554] defines molecular characteristics of firm adhesion, rolling adhesion and non-adhesion, but only in the limited domain of leukocyte-vascular rolling interactions. In other studies, computer simulations suggest that organic molecules may be readily bonded to diamond or other nanorobotic surfaces to impart desired biocompatibility characteristics. Examples include a recent density functional theory (DFT) study of cycloadditions of dipolar molecules to the C(100)-(2x1) diamond surface[4738] and related experimental investigations[4748]), and the covalent immobilization of enzymes onto gamma-alumina surfaces.[4772] Conventional means can be employed to orient rod-shaped molecules on DLC surfaces (as in liquid crystal arrays[4742]) or to orient nanowires[4785] or carbon nanotubes[4793] on sapphire/alumina surfaces.

As of 2002, numerous companies[2281] including Advanced Surface Technologies (Billerica, MA), MetroLine Industries, Inc. (Corona, CA), Spire Corp. (Bedford, MA), SurModics Inc. (Eden Prairie, MN), Ultramet (Pacoima, CA), and Vitek Research Corp. (Derby, CT) were providing commercial design services to create customized biocompatible surfaces on implantable medical devices and medical materials.

15.2.2.1 Nonadhesive Nanorobot Surfaces

The non-specific adsorption of blood proteins on nanorobot surfaces could lead to clinical difficulties such as thrombosis and unwanted protein-mediated recognition interactions such as cell-nanorobot and nanorobot-nanorobot adhesion (aggregation). Such interactions could not only result in injury to the patient but also inactivation of the nanorobots with a subsequent failure of the nanomedical mission. With many hundreds of plasma proteins (the predominant plasma protein is albumin) to choose from, unmodified implanted devices may quickly adsorb a monolayer containing many proteins in a distribution of conformational and orientational states. Early-arriving proteins may be partially or wholly displaced by later-arriving proteins that have a greater affinity for the particular surface, a phenomenon widely known as the Vroman effect.[950,1442] A variety of local and systemic cellular processes may be triggered depending upon which proteins are adsorbed to the surface (e.g., as opsonins) and their biological activity. This depends, in turn, upon whether specific active peptide sequences in specific proteins are accessible to arriving cells such as neutrophils and macrophages. The ultimate reaction to the implant would be dictated by the complex competition among simultaneous parallel reactions, producing a relatively stochastic or chaotic outcome — the very opposite of an engineered process.** [342]

Fewster et al[474] point out that in some situations it is vital for an implant to resist cell attachment, as for instance within the cardiovascular system if an artificial blood vessel is to resist thrombosis. In the case of large implants, Fewster writes, "there may be a 'race for the surface', with the body's own tissues moving to wall off an implant before bacteria and other microorganisms can become adherent and secrete a glycocalyx of slime in which they may flourish and resist all attempts of the body's immune defenses to ingest or destroy them."[474]

Note also that the amount of serum protein adsorbed on a nanorobot surface[24] varies inversely with nanorobot size for a constant mass, volume, or dosage of implanted medical nanomachinery. Cell adhesion, thrombogenicity, foreign body response and other reactions to implanted materials are related to the amount of

** Plasmin degradation of purified fibrinogen into defined domains reveals that the proinflammatory activity resides within the D fragment of the fibrinogen molecule, which contains neither the fibrin cross-linking sites nor RGD sequences.[567] After contact with blood or tissue fluid, the D domain tends to interact with biomaterial surfaces and is important in the tight binding of fibrinogen to implant surfaces.[568] The biomaterial surface then promotes conformational changes within the D domain, exposing P1 epitope (fibrinogen gamma 190-202, which interacts with phagocyte CD11b/CD18 (Mac-1) integrin).[568] The engagement of Mac-1 integrin with P1 epitope then triggers subsequent phagocyte adherence and reactions,[568] as demonstrated by experiments which show that phagocyte accumulation on experimental implants is almost completely abrogated by administration of recombinant neutrophil inhibitory factor (which blocks CD11b-fibrin(ogen) interaction).[567]*

*** M. Sprintz notes that the binding of plasma proteins has relevance to the displacement of other highly protein-bound drugs, such as phenytoin (Dilantin), barbiturates, propranolol, and benzodiazepines. If nanorobots have a higher affinity for protein binding sites than certain drugs used in concert with the nanorobots during a nanomedical treatment, then those drugs could be displaced, consequently increasing the number of biologically active drug molecules and increasing the risk of toxic drug levels.[5489] S. Flitman points out that newer anticonvulsants are less protein-bound, for this reason.*

adsorbed proteins, hence as an implanted object shrinks to smaller sizes (i.e., to micron-scale) the biological signal to local cell populations can increase enormously because the total amount of protein adsorbed on the implant mass is much greater.

Consequently, it will usually be desirable to suppress non-specific adhesive interactions involving individual physically-unlinked nanorobots, in order to permit unfettered nanorobot mobility and freedom of action within the human body and avoid particle aggregation. One early strategy to try to accomplish this in implants was to coat the artificial surface with an adsorbed protein, usually bovine serum albumin (BSA) or high-density lipoproteins, to serve as cell adhesion inhibiting proteins that would resist the adsorption of other proteins. This method was simple and inexpensive, but suffered from limited stability of the protein layer owing to exchange with other proteins in solution via the Vroman effect, and also from presentation of biologically active peptide sequences.[1443] The Vroman effect could be avoided by chemically bonding albumin itself, or a surface constructed to mimic an albumin coating, to the nanodevice exterior, such that no replacement of this camouflage layer would be possible.

Bacteria with very hydrophilic surfaces can avoid being destroyed by macrophages or neutrophils, and can remain circulating in the body for extended periods of time.[1444-1448] Various hydrophilic adsorbed coatings have been attached to artificial surfaces to make them more protein-resistant, in effect "passivating" them against protein adsorption and greatly reducing or preventing cell adhesion to biomedical implants.[754] Such coatings typically may include self-assembled monolayers containing surface-immobilized ethylene glycol groups, commonly known as poly(ethylene glycol) (PEG). "Pegylated" surfaces exhibit a brushlike arrangement of PEG molecules at the surface.* [569,1453-1459,5658]

Alkanethiol monolayers (on gold) terminated in short oligomers of the ethylene glycol group — e.g., $HS(CH_2)_{11}(OCH_2CH_2)_n$, n = 2-7 — resist entirely the adsorption of several proteins.[1462,1468,5259] Even monolayers containing as much as 50% hydrophobic methyl-terminated alkanethiolates, if mixed with oligo(ethylene glycol)-terminated alkanethiolates, remain hydrophilic enough to resist the in situ adsorption of protein.[1443] DeGennes and Andrade[1469] believe that surfaces modified with long PEG chains resist protein adsorption via "steric stabilization" — adsorption of protein to the surfaces would cause the solvated and disordered glycol chains to compress, so adsorption is resisted by the energetic penalty of desolvating the glycol chains and restricting the conformational freedom of the chains.[1443] (G.M. Fahy notes an analogy to Timasheff's observations[5871] that cryoprotectants like glycerol are preferentially excluded from the protein surface because the protein prefers to associate with water — if a nanorobot surface resembled close-packed glycerol, it might be easier for the nanodevice to evade interactions with both hydrophilic and hydrophobic proteins.) Polymer substrates composed of PEG in highly cross-linked matrices of acrylic acid and trimethyloylpropane triacrylate completely resist protein adsorption and cell adhesion, though they can readily support adhesion after derivatization with cell-binding peptides.[1470] Whitesides' group[2534] has used a gold-tethered polyamine monolayer to create a surface that reduces the number of adherent bacteria (*Staphylococcus epidermis* and *Staphylococcus aureus*) by a factor of 100 compared to bare gold and by a factor of 10 compared to traditional bacterial-resistant polyurethane.

A PEG coating on a ~200-nm poly(lactic acid) (PLA) nanosphere surface creates a brushlike steric barrier, hindering its opsonization and uptake by the mononuclear phagocyte system,[3325,3326] thus increasing its blood half-life.[1471] (G.M. Fahy likens the brush-barrier-coated particle to a "sea urchin" with the tips of the spines constituting a vary small surface area of inert material, thus limiting the possible interaction with the environment.) Pegylated nanospheres have been investigated as an injectable blood-persistent system for controlled drug release, for site-specific drug delivery (e.g., to spleen, liver, and bone marrow), and for medical imaging.[1449-1453] Adsorption of human serum albumin (MW = 66,000 daltons) on pegylated nanosphere surfaces at pH 7.4 at equilibrium (i.e., after 5 days) is 0.15 mg/m^2 (~1400 molecules/micron^2) compared to 2.2 mg/m^2 (~20,000 molecules/micron^2) for unpegylated polymer.[1453] These differences are of the same orders of magnitude as that observed for other hydrophobic surfaces.[1472,1473,2591] (Maximal HSA adsorption on hydrophobic surfaces is usually observed close to the isoelectric point, a pH of 4.8-5.0.[1453]) However, under in vitro conditions at 37°C and pH 7.4, about one-third of the adsorbed PEG detaches from the PLA nanospheres after 2 weeks at a near-linear detachment rate.[1474] Also, Langmuir film studies show that forming PEG "brush" requires close packing of extended hydrated random coil chains, but that such close-packed hydrated chains "dehydrate" and aggregate out of solution, which "explains why one is limited to less than 10 mol% when using PEG chains to stabilize nanoparticles such as liposomes for drug delivery" [Roger E. Marchant, personal communication, 2002]. So adsorbed-pegylated surfaces would not be a complete or perfect solution for nanorobots resident in vivo for long-duration missions, or for permanent implants or augmentations, though PEG-derived adhesioregulatory surfaces (Section 15.2.2.4) using periodically refreshed presentation semaphores might prove useful.

A more effective way to create nonadhesive nanorobot surfaces may be the biomimetic approach[753,2525] For example, the external region of a cell membrane, known as the glycocalyx,** is dominated by glycosylated molecules. These molecules direct specific interactions such as cell-cell recognition and contribute to the steric repulsion that prevents undesirable non-specific adhesion of other molecules and cells. Marchant and colleagues[753] have modified a pyrolytic graphite (Section 15.3.3.2) surface by attaching oligosaccharide surfactant polymers which, like the glycocalyx, provide a dense and confluent layer of oligosaccharides that mimics the non-adhesive

** Pluronic surfactants such as block copolymers have a central poly(propylene oxide) (PPO) chain with a poly(ethylene oxide) (PEO) chain attached at each end,[1460-1464,2542] and are not readily desorbed when they come in contact with high-affinity proteins or cells in blood.[1464] Other copolymers with PEO side chains[5258] or PEO-deposited surfaces[5260] largely prevent protein adsorption and platelet adhesion. HEMA (hydroxyethylmethacrylate)-based polymers[1465-1467] are nonadhesive for mammalian cells.[1466] In one experiment, the mechanical desorption force of adsorbed fibronectin was reduced from 100 pN/molecule on a 0% HEMA polymer to 27 pN/molecule on an 85% HEMA polymer.[1467] A coating of ultra-high molecular weight polyethylene also inhibits cell adhesion.[474] Similarly, injection of ~100-nm PEO-PEE polymersomes[5720] into the circulation of rats gives a bloodstream clearance half-life of ~20 hours,[5721] similar to the 15-20 hour clearance for stealth liposomes which are engulfed by phagocytic cells of the liver and spleen.[4372] The PEO brush delays the accumulation of plasma protein on the polymersome membrane[5722] and acts somewhat like a biomembrane glycocalyx.[5723] Knowledge of surfactant molecular structures is expanding via computational chemistry.[6017,6077]*

*** The glycocalyx (sugar cell coat) is a layer of carbohydrate on the surface of the cell membrane of most eukaryotic cells. It is made up of the oligosaccharide side-chains of the glycolipid and glycoprotein components of the membrane and may include oligosaccharides secreted by the cell. In bacteria, the glycocalyx is the outermost layer typically consisting of numerous polysaccharides plus various glycoproteins. The bacterial glycocalyx varies in thickness and consistency, forming in some species a flexible slime layer while in others a rigid and relatively impermeable barrier.[5490] See also Section 8.5.3.2.*

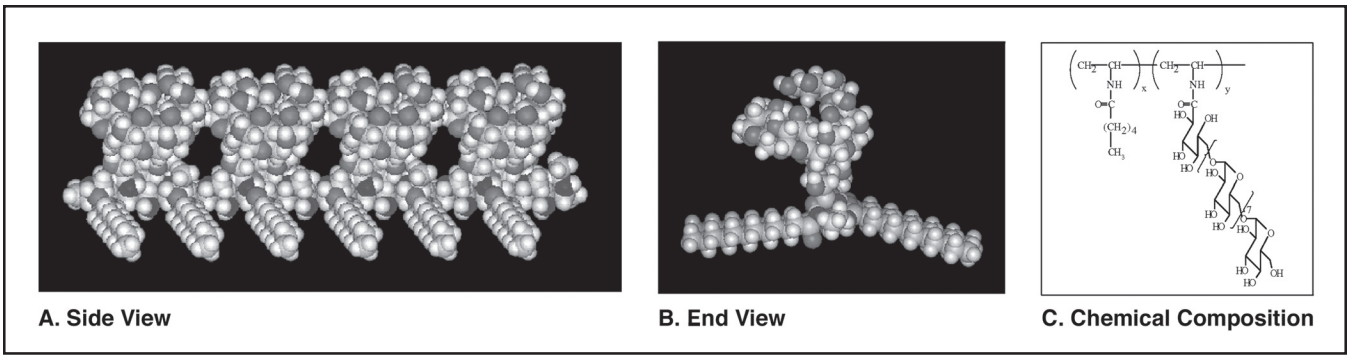

Fig. 15.5. Molecular models of engineered biomimetic non-adhesive glycocalyx-like surface using oligosaccharide surfactant polymers (courtesy of Holland, Qui, Ruegsegger and Marchant[753] and Case Western Reserve University).

properties of the glycocalyx (Figure 15.5). The surfactant polymers consist of a flexible poly(vinyl amine) backbone (MW ~ 6000 daltons, diameter 0.25 nm) with multiple randomly-spaced dextran (MW ~ 1600 daltons, diameter ~0.9 nm) and alkanoyl (hexanoyl or lauroyl) side chains which constrain the polymer backbone to lie parallel to the substrate. Solvated dextran side chains having a stable helical structure protrude into the aqueous phase with steric repulsion between adjacent dextrans.* This creates a glycocalyx-like monolayer coating approximately 0.7-1.2 nm thick as measured by tapping-mode AFM.[753] In vitro experiments show that the resulting biomimetic surface, which the authors have reported undergoes spontaneous adsorption on diverse hydrophobic biomaterials surfaces such as polyethylene,[5255] effectively eliminates at least ~90% of all plasma protein adsorption from human plasma protein solution.[753] According to the authors: "The steric barrier provided by the highly hydrated dextrans is designed to suppress non-specific adsorption of plasma proteins,[1475] whereas the high energy of desorption and low water solubility of the adsorbed surfactant polymer is designed to minimize possible displacement or exchange reactions with highly surface-active plasma proteins."

Similarly, Ruegsegger and Marchant[5255] added a series of oligomaltose surfactant polymers at full monolayer coverage to a surface of highly oriented pyrolytic graphite, using two (M2), seven (M7), or fifteen (M15) glucose units. Protein resistance increased with increasing coating thickness, to 81.4% (M2), 85.8% (M7), and 95.8% (M15), respectively. Static platelet adhesion decreased substantially to 15-17% for all coating thicknesses, compared to adhesion to glass normalized to 100%. Other researchers have attempted to engineer the chemical reactivity of cell surfaces using surface-bound oligosaccharides,[2549] or to reduce protein adsorption using polysaccharide surfactants[5256] or grafted polymers;[5274-5278] the possible immunogenicity[5626] of these substances must always be considered.

Another molecule that displays low protein and platelet adhesion is phosphatidylcholine (PC)[2526-2530] or phosphorylcholine.[4732-4736,4749,4750,5015,5717] PC is a major plasma membrane lipid component of eukaryotic cells (Table 8.18) and especially platelets. In one experiment,[2527] PC-coated silica did not support platelet adhesion, and platelet adhesion to PC-grafted polypropylene and PTFE was inhibited 80% and 90%, respectively. In another experiment,[5010] PC-coated guide wires used in coronary angioplasty showed no thrombus formation, unlike silicone-, hydrophilic polymer-, and Teflon-coated wires. Phospholipid-bound polyurethanes,[2531] phosphatidylcholine analogs[2532] and related polymers[2533] have also shown greatly reduced platelet adhesion. Phosphatidylcholine (17-19% of human erythrocyte membrane) and sphingomyelin (18%) are not found in *E. coli* membranes, unlike phosphatidylethanolamine (*E. coli* 65-70%, human 18%) or cardiolipin (*E. coli* 12%, human mitochondrion 21-23%) which are found in bacteria (Table 8.18 or refs. 4694-4696) and thus might more easily provoke an unwanted immune response.

Other methods that use covalent immobilization to confine camouflaging proteins at implant-biological interfaces may have many advantages over those that rely on physical adsorption of protein layers.[1443] Covalently attached layers of protein cannot easily dissociate from the implant surface, nor can they exchange with other proteins in solution. A variety of selective chemistries offer high levels of control over the adsorption process. For instance, a cytochrome c mutant protein molecule having only a single cysteine group gives a uniformly oriented layer of protein when immobilized to a self-assembled monolayer terminating in thiol groups.[1476] (Unfortunately, intracellular release of cytochrome c triggers cell apoptosis (Section 15.5.7.2.4), so this particular example might be a poor choice for a nanorobot camouflage protein.) Nanorobot surfaces could be covalently bound with masking groups such as plasma membrane components of young erythrocytes, which are invisible to the reticuloendothelial system.[1477] Similarly designed "long-circulating" nanoparticles and microparticulate drug carriers (typically 10-48 hours in the bloodstream[2489-2491]) and "long-circulating" bacteriophages[2492] have been studied, including ghost-red-cell-based "nanoerythrosomes".[5049] Detachment of adsorbed PEG might be prevented by better bonding chemistries, e.g., with PEG derivatized at one end to merge with the nanodevice surface.

Relatively nonadhesive polyhydroxylated species, called stealth liposomes,[1478-1481,5280-5282] exhibit reduced recognition and uptake by the body's reticuloendothelial system along with longer circulation half-life (~1 day)[1482,1483] and are in clinical trials.[5283-5290] Interestingly, diamond particles have already been encapsulated inside stealth liposomes. In one such experiment,[1484] hemoglobin molecules were irreversibly adsorbed onto carbohydrate-coated diamond particles measuring ~75 nm in diameter, then the complexes were encapsulated in a standard mixture of phospholipids. This produced endotoxin-free preparations of spherical liposomes which were

** Roger Marchant [personal communication, 2002] notes that dextrans, like most carbohydrates, have very little conformational freedom, so their 3D structure is largely dictated by the bonding configurations (e.g., alpha 1-6 glycoside linkage in dextran). If a structure (such as the dextran) has formed a helix, it cannot also form a "brush" (which requires a random polymer structure as with pendant surface-attached PEG chains) — the two structures are essentially mutually exclusive.*

stable for >48 hours with bound-Hb concentrations near 100 gm/liter with as little as 1% free Hb. Evaluation of oxygen lability showed normal sigmoidal O_2 binding behavior with p_{50} from 12 mmHg up to 37 mmHg under control of an allosteric effector.[1484]

The University of Washington Engineered Biomaterials group has an ambitious program to develop molecularly engineered stealth surfaces.[5292] These surfaces can then be decorated with surface-anchored peptides or proteins to allow specific signaling, as well as with trigger molecules or clusters of recognition sites that can remain accessible to cell receptors.[1485] The objective is to create a hierarchically structured modular system where individual building blocks can easily be exchanged, for example, to vary chemical functionality, and that can later be universally applied to coat a large number of different materials including polymers, metals and ceramics.[1485] Similarly, J. Genzer[2515] at North Carolina State University has produced mechanically-assembled monolayers using semifluorinated molecules anchored to prestretched substrate surfaces that are then released, compacting the monolayer to make a tightly-packed nonpermeable superhydrophobic surface that reportedly does not deteriorate even after prolonged exposure to water, and other superhydrophobic surfaces are known.[6176] Fluorous proteins have been suggested for antiadhesive surfaces;[5028] unnatural fluorous amino acids[5905-5907] have been used to synthesize artificial alpha-helical coiled fluoropeptides[5906] and to synthesize melittin analogs that have enhanced affinity for lipid bilayer membranes compared to the wild-type peptide.[5908]

Of course, by analogy to enveloped viruses and virosomes,[5355] the ultimate in stealth is cytocarriage (Section 9.4.7), wherein the nanorobot hides inside an otherwise innocuous native motile body cell such as a fibroblast or macrophage. External cell adhesion to the nanorobot is precluded, and only intracellular protein adsorption need be actively managed until the nanorobot is released.

Whether pure atomically-smooth diamondoid materials (Section 15.3.1.1) will give us sufficiently nonadhesive surfaces, or if instead thin engineered coatings or active semaphoric surfaces (Section 5.3.6) will be necessary to ensure adequate biocompatibility of medical nanorobots, is an outstanding research issue that can best be resolved by future experiments. This is a very critical topic because, unlike the materials used in a joint prosthesis, nanorobots may be present throughout the microvasculature of critical organs. The adhesiveness of many hundreds of serum proteins to the artificial nanorobot exterior must be evaluated, and the relative serum concentration of these proteins may change according to the time of day or the physiological state of the individual (e.g., TNF, IL-1, IL-2, and transferrin rise dramatically in the acute phase response to a pathogen). Relevant investigations are to be encouraged at the earliest possible opportunity.

15.2.2.2 Adhesive Nanorobot Surfaces

In many nanomedical applications, it will be important that the nanorobot exhibit a strong affinity for the specific biological tissue with which it is designed to interact. For example, diamondoid bone implant should show good osseointegration, preferably with bone tissue infiltrating some portion of the foreign diamondoid structure and with cells tightly adherent to the implant, locking it firmly in place in the manner of bioactive materials previously discussed (Section 15.2.1.3). Entry into the body by free nanorobots traversing the gut might be assisted using mucosal-binding attachments.[2592] It may be desirable for the surfaces of artificial nanorobotic organs to encourage attachment, migration and coating by certain types of cells. This could facilitate biochemical transfers between blood or tissues and the mechanisms within, help avoid immune system rejection, or establish good mechanical stability within the peri-implant space. In general, cells attach to synthetic surfaces via adsorbed adhesive proteins such as fibronectin. By controlling the chemistry of the surface, it is possible to modulate the adsorption of the proteins, which then govern cell attachment and spreading. Cell spreading has been correlated with fibronectin adsorption to a variety of surfaces.[1486-1488] Rates of cell migration have been shown to depend on the concentration of adhesive proteins preadsorbed on polymer surface.[1488-1490] These rates of migration are optimal at intermediate substrate adhesiveness,[1491] as expected from mathematical models of cell migration.[1492]

So far, no general principles have been identified that allow precise prediction of the extent of attachment,[1493,1494] spreading, or growth of cultured cells on various artificial surfaces such as polymers.[1491,5729,5730] Certain chemical groups present on a material surface can alter cell response.[1495] Interesting correlations have been found in vitro for specific cell types with parameters such as the density of surface hydroxyl[1496,1497] or sulfonic[1498] groups, surface C-O functionalities,[1499] surface free energy[1500-1502] or surface wettability,[756,1503,1504] hydrogenated amorphous "unsaturated" carbon phases,[1507] fibronectin adsorption,[1499] and equilibrium water content,[1497] but there are exceptions in all cases.[1491] The ability of macrophages to form multinucleated giant cells at a hydrogel surface has been correlated with the presence of certain chemical groups at the interface: macrophage fusion decreases in the order $(CH_3)_2N-$ > -OH = -CO-NH- > $-SO_3H$ > -COOH(-COONa).[1509,1510] Cell attachment and growth on surfaces with grafted functional groups decreases in the order $-CH_2NH_2$ > $-CH_2OH$ > $-CONH_2$ > -COOH.[1511]

In vivo, cell attachment to the surrounding environment may be mediated by various small, biologically active functional groups such as oligopeptides,[1543] saccharides,[1512-1514] or glycolipids (patterns of glucose residues attached to membrane lipids)[1517-1519] via specific peptide sequences within proteins.[897] Peptides or peptide sequences may act as signaling molecules, attachment sites, or growth factors that mediate the conversation between cells and the surrounding extracellular matrix in an information-rich dynamic structure. The dynamics of these processes can be seen both in development and in wound healing, where fibroblasts lay down a matrix that guides regeneration or development in a specific controlled manner. Appropriately functionalized nanorobot surfaces may be able to strongly influence such processes.

Perhaps the best-known example is the peptide sequence arginine-glycine-aspartic acid (RGD)* [1520-1522] which was first identified in the cell-binding domain of fibronectin,[1521] an adhesion-related glycoprotein that provides attachment sites for many cells through cell surface receptors called integrins (Section 8.5.2.2). RGD is also present in many other proteins such as collagen, entactin, laminin, tenascin, thrombospondin, and vitronectin without losing receptor specificity, so its interactions are probably conformation dependent.[1520] The YIGSR and IKVAV sequences in laminin[1491,1528] and the FHRRIKA sequence[1531] also show cell binding activity and mediate adhesion in certain cells.

In theory, a nanorobot surface functionalized with RGD should exhibit greatly enhanced adhesion to cells, because to the cells, the surface may appear much like ECM (extracellular matrix). As summarized by Saltzman,[1491] RGD has been experimentally attached

** Amino acids are customarily identified by one-letter abbreviations: A = alanine, B = asparagine (N) or aspartic acid (D), C = cysteine, D = aspartic acid, E = glutamic acid, F = phenylalanine, G = glycine, H = histidine, I = isoleucine, K = lysine, L = leucine, M = methionine, N = asparagine, P = proline, Q = glutamine, R = arginine, S = serine, T = threonine, V = valine, W = tryptophan, Y = tyrosine, and Z = glutamine (Q) or glutamic acid (E).*

to amine-functionalized quartz,[1530,1531] glass,[1528] and synthetic polymer surfaces including PEG,[1532] PET,[1533,1534] PEU,[1535,1546] PLA,[1536] polyacrylamide,[1537] poly(carbonate urethane),[1538] poly(N-isopropylacrylamide-co-N-n-butyl-acrylamide),[1539] PLGM films,[1540] PMMA/PEG latex,[1541] PTFE,[1533,1534] and PVA.[1542] Addition of RGD or RGDS[2540] to these surfaces induced cell adhesion, cell spreading, and focal contact formation on otherwise nonadhesive or weakly-adhesive polymers in vitro.[1543-1546] In one experiment,[1528] glass surfaces functionalized with spatially-precise patterns of cell-adhesive regions and cell-repulsive regions were able to control the direction of neuron cell adhesion and neurite outgrowth across the surface. Another experiment[1529] used a combination of adhesive (RGD) and nonadhesive (PEG) moieties to modulate cell spreading.

Since cells contain cell adhesion receptors that recognize only certain ECM molecules, surface functionalization with an appropriate cell-binding sequence can produce cell-selective surfaces[1547] in which the population of cells adhering to the artificial surface is determined by the peptide structure.[1545] In vivo, the presence of serum proteins can attenuate the adhesion activity of peptide-grafted surfaces,[1546] but this problem can be overcome by attaching the peptide to a base surface that is itself biocompatible yet resistant to protein adsorption, such as PEG-rich foundations.[1548-1551]

Besides cell-binding peptides, other biologically active molecules have been used to enhance cell adhesion to artificial surfaces. For certain cell types, adhesion can be improved by adsorption of homopolymers of basic amino acids such as polyornithine and polylysine. As an example, poly-L-lysine (MW ~ 21,400)[1552] is a water-soluble polycation that can bind to anionic (negative) sites on glycoproteins and proteoglycans in the extracellular matrix, and on cell surfaces.[1553-1555] Covalently bound amine groups have influenced cell attachment and growth.[1556,1557] Polymer-immobilized saccharides can also influence cell attachment and function. For instance, in vitro rat hepatocytes adhered (via asialoglycoprotein receptors) to surfaces derivatized with lactose[1514-1516] or N-acetyl glucosamine,[1558] and remained in a rounded morphology consistent with enhanced function. Finally, whole proteins such as collagen can be immobilized to artificial surfaces, providing adherent cells with a substrate that most closely resembles the natural ECM found in tissues.[1559]

Various other simple surface modifications can improve cell adhesion.[1505-1508] For example, negative silver ions implanted in hydrophobic polystyrene at doses from 1-600 x 10^{18} ions/m^2 hydrophilize the surface and lead to enhanced growth of human vascular endothelial cells.[1508] Adhesion and proliferation of endothelial cells is likewise drastically improved when the cells are cultivated on an Ne^+ or Na^+ ion-implanted polyurethane surface with a ~10^{19} ions/m^2 fluence, though cells did not proliferate on such surfaces exposed to 10^{18} ions/m^2 or less.[1505] Endothelial cells are not capable of proliferating on polyurethane surfaces except in regions of carbon deposition; promotion of cell proliferation on a carbon-deposited surface is probably due to selective adhesion of adhesive proteins to the surface.[1506] Plasma ion-implantation is now routinely used to alter the top few atomic layers of medical polymers.[2280] This controls their wettability to allow adhesive bonding (1) for preparation of angioplasty balloons and catheters, (2) for treating blood filtration membranes, and (3) to manipulate surface conditions of in vitro structures to enhance or prohibit culture cell growth.[2280] "Smart" polymers with switchable hydrophobic/hydrophilic properties also are known,[2289] and various parameters of urinary bladder mucoadhesivity for microspheres have been investigated.[5454]

In their study of the systematic control of nonspecific protein adsorption on biocompatible materials, Satulovsky et al[5274] suggest that in systems where it is necessary to control protein adsorption during in vivo missions of modest duration (i.e., hours to days), it is probably best to use relatively dense polymer layers with long polymers that are not attracted to the underlying surface, a strategy that should provide the best kinetic control. For materials that must remain in contact with the bloodstream for years, the ideal type of polymer may be one that is attracted to the underlying surface, which should provide the best thermodynamic control. Because very high surface coverage of grafted polymers is hard to obtain using conventional experimental techniques,[5279] alternative approaches prior to the development of machine-phase nanotechnology might include mixtures of polymers (perhaps designed using Satulovsky's quantitative guidelines[5274]) that allow optimal kinetic and thermodynamic control under conditions that are experimentally realizable as of 2002. Molecular manufacturing will allow the fabrication and bonding to nanorobot surfaces of grafted polymer coatings having far greater variety, maximum packing densities, and more precise positioning than is possible today.

15.2.2.3 Cell Response to Patterned Surfaces

The microscale surface texture of an implanted nanoorgan may have a significant effect on the behavior of cells in the region of the implant.[1491,6246] Compared with smooth surfaces, roughened surfaces show improved osseointegration,[1560-1562] improved percutaneous implant integration,[1563] and reduced fibrous encapsulation with enhanced integration of breast implant materials.[1564] These improvements are due to increased adhesion of connective tissue cells onto roughened surfaces, resulting in closer apposition of tissue to the implant.[1565] Different cells types respond differently to texture. For instance, macrophages, unlike fibroblasts, accumulate preferentially on roughened and hydrophobic surfaces.[1566] Simple surface roughness (e.g., ~0.2 microns vs. 3-4 microns) appears to be one of the most important variables in determining the proliferation, differentiation, protein synthesis, and local factor Production in costochondral chondrocytes[1835] and in MG63 osteoblast-like cells.[1836]

One important class of surface features is pores, tunnels, and pegs. In one study,[1567] porous polymer membranes with pores >0.6 micron and <5-micron fibers or strands were associated with enhanced new vessel growth. Another study found that fibrosarcomas developed with high frequency (up to 50%) around implanted Millipore filters, with tumor incidence increasing with decreasing pore size in the 50- to 450-micron range.[1568] In general, fibrotic and vascular tissue invades pores larger than ~10 microns and the rate of invasion increases with pore size and with the total porosity of a device.[1569-1571] This invasion results in the formation of a capillary network in the developing tissue.[1572] Vascularization of the new adherent tissue may be required to meet its metabolic requirements and to integrate it with the surrounding tissue,[1573] although in urologic applications it is useful to have a nonporous luminal implant surface to prevent leakage of urine through the tissue.[1572] In another experiment[1565] involving 0.1- to 3.0-micron diameter pores >~100 nm deep, 0.9-micron and larger pores completely inhibited bovine corneal epithelial tissue outgrowth even when the surface had a chemistry that was adhesive to cells. Pore size rather than pore number density appeared to be the controlling factor.[1565] Migration of cell monolayers and dissociated cells was reduced but was not completely inhibited even on membranes with 3-micron pores, and individual cells could migrate through these largest holes.[1565]

As for pegs and pillars, osteoblasts and amniotic cells cultured on polyethylene terephthalate (Dacron) micropatterned with a square array of 15-micron pegs spaced 45 microns apart extruded bridging processes between the pegs.[474] Picha and Drake[1574] used silicone

implants with micropillars ~100 microns in diameter and 500 microns in height, and found that this surface texture reduced fibrosis and improved blood vessel proximity around the implants.

The study of the response of cells to steps and grooves began in 1911 when Harrison[1575] described the reactions of cells grown on spider web fibers. In the 1960s, Curtis and Varde[1576] found that cells grown on cylindrical glass fibers would align on the fibers and were very sensitive to curvature. In many cases, cells orient and migrate along fibers or ridges in the surface, a phenomenon that has been called "contact guidance"[1581] (or "topographic reaction"[5726]) originating from the earliest studies on neuronal cell cultures.[1577] It is now known that the behavior of cultured cells on surfaces with edges, grooves, or other features is significantly different from cell behavior on smooth surfaces.[1491,1581,5725] Typically a step inhibits the movement of a cell across it.[1578,1583] Cells possess an internal cytoskeleton (Section 8.5.3.11) and their normal behavior is to avoid movements that bend this cytoskeleton unduly.[1580-1583] One theory holds that contact guidance is caused by mechanical forces on the cells' filopodia, which induce the cells to reshape their actin filaments to adjust to the substrate topography.[1584] Cells approaching a step tend to withdraw or to proceed along its edge, only rarely crossing the angular surface. For example, fewer than 10% of baby hamster kidney cells will cross a 10-micron-high step.[1583] Different cells react differently to steps, depending on their biological role: white blood cells tend to cross steps more readily, whereas epithelial cells show a marked aversion to sharp angles.[1583] Some cells types (e.g., endothelial cells,[5732] fibroblasts,[5733] macrophages,[5734] and others[5736]) can react to nanoscale roughness and nanotopographies such as steps as shallow as 11-13 nm,[5726] and synthetic nanostructured textured surfaces[5738] have been shown to affect cell behavior.[5727,5731] According to Curtis and Wilkinson,[5726] cell reactions to topography are probably due to stretch reactions to the substratum, not to substratum chemistry: "A given cell type reacts in much the same way to the same topography made with different materials; when both chemical patterns and topographic ones are offered to cells, topography tends to have a greater effect than chemical patterns."

Cells react to grooves in several ways.[5725] They tend to align to the direction of the grooves, they tend to migrate along the grooves, and they tend to elongate more than they would on a flat substrate.[1579,1583] The degree of alignment and the rate of orientation depend most on the groove depth[600,1583,1585] and pitch,[1586] and to some extent on the width,[1583] with both motile cells and their processes aligning with the grooves.[1583] Human fibroblasts adherent on surfaces with V-shaped grooves exhibit higher levels of fibronectin synthesis and secretion, relative to similar cells grown on smooth surfaces.[1587] Fibroblasts have been observed to orient on grooved surfaces,[1588] particularly for texture dimensions of 1-8 microns.[1589] In one series of experiments,[1563,1588] fibroblasts oriented themselves along 3- and 10-micron deep grooves but inserted obliquely into 22-micron deep grooves. Cells cultured on otherwise identical surfaces may vary in their response to grooves much narrower than one cell diameter. BHK (baby hamster kidney) and MDCK (Madin-Darby canine kidney) cells oriented on 100 nm and 300 nm scale grooves in fused quartz, while cerebral neurons did not.[600] Fibroblasts, monocytes and macrophages spread when cultured on silicon oxide with grooves with a 1.2-micron depth and a 0.9-micron pitch, but keratinocytes and neutrophils did not.[1586] Inflammatory cells show little contact guidance compared to fibroblasts.[1586]

A primary failure mode of certain implants is "marsupialization" (Section 15.4.3.5) or "expulsion",[1565] due to downgrowth of epithelial tissue along the edge of an implant in the region where the device penetrates an epithelial layer.[1590] Modification of the microtopography of titanium implants can inhibit this downgrowth of skin epithelial tissue. For instance, grooves measuring 10 microns or 19-30 microns[1563] were sufficient to limit epithelial downgrowth and to promote connective tissue integration at the implant surface.

Patterned surfaces with well-defined peaks, valleys, and islands also influence the function of attached cells. For example, PDMS surfaces with 2- to 5-micron topography maximize macrophage spreading.[1591] Similar surfaces with uniformly distributed 4- to 25-micron^2 peaks encourage better fibroblast growth than 100-micron^2 peaks or 4-, 25-, or 100-micron^2 valleys.[1591] In another experiment, micron-scale adhesive islands of self-assembled alkanethiols stamped on gold surfaces confined cell spreading to those islands.[1592] Larger islands (~10,000 micron^2) promoted growth of hepatocytes, while smaller islands (~1600 micron^2) promoted albumin secretion. Fibroblast cells attach but do not spread on microlithographically-produced ~500-micron^2 palladium islands on pHEMA substrate, but attach and spread to the same extent as an unconfined monolayer culture on ~4000-micron^2 islands.[1593] Donald Ingber's group[3965,6239-6245] has created surfaces with circular and square islands similar in size to a single cell. When the islands are coated with ECM proteins, cells spread out to assume the shape of the island, regardless of whether the island is a circle or a square.[4942,4943] Round cells extend lamellipodia (variable extensions of the cell membrane, literally "layered feet") in random directions, but square cells send out extensions primarily from their corners.[4942] Computer simulations of related processes have been attempted.[4941]

Surfaces impressed with biological activity gradients have been found useful in cell biology for examining haptotaxis, the directed migration of cells along surfaces with gradients of immobilized factors.[1594,1595]

15.2.2.4 Sorboregulatory and Adhesioregulatory Surfaces

In more complex applications where specific or nonspecific adhesive interactions are needed during only one portion of the nanomedical mission, or where alternative specific adhesivities are desired during different mission segments or at different times or physical locations during the mission, it may be necessary to actively regulate the adhesive characteristics of the nanorobot surface. A sorboregulatory surface may be an active metamorphic surface (Section 5.3) that allows the nanorobot to alter the character, number density,[5737] or spatial pattern of its display ligands or surface receptors in real time, to encourage or discourage the adhesion of specific biomolecular species. In sum, a sorboregulatory surface enables in situ regulation of the selective binding characteristics of surfaces, in response either to commands by medical personnel or to programmed procedures executed by an onboard nanocomputer that is making choices driven by sensor data, predetermined conditions, or timing schedules.

One simple model of a sorboregulatory surface is the presentation semaphore design described in Section 5.3.6. In this model, piston-bonded ligands of various types are alternatively exposed or retracted at the nanorobot surface, producing, for example, a surface that may be switched from hydrophobic to hydrophilic in ~1 μsec, assuming a ~10 nm piston throw at ~1 cm/sec. Somewhat longer times may be required if semaphore molecules must be reconditioned prior to reuse, perhaps because of the unwanted attachment of an exogenous biomolecule to the display ligand during exposure (which biomolecule is then dragged back into the nanodevice along with the display ligand during the retraction cycle). Alternatively, the employment of sacrificial display ligands which are jettisoned after use avoids the need for reconditioning (Chapter 19), but requires the storage or synthesis of new display ligands which must then be regarded as consumables.

Display ligand-based sorboregulatory surfaces can manifest specific sorption patterns on the nanorobot surface, such as a hydrophobic head and a hydrophilic tail (Section 9.4.5.3). Such surfaces could also deploy a steric barrier during part of the nanomedical mission, then retract or eject it during other parts of the mission, thus enabling nonspecific adhesive interactions to occur only at that time. Or such surfaces could deploy sacrificial fusion protein coatings to facilitate cytopenetration (Section 9.4.5.4). Nanorobotic organs coated with a sorboregulatory surface could periodically slough off biofilm attachments by initiating end-to-end traveling waves of adhesion to the polysaccharide interstitial matrix, or could encourage cell attachment and migration in specific patterns across the surface.[1523-1528]

By 2002, experimental research on ligand presentation surfaces had just begun.[6247] In one study,[1596] 5-300 nm diamond nanoparticles that were surface-modified to serve as adjuvants to enhance immunity to antigens (e.g., as antigen delivery vehicles) provided conformational (e.g., vertical) ligand stabilization, as well as a high degree of surface exposure and coating efficiency, for protein antigens.

Another approach to building a sorboregulatory surface is to use surfaces coated with artificial receptors* rather than ligand display mechanisms. For instance, a surface of receptors having maximum specificity for albumin would preferentially attract a predominantly albumin coating when exposed to serum, thus immediately providing a steric barrier to most other adhesive interactions. Periodically, ejection rods could be thrust into the receptors from below (Sections 3.4.2 and 4.2), jettisoning bound species (also scraping off any species adhering to the rods; see Figure 3.7) and allowing regular and rapid refreshment of the barrier coating. Note that a complete monolayer coverage by fibrinogen molecules amounts to ~10^4 molecules/micron^2,[542] or ~100 nm^2/molecule which is very roughly the same surface area as a single molecular sorting rotor (Section 3.4.2). In even more advanced systems, reconfigurable binding sites (Section 3.5.7.4) might be programmed to adopt different receptor specificities as the nanomedical mission progresses. A brachiating nanorobot is yet another example of a device with modulated adhesivity — the arms successively attach and detach from extracellular matrix (Section 9.4.4.2) or intracellular cytoskeleton components (Section 9.4.6). Although the experimental research discipline of artificial receptors is now well established,[5296-5302] a more systematic approach to artificial binding site design[5303-5309] and further experiments involving single molecules in nanocavities[5310] are needed. Potential differences in protein conformations in the rich in vivo environment (compared to the more controlled in vitro environment) must also be taken into account.

Adhesioregulatory surfaces are metamorphic surfaces (Section 5.3) that can modify adhesive characteristics by, for example, altering surface geometries — either in addition to, or in place of, the surface chemistry changes already described above. For instance, an adhesioregulatory mechanism could erect, move, or retract steps, grooves, or pillars across nanoorgan surfaces to influence cell mobility (Section 15.2.2.3). Alternatively, noncovalently adhered proteins (including complement or antibodies) or other biomolecules might be physically desorbed by cleaving them using close-fitting sliding plates in an appropriate metamorphic surface design (Section 5.3.2.2), or by using surface-embedded dynamically sized and shaped nanopores (Section 3.3.2), or by using various externally-mounted self-cleaning wiper-blade or scraper mechanisms. Surfaces containing embedded vents or reversible sorting rotors could blow off many cells that were trying to become attached, or could secrete internally stored or in situ manufactured detergent molecules with similar effect. All such adhesioregulatory mechanisms can equally well be employed to encourage or discourage bioadhesion at the nanorobot or nanoorgan surface. Significant research will be required to ensure adequate competitive binding specificity of engineered nanorobot surfaces and receptors (Section 3.5.3), and to ensure that nanorobot ligands will not trigger unintended signaling pathways via cellular receptors not located near the nanoorgan. Subtle entropic effects such as the spontaneous formation of surface undulations known as capillary waves[5724] must also be taken into account.

The control of wettability has already been demonstrated by light-induced[6069,6070] and electrochemical[6071-6074] surface modifications involving chemical reactions, but Lahann et al[6075] have demonstrated an alternative approach for dynamically controlling interfacial properties that uses a change in electrical potential on gold surface to achieve fully reversible conformational transitions (switching) of surface-confined molecules between a hydrophilic and a moderately hydrophobic state without altering the chemical identity of the surface. According to one report:[6076] "The new switchable surface essentially consists of a forest of molecules only a billionth of a meter tall, engineered to stand at a precise distance from each other. In this particular case, the team makes the top of each molecule negatively charged and hydrophilic (water-loving), and the trunk positively charged and hydrophobic (water-repelling). When a positive electrical potential is applied, the induced attractive force causes the top to bend down. The resulting loop that is now exposed is hydrophobic. Reverse the electrical potential and the molecules will straighten to their full height, the hydrophilic tops once more attracting water." Note the researchers:[6075] "This study demonstrates reversible control of surface switching for a low-density monolayer. The fact that controlled conformational reorientations of single-layered molecules induced observable changes in wettability suggest that these findings may, with further study, have implications in dynamic regulation of macroscopic properties, such as wettability, adhesion, friction, or biocompatibility."

An interesting example of adhesioregulation in nature is found in the bacterium *E. coli*. Researchers at the University of Washington have recently discovered[5446] a mechanism by which the bacterial adhesion protein FimH can detect the presence of urinary tract shear flow and "lock down" the bacterium on the surface being invaded, binding tighter as shear forces rise. The protein acts as a nanometer-scale mechanical switch that senses when the force is reduced, enabling bacterial motility only during periods of low flow when the risk of dislodgment is minimized.

** Ratner and colleagues at the University of Washington Center for Bioengineering have researched the engineering of polymer surfaces containing arrays of artificial receptors. In one series of experiments, Ratner et al[1597,1598] used a radiofrequency-plasma glow-discharge process to imprint a polysaccharide-like film with nanometer-sized pits in the shape of such biologically useful protein molecules as albumin, fibrinogen, lactalbumin, glutamine synthetase, lysozyme, ribonuclease, immunoglobulin, and streptavidin. Each protein type sticks only to a pit with the shape of that protein. Ratner's engineered surfaces may be used for quick biochemical separations and assays, and in biosensors[1599] and chemosensors,[1602] because such surfaces will selectively adsorb from solution only the specific protein whose complementary shape has been imprinted, and only at the specific place on the surface where the shape is imprinted. Novel molecular imprinting techniques continue to emerge.[5311] The RESIST Group at the Welsh School of Pharmacy at Cardiff University[1600] and others[1601,1602,5312-5330] have looked at how molecularly imprinted polymers could be medically useful in near-term applications such as analysis,[5317-5319] separations,[5320] sensors,[5320-5325] binding assays,[5326] screening for drug discovery,[5327] controlled drug release,[1600] drug monitoring devices,[1600] catalysis[5328-5330] including "plastizymes",[5329] and biological and antibody receptor mimics.[1601] Ratner believes that on implants designed to attract a specific class of proteins — for example, osteopontin, a protein found in healing wounds — the macrophages might respond differently and the implant coating might stimulate healing rather than scarring or inflammation.[1603]*

15.2.3 Nanorobot Immunoreactivity

The human immune system is designed to recognize and react to foreign material that enters the body. Hence the immunoreactivity of a foreign substance is a key measure of the biocompatibility of that substance. Before we consider how such reactivities might be purposely engineered, it is useful to briefly review the broad outlines of the human immune system (Section 15.2.3.1). This is followed by a discussion of the complement (Section 15.2.3.2) and antibody (Section 15.2.3.3) systems, including an evaluation of their potential interactions with medical nanorobots. We conclude with a brief description of purposeful immunosuppression and tolerization (Section 15.2.3.4), immune privilege (Section 15.2.3.5), and immune evasion (Section 15.2.3.6), all of which are relevant in nanomedicine. An analysis of the phagocyte system and its interactions with nanorobots is deferred to Section 15.4.3.

15.2.3.1 Overview of the Human Immune System

The human immune system[348-351] consists of two main branches:

1. the natural, inherited, or innate system that is relatively fast-acting (e.g., responding to challenges in a few minutes), constituting the nonspecific immune response (Section 15.2.3.1.1); and
2. the acquired, learned, or adaptive system that is relatively slow-acting (e.g., requiring at least 5-7 days to respond in a primary infection scenario and 1-3 days for a secondary infection), constituting the specific immune response (Section 15.2.3.1.2).

15.2.3.1.1 Nonspecific (Innate) Immune Response

The nonspecific-response branch of the immune system is "innate" in the sense that the human body is born with the inherent ability to recognize certain foreign materials automatically. The innate response occurs to the same extent however many times an infectious agent is encountered. Besides purely mechanical mechanisms or barriers such as skin and mucous membranes, the nonspecific-response branch of the immune system has three major components — complement, phagocytes, and NK (natural killer) cells.

The first component of the nonspecific immune response is complement (Section 15.2.3.2), a set of ~20 bloodstream proteins that operate in a functional cascade (with one protein activating the next protein) to directly identify and destroy microbial invaders.* These proteins influence the inflammatory process and serve as the primary mediator in the antigen-antibody reactions of the B-cell mediated immune response (see below). With just a few exceptions, proteins of the complement system are designated with the letter "C" — e.g., C2, C3, C4a, C5, and so forth. Once activated, one of the main functions of the complement cascade is to assemble a multi-component biomolecular product called the membrane attack complex (MAC) that renders bacterial cell walls porous, leading to cell death — the MAC is directly bactericidal.[234] The system is highly regulated and there are counter-regulatory proteins to ensure it is not indiscriminately activated.

The second component of the nonspecific immune response is the phagocytic cells, comprised of monocytes, macrophages (activated monocytes), and neutrophils (Section 15.4.3.1). For example, macrophages are tissue-resident large phagocytic white cells equipped with chemical receptors sensitive to the polysaccharides found in bacterial cell walls. The receptors enable macrophages to recognize, then engulf and destroy, these bacteria. Upon encountering an invading microbe that is otherwise invisible to the complement system, macrophages can also secrete cytokines (Section 7.4.5.1), soluble mediators such as interleukin-6 (IL-6), α- and β-interferon, and tumor necrosis factor (TNF) that activate other immune cells. One of the functions of IL-6 is as a signaling protein that instructs the liver to secrete a second signaling protein that in turn binds to mannose residues present on bacterial surfaces. This renders the microbe visible to the complement system and triggers the complement cascade. Macrophages also act as antigen-presenting cells (MHC class II; Section 8.5.2.1). Bloodstream-resident phagocytic cells such as neutrophils (the predominant leukocyte found in pus) have receptors for complement and immunoglobulin. Neutrophils are recruited to the scene of inflammation and assist the macrophages in the digestion of microbial invaders. Basophils, another granulocytic white cell, have an important role in nonspecific inflammation — particularly the release of histamine[5926] and other biochemicals such as IL-4 and IL-13[5927] that act on blood vessels. Eosinophils moderate the immune response and are closely associated with IgE antibodies, parasitic infections (specifically helminthic), antibody-dependent cell-mediated cytotoxicity (ADCC), and immediate-type hypersensitivity (allergic) reactions.[5491] Macrophages also recognize and ingest "self" cells undergoing apoptosis (Section 10.4.1.1) in vivo, protecting tissues from the toxic contents of dying cells and modulating macrophage regulation of inflammatory and immune responses.[5506,5765-5767]

The third component of the nonspecific immune response is the specialized white blood cells called large granular lymphocytes (LGL) or natural killer (NK) cells.[2167-2169] NK cells are granular lymphocytes slightly larger than B or T cells (Section 15.2.3.1.2) that can kill some microbes and virus-infected cells, and some types of tumor cells. The "natural" part of their name indicates that they are ready to kill their target cells as soon as they are formed[361] rather than requiring the maturation and education process needed by B cells and T cells (Section 15.2.3.1.2). NK cells kill by inducing nuclear fragmentation resulting in cell death (apoptosis; Section 10.4.1.1) or by releasing perforin protein which creates holes in the target cell membrane. NK cells do not directly threaten diamondoid-based medical nanorobots except possibly during cytocarriage (Section 9.4.2). In this situation, the apoptotic activity of NK cells can be prevented by expression of a signal or leader peptide (derived from the polymorphic classical major histocompatibility molecules HLA-A, HLA-B and HLA-C) bound to an HLA-E class I MHC molecule at the (cytocarriage vehicle) cell surface. This HLA-E molecule interacts with an NK cell-surface lectin receptor (CD94/NKG2A/B/C) and delivers an inhibitory signal to the NK cell.[2357-2359] The HLA-E molecule is released from nanorobot stores or manufactured (Chapter 19) onboard.

15.2.3.1.2 Specific (Acquired) Immune Response

The specific-response branch of the immune system is "adaptive" in the sense that the human body has the ability to learn to recognize novel foreign materials that it has never encountered before. The adaptive response increases in speed, in magnitude, and in defensive capabilities, after repeated exposure to a particular macromolecule. The specific-response branch of the immune system has two major components — the "humoral" and the "cell-mediated" responses.

The first component of the specific-response branch, also known as the humoral response, is the specialized white blood cells called bone marrow-derived cells, B lymphocytes, or B cells. Each of the ~0.1-1 trillion B cells usually present in the human body[352,1756]

** Other innate-system antimicrobial peptides are commonly employed by different animal and plant species.[2551]*

displays on its surface just one type of the ~10^8-10^9 possible antigen receptor types.[353,354,1764,1765] (~10^7 different specificities are thought to exist in a single individual,[1756] but combinatorial human antibody libraries approaching ~10^{11} in diversity have been created.[1766]) Each B cell makes a different receptor protein, so each B cell recognizes a different foreign molecule. Each B cell has ~10^5 membrane-bound antibody molecules which correspond to the one specific antibody that this cell is programmed to produce.[1436] If a B cell detects an intruder via a binding event to its particular receptor type, then that B cell divides rapidly, making a large number of clone cells bearing the same one unique receptor type. These cloned B cells then differentiate into plasma cells (cell lifetime ~1 week[1436]) that secrete free versions of the detected receptor type, also known as immunoglobulins (denoted "Ig"; Section 15.2.3.3) or, more commonly, antibodies,* into the bloodstream. These free antibodies bind to the surface of intruder cells. This makes the intruders visible to the innate system and allows them to be destroyed by the nonspecific complement/phagocyte system. There are five distinct classes of immunoglobulins — IgG, IgA, IgM, IgD, and IgE — representing ~25% of all human plasma proteins (Appendix B). Clones of the activated B cell line differentiate into memory B cells,[356-359] giving rise to germinal centers (specialized structures within lymphoid organs) which allow a more rapid response if the same antigen is ever encountered again.

The second component of the specific-response branch, also known as the cell-mediated response, is the specialized white blood cells called thymus-derived cells, T lymphocytes, or T cells. T cells serve a variety of purposes, such as recognizing and killing cells bearing nonself molecules on their surface, or helping B cells produce antibodies. Both B and T lymphocytes range from 6-12 microns in diameter.[5334-5339] There can be as many as ~1 trillion T cells in the body.[353,360] To maximize the chances of encountering antigen, lymphocytes recirculate from blood to lymphoid tissues (Section 8.2.1.3) and back dozens of times per day — the ~10^{10} lymphocytes in human blood have a mean residence time of ~30 minutes in the blood.[1763] Each T cell has ~10^5 molecules of a specific antigen-binding T cell receptor exposed on its surface.[1436] The term CD or "cluster of differentiation" is used to designate surface marker proteins that distinguish various T cell subpopulations — including most importantly the CD4 lymphocytes (mature helper-inducer T cells) and the CD8 lymphocytes (cytotoxic/killer and suppressor T cells). The CD3 polypeptide complex is expressed on the surface of T cells and thymocytes. About 75% of all peripheral blood lymphocytes of normal individuals are T cells (i.e., ~25% are B cells), of which ~50% are helper-inducer CD4 T cells and ~25% are suppressor or cytotoxic CD8 T cells.[1756] Many T cell functions are mediated by cytokines (Table 7.2), most notably the interleukins (IL), interferons (IFN), tumor necrosis factor (TNF), and granulocyte-macrophage colony stimulating factor (GM-CSF). Surface markers and life span of a population of human T cells equivalent to murine memory T cells have been demonstrated,[362,363] thus the existence of memory T cells in humans, though once controversial,[364] is now well established.[365-370]

The immune system employs two systems of recognition elements — soluble antibodies and cell-attached T-cell receptors. Both are produced by similar types of genetic elements (the immunoglobulin gene superfamily). Opsonization is the process by which soluble antibodies bind to and coat antigenic particles to mediate destruction by phagocytosis (Figure 15.8) or complement activation,[5491] and can also block the action of proteins required for pathogen invasiveness. Cell-bound T-cell receptors (having binding sites biochemically similar to antibodies) provide protection against intracellular microbes such as viruses and mycobacteria. Such microbes are shielded from antibodies by the host cell membrane. But nearly all vertebrate cell types exhibit a sample of peptides on their surface, derived from the digestion of proteins in their cytosol, which includes fragments of microbe or virus proteins, if any are present. T cells use their T-cell receptors to continually scan the surfaces of cells in order to detect, and then kill, any cells displaying recognized foreign markings.

Both humoral and cell-mediated immune responses require a signaling step that announces the presence of non-self protein. In most cases this signaling step is the end result of a sequence of intracellular processes during which a foreign protein is broken down and processed into short oligopeptides, typically 8-10 amino acids long. Inside the cell, these antigenic fragments then become associated with a set of glycoproteins called the major histocompatibility complex (MHC) molecules (Section 8.5.2.1). The function of the MHC molecules is to pick up the peptide fragments and convey them to the cell membrane for the purpose of T-cell recognition and proliferation, a process called antigen presentation. (Autoimmune disease results when self-proteins presented on the MHC are misrecognized as non-self.)

Peptide fragments derived from endogenous intracellular microbes are transported to the outside of the cell complexed with MHC class I molecules (Figure 8.33) where they can then present antigen to CD8 lymphocytes. Most cells have MHC-I molecules and the constant sampling of the cytosolic protein population provides a powerful surveillance mechanism geared to detecting viral infection or intracellular bacteria. Protection against intracellular microbes is largely the domain of cell-mediated immunity, although for several pathogens antibody responses also contribute to host defense.[1760] It would seem that, from the point of view of avoiding immune attacks on cells in which intracellular cell repair machines are present, it will generally be important to avoid allowing these machines to be swept along on the MHC antigen presentation machinery and presented on the surface of cells.

Peptide fragments derived from exogenous antigens (either free or complexed with antibody) that have been endocytosed into the cell are transported to the cell surface and presented to CD4 cells by MHC class II molecules (Figure 8.34). Class II molecules occur only in specialized cell types called antigen presenting cells (APCs) such as B cells, macrophages, and dendritic cells. Peptides presented by MHC II molecules can activate the appropriate cascade of chemical processes that lead to antibody formation.** Of course, intracellular nanorobots could load the local MHC population with artifactual or manufactured antigens to manipulate the immune system response.

Dendritic cells (DCs) are antigen presenting cells scattered throughout the body, including the various portals of microbial entry, where they reside in immature form as immunological sensors.[2555] They are leukocytes of bone marrow origin.[5342] Like lymphocytes, DCs form subsets differing in phenotype, function, and locale. In

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** "Natural" antibodies, produced spontaneously even in organisms raised in sterile environments, are often considered as part of the innate immune system[785,786] and may serve a pathogen-herding function.[787] They usually have lower affinity and functional activity than antibodies developed as part of a specific immune response.*

*** Superantigens are polypeptide toxins secreted by bacteria[2243] or produced by viruses[2244] that interfere with normal immune function by directly activating T cells in a nonspecific manner. Superantigens are thought to induce aberrant cell-cell interactions by binding simultaneously to T cell antigen receptors and to MHC class II molecules containing certain relatively rare peptide fragments.[2238-2241] They are believed to be associated with toxic shock,[2241,2242] food poisoning,[2245] and various autoimmune disorders.[2246]*

human skin, DCs called Langerhans cells[5340-5342] are found in the epidermis. Interstitial DCs are found in the dermis. In human blood, one type of immature DC differentiates into mature DCs in response to inflammatory stimuli, and another precursor DC responds to viruses, tumors, and other stimuli by differentiating into mature plasmacytoid DCs.[2556-2559] In mice, other DCs have also been found in the thymic cortex and T cell areas of secondary lymphoid organs, in the marginal zones of the spleen, in the subcapsular sinuses of the lymph nodes, and in the subepithelial dome of Peyer's patches (oval masses of lymphoid tissue on the mucous membrane lining the small intestine).[2557-2559]

When a microbe invades a tissue, resident immature DCs employ pattern recognition receptors[2560-2565] embedded in their plasma membrane surface to sense the microbe by recognizing evolutionarily conserved molecular patterns that are integral to microbial carbohydrates, lipids, and nucleic acids.[2555] For example, lipopolysaccharide (LPS) from *E. coli* is recognized by Toll-like receptor TLR4; peptidoglycans from *Staphylococcus aureus* and LPS from *Porphyromonas gingivalis* are recognized by TLR2; bacterial flagellin is recognized by TLR5; and so forth.[2561-2564] Once a specific microbe is detected, physical information about the pathogen is captured via phagocytosis, endocytosis, or micropinocytosis for soluble antigens[2557] and is relayed to naive T lymphocytes in the draining lymph nodes. Immature DCs exit the site of infection and migrate toward the T cell areas of the proximal lymph nodes via the afferent lymphatics, following rising gradients of 6Ckine and MIP-3β cytokines expressed in lymphoid organs.[2557] During this journey the DCs mature, losing their antigen-capturing capacities but acquiring the ability to process and display peptide antigens on their surface via MHC class II molecules for antigen presentation to T-lymphocytes, as previously described.

15.2.3.2 Complement Activation

The complement system[1613,1616-1624,2331,2539] consists of a series of ~20 plasma and cell membrane proteins (e.g., named C1-C9, etc.) synthesized mainly by the liver and certain cells of the immune system (e.g., macrophages). These proteins interact in a sequential or regulatory manner, leading (1) to the general promotion of inflammatory reaction, including mediating vascular responses such as histamine release and recruiting phagocytic leukocytes via chemotaxis, and (2) to the lysis of certain kinds of cells and susceptible microorganisms following attachment of the membrane attack complex (MAC) to their plasma membranes (Figure 15.6). The targets of this process may be bacteria, virus-infected human cells, mycoplasmas, spirochetes, protozoa, or tumor cells.[1620] The complement system may follow two different activation pathways* — the classical pathway or the alternative pathway — either of which can initiate the terminal sequence of complement activation which involves assembly of the MAC.

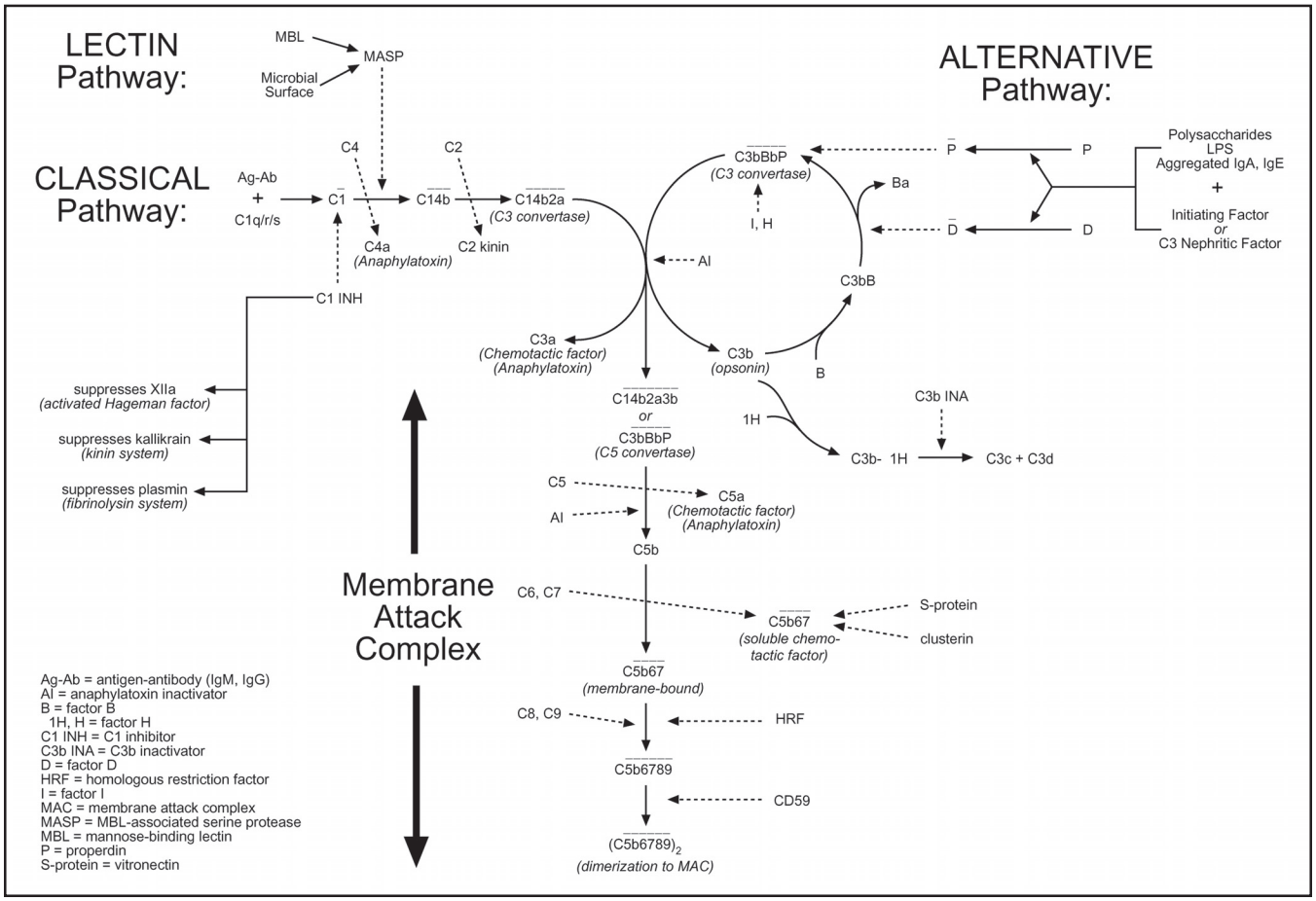

Fig. 15.6. The complement system (modified from Spira[1620] and from Trowbridge and Emiling[2331])

** A third "lectin pathway" for complement activation via foreign carbohydrates on microbial surfaces, leading to cell lysis, has recently been discovered,[1608-1613,5343] with activity similar to that of the classical pathway[1606] but apparently predating it evolutionarily.[1607] As with other pathways, the lectin pathway can be inhibited.[5344-5347]*

The classical pathway of the complement system is activated by antigen-antibody complexes that have formed on the surface of a target cell. Complement factor C1 (900 kD) binds to the Fc (Section 15.2.3.3) portion of either a single antibody molecule of IgM or to a pair of antibody molecules IgG1, IgG2, or IgG3, in apposition on the surface of the antigen. C1 is a macromolecule composed of C1q (410 kD) and doublets of C1r (85 kD) and C1s (85 kD) linked by Ca^{++} ions. The C1q component binds to the antibody,* activating C1r and C1s to form $C\bar{1}$ which itself has enzymatic activity to cleave C4 (210 kD). The cleavage of C4 releases the C4a (6 kD) fragment into solution and attaches the larger C4b fragment at the site, making the $C\overline{14b}$ complex, which can now bind C2 (110 kD). Once bound (the process is complete in 5-10 min[1617]), C2 can be cleaved by the $C\bar{1}$ complex (or other proteolytic enzymes like trypsin or chymotrypsin). This releases the smaller C2b (35 kD) fragment into solution and leaves the larger C2a (75 kD) fragment attached at the site, making the $C\overline{14b2a}$ complex. The $C\overline{14b2a}$ complex is the first of the two forms of C3 convertase.

The alternative pathway of the complement system is of greater importance in the initial defense against infection, because it does not depend solely upon the time-consuming production of specific antibody.[2331] It may be activated by contact with the Fab (Section 15.2.3.3) portions of aggregated IgA or IgE, or in some cases the $F(ab')_2$ portion of IgG antibodies complexed with antigen on the surface of a target cell. More importantly, the alternative pathway may be activated in the absence of antibody complexes by certain foreign molecules such as repeating sugars or proteins, as, for example, plasmin (see Figure 15.10), bacterial lipopolysaccharide (LPS), yeast zymogen, trypanosomes, plant (inulin) polysaccharides, polyanionic substrates (e.g., dextran sulfate), cobra venom factor, heterologous erythrocytes, carbohydrates (e.g., agarose), and many other materials. These substances activate factor P (properdin, 220 kD), activating in turn a C3-convertase amplification loop. In this amplification loop, pre-existing C3b (180 kD) fragments opsonize** (attach to) the target cell. Factor B (93 kD) reversibly binds to a receptor on the surface-bound C3b fragment. Factor D (an enzyme circulating at low concentration in active form, 22 kD[1618,1675-1677]) cleaves the bound factor B, releasing Ba (30 kD) into solution and leaving attached the larger Bb (63 kD) segment. This makes the $C\overline{3bBb}$ complex which can cleave many more C3 (195 kD) molecules, some of which bind covalently to the activating surface. However, the $C\overline{3bBb}$ enzyme dissociates fairly rapidly unless it is stabilized by the binding of activated factor P, creating the $C\overline{3bBbP}$ complex.*** The $C\overline{3bBbP}$ complex is the second of the two forms of C3 convertase, and completes the amplification loop, resulting in the binding of many more molecules of C3b to the same surface.

The terminal sequence of the complement system actually builds the MAC. This process is triggered when either form of C3 convertase accumulates on the target surface. C3 convertase has specific enzymatic activity to cleave C3, releasing C3a (9 kD) into solution and attaching the larger C3b fragment to the C3 convertase molecule at the site, making C5 convertase. C5 convertase has specific enzymatic activity to cleave C5 (190 kD), releasing both the smaller C5a (11 kD) fragment (a 74 amino acid glycopolypeptide) and the C5b (180 kD) fragment into solution.**** The subsequent assembly of the MAC is nonenzymatic. Fluid-phase C5b binds first C6 (120 kD) and then C7 (110 kD), forming a stable C5b67 complex. The binding of C7 converts the complex from a hydrophilic to a hydrophobic state, which then preferentially inserts the complex into lipid bilayer — including other cell membranes in the immediate vicinity of the primary surface on which complement activation is focused. C8 (152 kD) then binds to the C5b67 complex at a site on C5b, forming C5b678 as it inserts itself into the lipid bilayer membrane. Finally, the C5b678 complex induces C9 polymerization[1627] into the form of a hollow tubular structure, with 12-18 C9 monomers (69 kD) attached to each C5b678 complex,[1613,1629] completing the MAC. Poly(C9) is a cylinder with inner and outer diameters of 9 nm and 15 nm respectively, tube length 15 nm, rimmed by a 4.6 nm thick torus with inner and outer diameters of 11 nm and 22 nm on one end.[1628,1629]

The MAC,[1613-1616] a dimer of the ~1650 kD[1630] C5b6789 complex, makes a single transmembrane channel through which water and electrolytes may pass,[1631] resulting in an impairment of osmotic regulation and subsequent cytolysis.[1632] This is similar to the action of mammalian cytolytic T lymphocytes that can kill targeted cells by inserting into their membranes a 67-kD pore-forming molecule called perforin[1633-1635] which has structural homology to C9.[1634,1638] Similar molecules are found in the granules of eosinophils,[1639] various bacterial pathogens,[1635-1637] and in the protozoan parasite *Trypanosoma cruzi*.[1640] Complement-mediated lysis has been shown for many kinds of cells including erythrocytes, platelets, lymphocytes, bacteria, and viruses possessing a lipoprotein envelope.[1617] S. Flitman notes that flares of autoimmune diseases like lupus produce clinically detectable drops in C3 and C4 levels.

Despite being targeted principally against microbial intruders, complement is relevant to nanorobotic nanomedicine because several possible nanorobot building materials are already known to interact with components of the complement system. For example, graphite adsorbs C1q and C3 (Section 15.3.3.3) and Teflon activates C5a (Section 15.3.4.3). Alumina ceramic (sapphire) has not yet been found to activate complement[613] or complement receptors,[1641] but some fullerenes can induce the production of specific IgG antibodies[724,725] which could enable complement activation along either pathway. Diamond may adsorb some C3 like many other hydrophobic surfaces (Section 15.3.1.1), though diamond is generally considered noninflammatory relative to the complement system. In one experiment,[1642] diamond particles caused insignificant complement activation, unlike crystals of monosodium urate monohydrate, hydroxyapatite, brushite, and calcium pyrophosphate dihydrate, and particles of blackthorn, all of which demonstrated activation of C3 via the alternative pathway as determined by immunofixation following electrophoretic separation of C3 and its

** A variety of other substances interact directly with C1 and C1q,[1626] including negatively-charged polyanionic substances which form a complex with cationic C1q, the most basic serum protein with an isoelectric point of ~pH 9.2. Direct binding of C1q has been shown for polynucleotides, heparin, dextran sulfate, condroitin sulfate, cardiolipin, LPS, the envelopes of some RNA viruses,[1617] certain microorganisms and some retroviruses and mycoplasmas;[1618] C1q can be involved in viral lysis initiation.[1620]*

*** Opsonins are substances that coat foreign antigens, making those antigens more susceptible to recognition by macrophages and other leukocytes and thus increasing phagocytosis of the organism or object displaying those foreign antigens. In effect, opsonins promote cytocarriage (Section 9.4.7) by macrophages. The two main opsonins in human blood are complement and antibodies.*

**** The $C\overline{3bBb}$ enzyme can also be stabilized by C3 nephritic factor, an IgG autoantibody directed against an antigen of $C\overline{3bBb}$.[1620]*

***** C5b also appears to enhance the phagocytosis of yeast.[1620]*

activation products.* Complement activation at the site of surgical trauma has also been reported during cardiac surgery.[4953-4960]

There are three principal physiological consequences of complement activation,[1613] all of which are directly relevant to nanomedicine. Nanorobots could potentially activate complement causing (1) inappropriate cell death, (2) release of vasoactive substances and shock, or (3) stimulation of an autoimmune-type response, as follows:

First, the cytolytic MAC is assembled on the target surface. This may not be a direct threat to hard nanorobot targets, whose exteriors typically will be dissimilar to those of foreign cells or viruses and may be made of tough materials impossible for the MAC to breach. However, the MAC can attack nearby native cells as well as foreign cells (e.g., in cell transplants), causing undesirable cellular necrosis.[234] Native blood cells have some protection against such attack. For instance, an average of 25,000 MACs can be assembled on a neutrophil surface without lysis because MACs are rapidly shed with a clearance half-life of ~2 minutes at 37°C[1692] — about two-thirds of the MACs are ejected from the cell in plasma membrane vesicles via an exocytic process, and one-third are removed via endocytic internalization and proteolysis. Similar processes are observed on platelets[1693] and other native cell types.[1694,1695]

Second, the many short peptide cleavage fragments resulting from the sequential complement activation chain may induce potentially harmful side effects. These effects may include: (1) local inflammation (Section 15.2.4) (e.g., via C2b, or C2 kinin after plasmin modification), (2) inhibition of the growth of antigen-antibody complexes (e.g., via C3a),[234,5928] and (3) anaphylactic reaction (Section 15.2.6.1) to C3a and C5a (and to a lesser extent C4a) which are themselves potent anaphylatoxins that bind to mast cells, degranulate mast cells and basophils, and induce release of vasoactive substances like histamine that mediate vasodilation, increased vascular permeability, and contraction of bronchial smooth muscle.

Third, complement cleavage fragments also include chemotactic factors such as C3a, C5a, and soluble C5b67 complex. These factors attract neutrophils, macrophages, and other phagocytic cells to the vicinity, thus increasing the opportunity for phagocytic uptake of nanorobots by these protective native cells. Macrophages display receptors** for C3b on their surfaces, enhancing uptake of non-self particles bound to C3b. Soluble C5b67 released into solution phase as a result of either the presence or the activities of medical nanorobots could enter the membranes of nearby uninvolved cells, possibly leading, eventually, to cytolysis of those nearby cells.

The ideal medical nanorobot design would include an exterior surface that does not activate complement.[5825] It is possible that a pure diamond or sapphire surface will not activate complement. However, nanorobot exteriors may need to display sorboregulatory or adhesioregulatory (Section 15.2.2.4), anti-inflammatory (Section 15.2.4), or antithrombotic (Section 15.2.5) ligands whose complement activation potentials have not yet been widely studied. One approach might be for nanorobots to mimic autologous human self-surfaces,[1613,1625] that contain molecules of CR1 (a natural C3b receptor) and/or membrane cofactor protein (MCP)[1685] that bind to C3b and also promote the preferential binding of factor H (see below) rather than factor B to C3b.[1618] This would effectively limit C3 deposition and prevent the formation of stable C3 convertase enzymes. By comparison, non-self-surfaces allow the rapid deposition of many molecules of C3.[1618] The additional presence of decay accelerating factor (DAF)[1643,1684] on self-surfaces, along with CR1, is known to inhibit the association between C3b and B, and to promote dissociation of the $\overline{C3bBb}$ complex.[1618] Membrane sialic acid also appears to be one of the carbohydrate components protecting autologous cell membranes from amplified C3b deposition.[1618] Malignant tumor cells are observed to use membrane-bound complement regulatory proteins to evade complement-mediated injury.[1644]

Other complement-resistant surfaces have been investigated. For instance, polymers containing phosphorylcholine polar groups can achieve a marked reduction in complement activation as measured using radioimmunoassay for C3a.[578] Another investigation[1645] of biomaterial-mediated complement activation used an animal implantation model and gold surfaces bearing various thiol-linked functionalities. This study found that mercaptoglycerol- and mercaptoethanol-bearing surfaces engendered the strongest inflammatory responses (as reflected by the accumulation of large numbers of adherent neutrophils and monocytes/macrophages) whereas L-cysteine-coated surfaces caused only minor inflammatory responses. Both glutathione-modified and untreated gold implants attracted minimal numbers of inflammatory cells.[1645] The mercaptoglycerol surface — which has hydroxyl groups (alternative pathway) and high IgG affinity (classical pathway) — caused pronounced production of C3b and C5b6789 in serum and increased C3 deposition on the surface. By comparison, bare gold surface and mercaptopropionic acid surface caused very little complement activation.[1646] Particle surface coatings of PLA-PEO diblock copolymer exceeding ~0.20 molecules/nm^2 significantly reduce complement opsonization of PLA-PEO nanoparticles.[2487] Acceptable levels of complement activity reduction may be determined experimentally. Generally, surfaces with negative or neutral charge do not activate complement, as compared to positively charged surfaces.

If complement-active surfaces cannot be avoided, active nanorobots may interrupt the complement activation process in their vicinity via controlled emissions of one or more of the >11 activation control proteins,[1613,1622,1647] by depleting essential factors, or by other means, as may be appropriate for the particular mission and nanorobot design. Complement is continuously activated in the body, both in health and in disease — endothelia, circulating cells, and other plasma-exposed tissues are under constant attack.[1613] To prevent significant damage to self-cells, the complement system must be tightly regulated.

On the classical pathway, human C1 esterase inhibitor (C1 INH)[1620] or C1 inactivator (C1 INA)[1648] is a naturally-occurring heat- and acid-labile serum α_2-neuraminoglycoprotein (MW = 109,000 daltons) that stoichiometrically binds $C\bar{1}$ and inhibits not only C1r and C1s, but also plasma kallikrein, plasmin, trypsin, chymotrypsin, activated Hageman factor (clotting factor XIIa), and activated thromboplastin antecedent (factor XIa).[1617] Normal plasma concentrations of C1 are ~6 x 10^{-5} gm/cm^3 (~360 molecules/micron^3) in human blood (Appendix B). A release rate of ~10^3 molecules/sec (~0.0002 micron^3/sec) would maintain an equal concentration of C1 INH in a 1-nm skin layer around a 1-micron spherical nanorobot washed by a 1 mm/sec capillary blood flow.

** Urate crystals directly activate[2327,2328] and amplify[2322] the classical complement pathway, induce alternate pathway activation when the classical pathway is inhibited,[1648] and promote C5a production via assembly of a stable C5a convertase on the crystal surface.[2522]*

*** Four commonly known receptors for C3b and C4b are CR1, CR2, CR3, and CR4, some or all of which are found on B lymphocytes, epithelial cells of cervix and nasopharynx, erythrocytes, follicular dendritic cells, glomerular epithelial cells, macrophages, monocytes, neutrophils, and NK cells.[1618] Bacteria opsonized with antibody and complement are often observed adhering to human red cells.[1618]*

Natural serum also contains a glycoprotein called C4bp or C4b-bp (540 kD)[1649] that has a specific binding affinity for C4b (e.g., it competes with C2a for binding to C4b) and is the control protein for the classical C3 convertase.

On the alternative pathway, factor H (β1H or C3b INA accelerator, 150 kD)[1650] can stabilize C3b and prevent its interaction with factor B. The C3b-factor H complex is then cleaved by factor I (C3b/C4b inactivator or C3 INA, 93 kD), for which MCP (membrane cofactor protein) is a necessary cofactor.[1620,1685] DAF (see above) is a surface-bound glycoprotein that accelerates the decay of both classical and alternative pathway C3 convertases.[1620,1643,1684] Nanorobots could also employ molecular sorting rotors (Section 3.4.2) to deplete[1677-1679] local supplies of activated factor D (MW = 22,000 daltons, serum conc. ~ 1.5 x 10^{-6} gm/cm^3 or ~40 molecules/micron^3),[1617,1677] or to deactivate local factor D molecules using a catch-and-release process. (While it might appear harmful to inactivate complement in a septic patient, this inactivation is temporary and would occur only as a part of a comprehensive nanorobotic-based anti-infective treatment.) A similar process is employed by neutrophils to deactivate anaphylatoxins. For instance, neutrophil surfaces include 50,000-113,000 receptors (C5aR, MW ~ 40-60 kD) for C5a.[1618] Following receptor binding, the C5a is internalized and degraded to inactive peptide fragments.[1618] A related strategy is to release solubilized complement receptors to deplete complement components.[1655]

Farther downstream, plasma enzyme carboxypeptidase N (CPN) or anaphylatoxin inactivator (AI) (280 kD) abolishes the activities of C3a and C5a by removing the C-terminal arginine from both molecules.[1617] The 56-kD serratial protease eliminates C5a chemotactic activity at a dose of 1 μg/cm^3 (~10 molecules/micron^3).[1651] Still farther downstream, S-protein (vitronectin, 83 kD) binds to fluid-phase C5b67, preventing its insertion into lipid bilayers.[1618] The regulatory glycoprotein clusterin (~80 kD) serves a similar function[1686-1689] and is a more active inhibitor on a molar basis, but the effects of the two inhibitors are additive.[1686] Autologous cells also have two MAC-inhibiting proteins, called homologous restriction factor (HRF C8-binding protein, 65 kD)[1652] and 20-kD glycoprotein CD59,[1653] which protect them against lysis by the MAC.[1618] CD59 is present on all circulating cells, endothelia, epithelia, and in most organs[1613] — erythrocytes display ~25,000 copies/cell[1690] and many nucleated cell types express much more. But interrupting the cascade this far downstream cannot prevent the adverse inflammatory and chemotactic effects of the upstream peptide cleavage fragments.

Control protein-oriented strategies have already been pursued experimentally. In one study,[1654] the modification of reactive surface hydroxyl groups on regenerated cellulose with various dicarboxylic-acid anhydrides was found to significantly limit the complement-activating potential of these materials. Maleic anhydride displayed the most dramatic and consistent diminution of complement activation compared to unmodified cellulose (i.e., 0-10% of control values for C3b deposition and C3a/C5a production[1654]). This maleated derivative was found to facilitate the factor H control of C3 convertase and C5 convertase activity, thus limiting complement activation and the production of other inflammatory mediators via the normal regulatory mechanisms. A chimeric molecule combining DAF and CD59 retained the inhibitory activities of both component molecules.[1709]

Monoclonal antibodies have been raised against C4,[1710] C5,[1711,1712] C5a[1713,1714] and C5a receptor,[1715] C6,[1716] and C8,[1711] and peptide antagonists to C5a receptor have been tested in vitro.[1717-1721] A variety of therapeutic complement inhibitors are under active investigation,[1655-1657,5348] including an RNA aptamer[5492] inhibitor of C5.[1722] Heparin also inhibits complement activation[2485] but would not be a particularly viable option here due to its principal activity as a potent anticoagulant.

As might be expected, bacteria have evolved many techniques of evading complement activation. Some of these, in principle, could be mimicked by medical nanorobots. (Bacteria that are not killed and lysed in serum by the complement MAC are said to be serum resistant. Many of the Gram-negative bacteria that cause systemic infections (e.g., septicemia) are serum resistant.) For example:

1. *Brucella abortus* bacteria may use O-antigen to shield outer membrane proteins from C1q binding;[1671]
2. the bacterial capsule of *Neisseria meningitidis* contains sialic acid (a common component of host cell glycoproteins) which inhibits C3b opsonization and inhibits activation of the alternative pathway;[1658-1661]
3. *Helicobacter pylori* urease is believed to degrade bound C3b, reducing opsonization;[1672]
4. YadA protein produced by *Yersinia enterocolitica* binds factor H, reducing C3b deposition on the bacterial surface probably by rapid inactivation of C3b;[1668]
5. *Neisseria meningitidis* and *Haemophilus influenzae* (which cause bacterial meningitis) can covalently attach sialic acid residues to the O-specific sugar portion of LPS, preventing the formation of C3 convertase and thus imparting resistance to MAC;[1437]
6. lipooligosaccharide sialylation of serum-sensitive *N. gonococci* in vivo converts them to serum-resistant;[1659,1662]
7. *Pseudomonas aeruginosa* produces extracellular elastase and alkaline protease enzymes that inactivate components of complement;[1663-1666]
8. a protease produced by *Bacteroides gingivalis* inactivates C3;[1667]
9. streptococcal M protein binds factor H, inhibiting complement activation;[1669,2517]
10. group A and B streptococci express on their membranes an enzyme that cleaves 6 amino acids from C5a, rendering this agent inactive;[1691]
11. 17-kD outer-membrane protein Rck promotes resistance to complement killing of S*almonella typhimurium* by interfering with C9 polymerization;[1670]
12. some bacteria with LPS molecules having long intact O-antigen side-chains can prevent effective complement killing by holding the MAC complex too far from the vulnerable outer membrane to be effective.[1673,1674]

Numerous viruses have acquired host complement regulators, especially CD59,[1696-1702] glycoprotein C (gC)[2344] which is found in the envelopes of herpesviruses HSV-1 and HSV-2 that binds to C3b, and glycoprotein III (gIII)[2345] which is found on pseudorabies virus and serves a similar function. Several parasites have been reported which express surface molecules that inhibit MAC formation, particularly *Schistosoma mansoni*,[1703-1705] *Trypanosoma cruzi*,[1706] and *Entamoeba histolytica*.[1707,1708]

15.2.3.3 Immunoglobulins (Antibodies)

The "humoral" (B-lymphocyte) branch of the specific immune system (Section 15.2.3.1.2) responds to the presence of different

antigens (such as foreign molecules) in the body by manufacturing large numbers of complementary antibodies capable of binding to those antigens, then releasing these antibodies into the bloodstream after a delay of up to 4-10 days. An antibody molecule has two* principal functions: (1) to recognize and bind to an antigen, and (2) to assist in the destruction and elimination of that antigen.[353] This dichotomy of function is reflected in structure because every antibody molecule has discrete domains that participate in one of these two functions — a variable region to enable recognition, and an effector ("common") region to enable elimination. Specific antibodies can be made against virtually any foreign chemical group (but see discussion of immunogens in Section 15.3.7).

Antibodies are a class of glycoproteins called immunoglobulins, abbreviated Ig, which collectively comprise ~25% of total noncellular blood plasma protein. Each monomeric antibody molecule has an approximate molecular weight of 150-190 kD,[1753] and there are ~10^{20} antibody molecules in every adult human body.[1767] In general, antibodies can be found: (1) inside cytoplasmic membrane-bound compartments such as ER (endoplasmic reticulum) and Golgi, (2) on the surface of B-cells, (3) in blood plasma, (4) in the interstitial fluid of tissues where secreted antibodies from B-cells accumulate, (5) in secretory fluids such as mucus and breast milk into which certain types of antibody molecules are specifically transported, and (6) on the surface of certain immune effector cells such as mononuclear phagocytes, NK cells, and mast cells, which do not synthesize antibody but have specific receptors for binding antibody molecules.[5491]

The most common human antibody molecules consist of two identical ~50-70 kD "heavy (H) chains" that are noncovalently joined in the lower half (the "constant," "effector" or "Fc" region) and separated in the upper half (the "antigen-binding" or "Fab" region), forming a "Y" shape (Figure 15.7). Each heavy chain is ~446 amino acids long,[1765] and has a hinge region of 10-60 amino acids near the middle, allowing the two upper arms of the Y to swing and rotate relatively freely. Two identical ~23 kD "light (L) chains" are attached to the two heavy chain upper arms, one per arm, with each L chain ~214 amino acids long (Figure 15.7). The L chains and H chains are synthesized as separate molecules, then assembled into mature Ig molecules inside the B cell or plasma cell, at production rates up to 1000-3000 Ig molecules/sec-cell.[1754,1755]

The top halves of each upper arm on each chain are designated as the variable (V_L and V_H) domains. These domains are ~117 amino acids in length and have sequences that differ from other antibody molecules, enabling the binding of a specific antigen and allowing molecular recognition to occur. Antibody specificity for antigen varies for different epitopes (active binding regions on antigens) and is somewhat degenerate — that is, a given antibody can react with more than one epitope, provided these epitopes are closely related structurally. A given antigen may contain several unrelated epitopes; however, an antibody cannot have two different antigenic binding sites.

Each clone of antibody-producing cells makes a unique antibody. The variable domains from different humans also contain unique allotypic amino acid sequences. But each variable domain also includes 3 light-chain "hypervariable" regions and 3 heavy-chain "hypervariable" regions[5491] where most of the epitope-specific sequence variation occurs. Each of these widely separated hypervariable regions consists of only 5-10 (or in one case 15) contiguous amino acids, so most of the variability in both L and H chains is restricted to about 15-30 amino acids per chain. Note that the variable

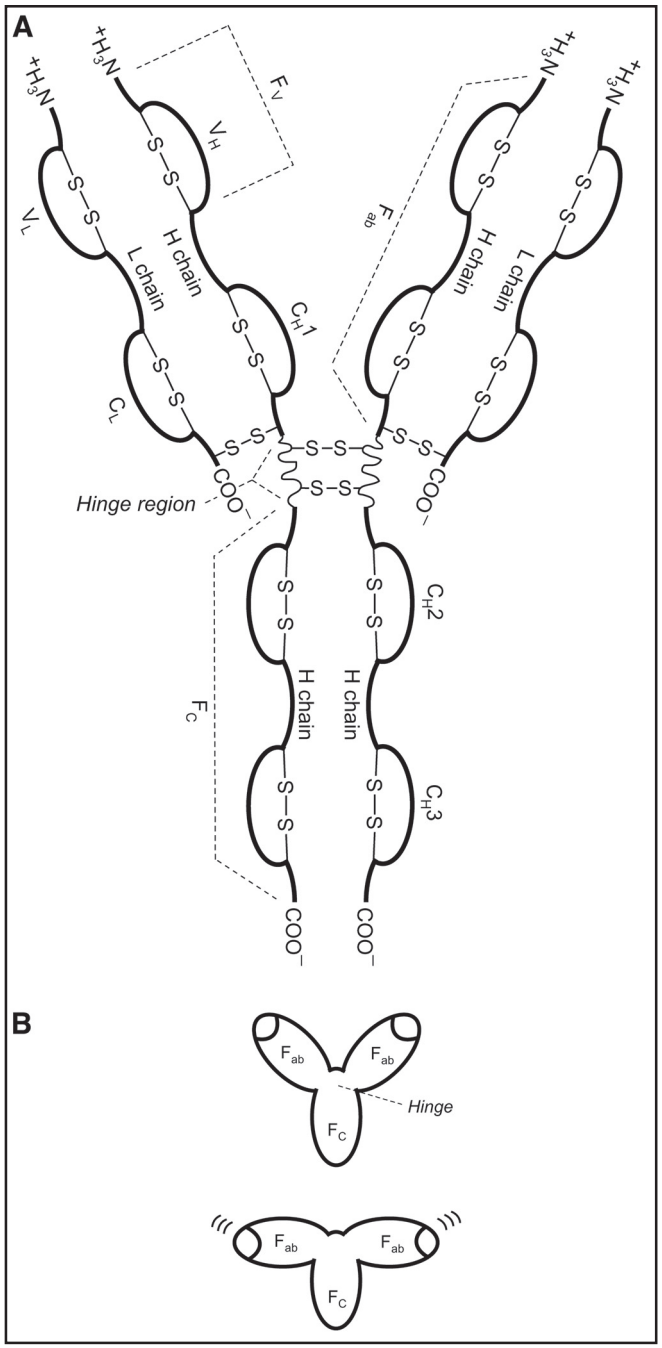

Fig. 15.7. Simplified model of a human IgG antibody molecule, showing the basic 4-chain structure (modified and redrawn from Harfenist and Murray[1753] and from Stryer[1765]).

domains are not simple linear sequences of amino acids, but rather form globular regions with secondary and tertiary structure in order to effect binding of specific antigens.[1753] The antigen binding sites are pockets formed when the hypervariable regions fold into close proximity, producing a 3D structure with a surface complementary to the 3D surface of the bound antigen.[5491] Antibody configurations are produced by somatic recombination of ~78 light-chain and ~84 heavy-chain gene segments,[1758] which, along with other sources of variability, allow for up to ~10^9 chemically

** In late 2002, a possible third function was reported: evidence that antibodies can directly catalyze the production of highly active forms of oxygen (likely including ozone) that may not only kill bacterial pathogens directly but might also promote inflammatory and other immune responses.[6018]*

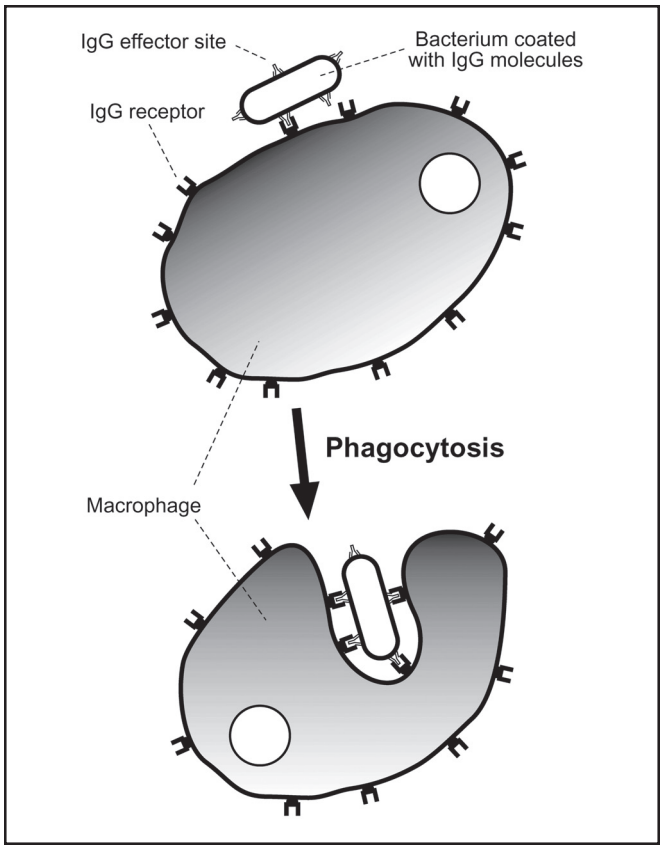

Fig. 15.8. Phagocytosis of a bacterium coated with immunoglobulin IgG molecules (modified and redrawn from Becker and Deamer[353]).

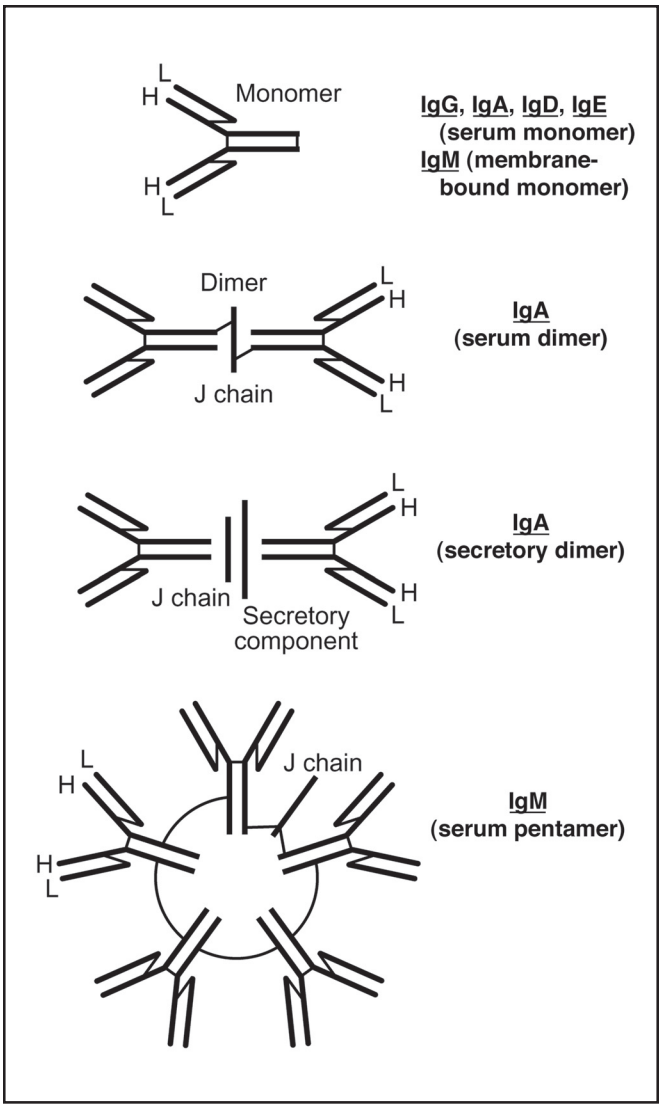

Fig. 15.9. Schematic illustration of human immunoglobulin molecules (modified and redrawn from Harfenist and Murray[1753]).

distinct antibody receptor specificities,[353,354] although only ~10^7 specificities are found in a single individual.[1756]

The remainder of each chain is designated as constant (C_L and C_H) domain of several types, which varies relatively little among immunoglobulin molecules of similar class (isotype) and thus determines the class of antibody. The Fc or effector region of each molecule can be recognized by complementary antibody receptors present on the outer surface of monocytes, neutrophils, eosinophils, NK cells and macrophages (IgG1 and IgG3 only). This permits phagocytic elimination of the antibody-bound antigen on, say, a bacterial outer membrane (Figure 15.8). Because each antibody molecule has two or more antigen binding sites (Figure 15.9), antigens can be crosslinked by antibodies into chains, lattices, and networks, forming immune complexes that facilitate phagocytosis and complement activation.* The formation of immune complexes on the surface of a biochemically active antigen can block its binding site, thus inhibiting its biological activity.

There are 5 classes of immunoglobulin molecules:[353,1753,1756-1760]

Immunoglobulin G (IgG) is the most abundant antibody in the blood, as well as the most common antibody produced in late primary and in secondary immune responses. IgG is a 150 kD monomer (~76% of total serum Ig, or ~13.5 mg/ml) with a half-life of ~3 weeks. It is also distributed in extracellular fluid and is present in milk, and maternal IgG is the only Ig that normally crosses the placenta. IgG binds to the surface of somatic and microbial cells, which allows those cells to be phagocytosed or killed by cytotoxic cells (Figure 15.8) — along with IgM, IgG is the primary activator of the complement system. IgG also binds complement via an Fc receptor present in the constant region of the heavy chain. S. Flitman notes that only IgG crosses the blood-brain barrier (0.1% of all IgG is in the CNS compartment at all times.) There are four subtypes with differing activities and concentrations: IgG1 (~9 mg/ml), IgG2 (~3 mg/ml), IgG3 (~1 mg/ml), and IgG4 (~0.5 mg/ml).

Immunoglobulin A (IgA) is the most important class of antibody found in secretions such as tears, sweat, saliva, colostrum and breast milk, and in mucus secretions of the bronchial, gastrointestinal and urogenital tracts, where it is present as "secretory IgA", a 335 kD dimer consisting of two Y-shaped units linked together at the foot of each Y by a transverse 15-kD "J chain". A 70-kD polypeptide called secretory component is attached to the Fc portion after the dimer has been endocytosed into the lumen of secretory tissue, so a ~400 kD complex is normally found in secretions with a half-life of ~6 days. Secretory IgA plays an important role in host defense against viral and bacterial infections by binding to microbes and thus blocking their attachment and transport across mucosa, and

** The reactions of antibody with multivalent insoluble particulate antigens results in the crosslinking of the various antigen particles by the antibodies, eventually producing clumping or agglutination of the antigen particles by the antibodies[1760] — the basis for the standard agglutination test.*

provides passive immunity to breast-fed babies. "Serum IgA", a simple 160 kD Ig monomer, is the second most common Ig in the blood, constituting ~15% of serum Ig (~2.7 mg/ml). There are two subtypes: IgA1 and IgA2.

Immunoglobulin M (IgM) is the first class of antibody to be produced during B cell development. IgM is also the major class of antibody secreted first into the bloodstream during a primary immune response. IgM is found mainly in the intravascular compartment and on B-cell surfaces. It is normally absent from organs and tissues, and usually doesn't cross the placenta. Carbohydrate antigens such as blood group substances stimulate IgM, and IgM efficiently activates the complement system, facilitating the death of invading microbes. (IgM, IgG1, IgG2, and IgG3 are complement-fixing antibodies; the rest of the Ig's are non-complement-fixing antibodies.) Membrane-bound IgM is the usual ~175 kD Y-shaped monomer, hydrophobic at one end to remain anchored in cell membrane where it serves as a surface receptor. Serum IgM molecules are soluble (hydrophilic) pentamers bound together by disulfide bridges plus a 15-kD J chain, with total molecular weight of ~900 kD, constituting ~8% of all serum Ig (~1.5 mg/ml) with a half-life of ~5 days.

Immunoglobulin D (IgD) is a monomeric 180 kD antibody very prominent on mature B-cell surfaces where it is co-expressed with IgM. But IgD is secreted by very few B cells, hence constitutes only ~0.2% of all serum Ig (~0.03 mg/ml) with a half-life of ~3 days. IgD functions as an antigen receptor optimized to efficiently recruit B cells into antigen-driven responses,[1761] and can substitute for IgM functions.[1762] Expression of membrane IgD appears to correlate with the elimination of B cells having the capacity to generate self-reactive antibodies, so the major biologic significance of IgD may be the silencing of autoreactive B cells during development.[1760]

Immunoglobulin E (IgE) is a monomeric 190 kD antibody that constitutes only ~0.003% of all serum Ig (~0.0005 mg/ml) with a half-life of ~2 days. IgE is important in allergic disease because it binds to the surface of mast cells and basophils. The capacity of IgE to trigger inflammatory reactions, specifically with eosinophils, is also beneficial in the clearance of extracellular parasitic infections. In the presence of specific antigen which ligates (cross-links) two adjacent surface-bound IgE molecules, IgE induces the cell to release granules containing vasoactive amines (e.g., histamine and serotonin) and various allergic-response molecules including leukotrienes, prostaglandins, platelet activating factor, proteases and cytokines, resulting in bronchospasm, vasodilation, smooth muscle contraction, and chemoattraction of other inflammatory and immune cells.

No covalent bonds are formed during the interaction between antibody and epitope (the specific antibody binding portion of an antigen or immunogenic macromolecule).[1760] Binding forces are relatively weak, consisting mainly of van der Waals, electrostatic, and hydrophobic forces (Section 3.5.1), all of which require a very close proximity between the interacting moieties that is often compared to a lock and key. The low binding energies allow antigen-antibody complexes to be readily dissociated by low or high pH, by high salt concentration, or by chaotropic ions such as cyanides that interfere with the hydrogen bonding of water molecules.[1760]

Can the human immune system recognize medical nanorobots? The answer may depend largely upon the composition of the nanorobot exterior surfaces. Pure diamond is generally considered nonimmunogenic — e.g., chemical vapor deposition (CVD) diamond coatings for artificial joints are said to have "low immunoreactivity",[535] and as of 2002 there were no reports in the literature of antibodies having been raised to diamond. Even low molecular weight adamantane-based derivatives yield inherently non-antigenic antiviral drugs, though when incorporated into dipeptide gels these drugs can induce the production of high-titer specific antibodies in rabbits.[5561] Other adamantane derivatives such as rimantadine interfere with and suppress the generation of cellular immune responses.[5562]

As for nondiamond carbon materials, graphite-based endoprostheses elicit no immunological reactions.[820] Carbon particles in India ink induce a reaction to human serum IgG only if the particles are pretreated with staphylococcal protein A.[863] On the other hand, carbon black can have a significant adjuvant effect on the systemic specific IgE response to allergen (ovalbumin) in mice.[867] Solubilized (derivatized) C_{60} and C_{70} fullerenes can induce the production of specific antibodies,[724,725,2387-2389] usually by interaction with the combining sites of IgG.[725] It is speculated that highly hydrophobic pure fullerenes would be recognized by antibodies with hydrophobic amino acids in their binding sites[725,2164] or would interact with donor $-NH_2$[914] and -SH[915] groups. There are several reports of antibodies being raised to single-walled carbon nanotubes.[2164,2385-2387,4630] For example, antibodies raised to C_{60} in mice strongly bind to single-walled nanotubes.[2386] Computer simulations suggest that it may be possible to build antibodies that selectively bind to nanotubes of a specific diameter or chirality.[2164] As for noncarbon materials, pure sapphire appears reasonably nonimmunogenic, although similar hydrophilic surfaces do adsorb immunoglobulin IgG.[543] Adsorption-induced denaturation of immunoglobulin G (IgG) on Teflon doesn't lead to complete unfolding into an extended polypeptide chain, but leaves a significant part of the IgG molecule (the Fc fragment) in a globular form.[1336] Crystalline silicon,[1769] silica ceramic,[1770] PTFE membrane[1771] and Teflon[1772] immunoisolation microcapsules appear to be nonimmunogenic during extended periods of implantation. Various biological materials appear immunologically inert, such as hydroxyapatite.[1834]

However, concerted experimental searches for antibodies to diamondoid materials have yet to be undertaken, and experimental failures rarely find their way into the literature. Immunologists usually work on the assumption that the available antibody repertoire is diverse enough to ensure the production of antibodies to virtually any potentially antigenic molecule[1768] (but see Section 15.3.6). Izhaky and Pecht[724] suggest that since fullerenes (and other diamondoid materials) are highly ordered and symmetric molecules for which scant experimental data exists, it might be useful to compare the ability of vertebrate immune systems to respond to analogous non-diamondoid water-insoluble highly-ordered antigens.

For example, water-insoluble crystals introduced into experimental animals are found to be treated as antigens,[5035] inducing specific antibodies. Kessler et al[1774] raised monoclonal antibodies (MAbs) specific for crystals of 1,4-dinitrobenzene having well-defined molecular-level structures. These antibodies were so specific they would not bind to the same molecule when it was conjugated to a protein carrier. Antibody binding sites typically span a contact area of 6-9 nm^2,[1775,1776] so an antibody can bind to arrays of 5-20 molecules exposed at the crystal surface[724] like an artificial semaphore presentation array (Section 5.3.6). IgG antibodies isolated from the serum of rabbits injected with crystals of monosodium urate monohydrate or magnesium urate octahydrate evidently bear in their binding sites an imprint of the crystal surface structure because they can act as nucleating templates for crystal formation in vitro with extremely low cross-reactivity, despite the similar molecular and structural characteristics of the two crystals.[1777] Antibody binding to monosodium urate crystals has been known for decades[5037-5039] and viruses have been engineered with a specific recognition moiety for

ZnS nanocrystals used as quantum dots.[5040] Interestingly, antibodies specific to in vivo water-ice crystals have even been reported.[1773]

Like antigens with ordered multiple epitopes, crystals expose chemically and geometrically distinct surfaces. It is conceivable that different antibodies may recognize distinct faces of a crystal (possibly including diamond or sapphire crystal faces exposed at the surfaces of medical nanorobots) in an interaction similar to that of antibodies for repetitive epitopes present on protein surfaces.[724,5036] For instance, one MAb to 1,4-dinitrobenzene crystals was shown to specifically interact with the molecularly flat, aromatic, and polar (101) face of these crystals, but not with other faces of the same crystal.[1778] MAbs have also been elicited against cholesterol monohydrate crystals,[1779,5034] one of which[1779] was shown to specifically recognize the crystal's stepped (301) face. Here, the hydrophobic cholesterol hydrocarbon backbone is exposed on one side of the molecular steps while hydroxyl residues and water molecules are exclusively exposed on the other side. In both cases, crystal-specific antibodies were of the IgM idiotype.[724] This accords with the assumption that (unlike most commonly used antigens) crystals cannot be processed by the antigen presenting cells, hence antibodies must be induced through a T cell-independent path.[1780] Semiconductor-binding[2170,5040] and calcite-binding[5243] proteins are known that can discriminate among the various crystal faces of the given material and can in some cases alter the pattern of crystal growth.[5244] Sulfur-free gold-binding proteins (GBPs) recognize and noncovalently bind preferentially to the Au (111) crystal surface — GBPs use multiple repeats of 14-30 residue sequences to bind to this surface.[2391] Hyaluronan is believed to be a crystal-binding protein for calcium oxalate monohydrate crystals.[5245]

Diamondoid surfaces coated with non-self adsorbed protein monolayers (Section 15.2.2) might prove antigenic, as might protein-based presentation semaphores (Section 5.3.6) that become detached via degradative intracellular chemical processes and whose fragments are subsequently presented at the cell surface by MHC molecules (Sections 8.5.2.1 and 15.2.3.1.2). Avoiding such detachment will be an important design objective for many nanorobot missions. Another concern is that antibodies may be raised against binding sites that are positioned on the nanorobot exterior, e.g., sorting rotor pockets (Section 3.4.2), which are similar to traditional bioreceptors, or manipulator end-effectors (Section 9.3.2). These antibodies could then act as agonists[1783] or antagonists[1781,1785] for such sites, since MAbs specific to biological binding sites are well known.[1781-1785] This risk may be increased if nanorobot binding sites employ non-self biomolecular components, or, conversely, may be decreased if binding sites employ purely diamondoid rigid structures or self-biomolecule receptors (e.g., whose natural antibodies have likely been eliminated by clonal deletion). This is an additional design constraint that must be addressed experimentally.

If antibodies to nanorobot exteriors can exist in the natural human antibody specificity repertoire, then to avoid immune recognition many techniques of immune evasion (Section 15.2.3.6) may be borrowed from biology, possibly including:

1. *Camouflage*. Coat the nanorobot with a layer of "self" proteins and carbohydrate moieties resembling fibroblast, platelet, or even RBC[1788] plasma membrane. Normally, antibodies for these surfaces have already been deleted from the systemic repertoire to avoid autoimmunity, so the coated nanorobot will be theoretically nonimmunogenic. Ideally, an artificial surface would be designed that displays the minimum necessary ligand set to ensure nonimmunogenicity. Presentation semaphores (Section 5.3.6) may be used if the required surface ligand concentration is significantly less than monolayer thickness. The existence of nonimmunogenic autologous cells such as NK,[2171] TH1, and malignant cells (via HLA-G expression)[2166] that escape immunosurveillance, and bacteria capable of evading the antibody response,[1786-1789] suggests that such nonimmunogenic exteriors are possible. Extended rejection-free allograft survival using a combination of T-cell costimulation inhibitor and anti-CD40 MAb has been demonstrated experimentally in primates.[2541] Personalized nanorobots exhibiting self-MHC receptors (Section 8.5.2.1) on their surfaces would possess a very specific type of camouflage. Autoimmune risk due to unwanted detachment of self moieties from the nanorobot surface, and pathogen borrowing of such detached moieties for the purpose of immune evasion, especially in the case of large localized populations of in vivo devices, should be studied further.

2. *Chemical Inhibition.* Nanorobots may slowly secrete chemical substances into the perirobotic environment to make it difficult for Ig molecules to adhere to an otherwise immunogenic nanorobot surface. For example, a >0.01% concentration of sodium dodecylsulfate surfactant destroys almost all antigen-antibody binding,[1790] but the emission would have to be very localized to avoid lysing other cells in the vicinity prior to denaturing an antibody. The low pH gastric environment produces poor Ig deposition, allowing *H. pylori* bacteria to evade humoral defenses.[1791] Bacteria such as *Pasteurella multocida*,[1792] *Pseudomonas aeruginosa*,[1793] and *Serratia marcescens*[1794] secrete extracellular proteases that can cleave Ig molecules. Covalent pegylation of otherwise antigenic proteins can induce specific tolerance.[1766,1833] There may be some risk of local inflammation with this approach.

3. *Decoys*. Release a cloud of soluble nanorobot-epitope antigens in the vicinity of the nanorobot. This will not affect nanorobot operations because the decoy molecules are noncomplementary to nanorobot surfaces. But the decoys will bind any antibodies specific to the nanorobot epitopes, preventing further antibody activity against the nanorobot.[1437] J.R. Baker notes that this would have to be done cautiously to avoid triggering serum sickness or complement activation. Alternatively, decoy fragments may be loosely bound to the nanorobot surface and jettisoned as soon as a binding event is detected (Sections 4.2.1, 4.2.2, and 4.2.3). This could limit mission duration to the exhaustion time of the onboard supply of decoy molecules. A. Kumar notes that decoy releases would have to be controlled very accurately for all the nanorobots in the body because there is a threshold level of antigen that triggers the immune response.

4. *Active Neutralization*. Equip the nanorobot with molecular sorting rotors designed with binding sites similar or identical to the nanorobot epitopes that raised the target antibodies. The target antibodies will bind to rotor pockets and be conveyed inside the nanorobot, whereupon the antibody molecules can be chemically altered (a) to eliminate their troublesome paratopes (sites of epitope attachment) or (b) to defunctionalize their effector region. They would then be released back into the body in a harmless neutralized state, care having been taken to avoid random chemical alterations which might trigger autoimmune responses. Less efficiently (especially when the immune system is fully activated), the ingested target antibody could be chemically degraded or cleaved[1792-1797] into safe peptides suitable for free release, or simply warehoused onboard until the end of the mission. M. Sprintz notes that if the nanorobotic mission is

short-term (a few days), then antibody production is not an issue for the first exposure, though subsequent exposure could produce a delayed-type hypersensitivity (DTH) response (Section 15.2.6.1); he suggests also the possible active nanorobotic prevention of memory cell formation.

5. *Tolerization*. Nanorobots introduced into a newborn may train the neonatal immune system to regard these foreign materials as "native," thus eliminating nanorobot-active antibodies via natural clonal deletion.[1828-1830] This process is often called "tolerance induction" and in this example assumes a mature nanomedical technology with well-defined nanorobot surface signatures that will not change over time as the neonate matures into an adult. Pregnant women may develop specific immunological tolerance to fetal antigens and foreign transplant tissue,[1831] thus might also become tolerized to nanorobotic antigens introduced during pregnancy. Nonpregnant patients could have tolerance artificially induced via engineered antigen-specific T-suppressor cells[371,5349-5354] or by other means (Section 15.2.3.4). This approach seems feasible if nanorobots use only a few key surface materials — deactivating immune responses could have serious implications, e.g., failure to recognize a pathogenic microbe due to cross-tolerance.

6. *Clonal Deletion*. Once the paratopes of antibodies that bind nanorobots are known, immunotoxin molecules can be engineered that display those paratopes.* Upon injection into the patient, these targeted immunotoxins would bind to all T cell receptors that display this paratope, killing the nanorobot-sensitive T cells.[1803-1810] Engineered immunotoxins may also eliminate all B cells capable of manufacturing antibodies having the proscribed nanorobot-binding paratope,[1811-1816] at EC50 concentrations as low as 2.5-70 ng/ml (~0.03-0.8 molecules/micron^3).[1814] Such interventions could be made at the local, lymphatic, or systemic levels.[2543] The end result is that the ability of the immune system to recognize nanorobot epitopes would be selectively eliminated, in effect adding "nanorobot surfaces" to the definition of "self" by a process of artificial clonal deletion against T cells[1817-1823] and B cells.[1824-1827]

15.2.3.4 Immunosuppression, Tolerization, and Camouflage

Transplantation is the transfer of living cells, tissues, or organs from one person, the donor, to another, the recipient (e.g., a blood transfusion), or from one part of the body to another (e.g., skin grafts) with the goal of restoring a missing function.[361] However, even if the patient's HLA types (histocompatibility locus antigens; Section 8.5.2.1) are closely matched to those of the donor, transplanted organs are usually rejected (beginning within minutes or hours of surgery[1832]) unless the recipient's immune system is carefully controlled. Immediately after the graft has been implanted, it is necessary to prevent sensitization of pre-existing mature T cells capable of recognizing the graft. Once the graft has escaped the initial acute phase rejection reactions, a cumulative unresponsiveness to the graft develops as the recipient is continually exposed to donor MHC, a stable state that sometimes depends on the development of antigen-specific T-suppressor cells.[371,5349-5354]

In an era of advanced nanomedicine, it should be possible to restrain or reprogram the immune system directly using genetic engineering (Chapters 19 and 23), or by using other means (e.g., temporary systemic white cell sequestration), to reduce or eliminate immunoresponsiveness during the period of nanomedical treatment. Traditional methods are much less desirable. The most general pre-nanomedical method to suppress immune system acute responsiveness is called antigen nonspecific immunosuppression. Antigen nonspecific methods include the use of cytotoxic drugs that interfere with all cell division in the body.[383] Since the immune response to antigen requires clonal proliferation, agents that block mitosis are effective inhibitors of the immune response. But this immunosuppression is general, not specific, thus the patient is more susceptible to infection. If infection occurs, immunosuppression must be suspended whereupon an implanted graft is usually lost due to rejection.[371] These agents also damage all tissues (e.g., gut epithelium, bone marrow) where rapid cell division is occurring, creating other undesirable side effects, thus often may not be suitable for use in medical nanorobotics.

The fungal metabolite cyclosporin A (cyclosporine)[384,385] has a greater specificity for lymphoid T cells than other cells. Used in isolation, cyclosporine at 10 mg/kg-day effectively suppresses the entire immune system indefinitely,[382] though at great risk of nephrotoxicity. Other newer calcineurin blockers may have fewer side effects.[2349] Other pre-nanomedical nonspecific lymphocytotoxic agents commonly include:

1. *Corticosteroids, Purine Analogs, etc*. Prednisone and prednisolone[386] act powerfully to suppress the inflammation accompanying a rejection crisis, and also appear to reduce the expression of class II histocompatibility antigens, thus reducing the immunogenicity of the transplant. First used as anticancer drugs, purine analogs such as 6-mercaptopurine interfere with DNA synthesis and thus are also powerful antimitotic (hence immunosuppressive) agents. Other well-known agents include azathioprine (Imuran),[386] tacrolimus (FK506),[387] sirolimus (rapamycin),[387] mycophenolic acid (mycophenolate mofetil; CellCept),[385,387] and leflunomide (and its malononitriloamide analogs).[387,388]

2. *Antilymphocyte Globulin (ALG)*. ALG is produced by immunizing a large animal such as a horse with human lymphocytes, then purifying the gamma globulin fraction of the serum. Injections of ALG into a graft recipient have a powerful suppressive effect on graft rejection.[402]

3. *Total Lymphoid Irradiation (TLI)*. A series of sublethal doses of radiation is directed at the patient's lymphoid tissue (spleen, thymus, and lymph nodes in the neck, chest, and abdomen), with bone marrow and other vital organs shielded from the exposure.[387] In due course, the stem cells in the bone marrow reconstitute the peripheral lymphoid system but the newly formed T cells seem to accept the graft as self.[403] TLI has enabled some transplant patients to quit using other immunosuppressive agents altogether. Photopheresis[387] is also used for treatment of recurrent rejection.

However, all of these approaches have severe complications and side effects, so the risk benefits would need to be carefully evaluated and almost certainly would be inappropriate in a mature nanomedical technology environment.

** Raising artificial MAbs against natural antibodies that react to a nanorobot is another approach, though this is more risky because anti-antibodies[1798] are found in several immunopathological or autoimmune diseases. Antibodies specific for determinants within the variable region of an antibody molecule are known as anti-idiotypic antibodies,[1799-1801] but these function as surrogate antigens and might actually stimulate additional anti-nanorobot immune response. Anti-anti-idiotypic antibody responses have also been elicited experimentally.[1802]*

4. *Other*. T cell activation could also be blocked by altered peptide ligands[389,390] or synthetic peptides;[391] or by antibodies to MHC class I[392-395] or class II[396,397] molecules, or to the T cell receptor;[398-401] or by the presence of solubilized forms of these molecules.[371] Anti-CD3 monoclonal antibodies (acting against all T lymphocytes)[404,405] are available commercially, as are various other agents. Other methods for terminating lymphocyte responsiveness have been discussed,[2545,2550] and M. Sprintz suggests considering plasmapheresis to decrease levels of preformed antibody.

Interestingly, a few viruses and protozoa can also cause antigen nonspecific immunosuppression, and suppressed immune responses are observed rarely during chronic bacterial infections such as tuberculosis and leprosy.[1437] In leprosy (caused by *Mycobacterium leprae*), the response both to leprosy antigens and to unrelated antigens is poor. Immunological reactivity reappears after successful treatment, an observation that implicates the microbe as the likely cause of the general immunosuppression. At present, little is known of the mechanisms by which pathogens initiate generalized immunosuppression, though it is probably due to interference with the normal immune functions of B cells, T cells, or macrophages.[1437] However, the strategy appears to be rare among bacteria because general immunosuppression is not particularly useful for the invader if it merely promotes infection by competing unrelated microorganisms.[1437] Many viruses also include genes that can modulate the immune response — for instance, Epstein-Barr virus encodes a gene which produces a protein that is a homolog of IL-10 that downregulates the immune response — and the fungus *Cryptococcus neoformans* sheds large amounts of capsular polysaccharide that interfere with the formation of inflammatory responses in tissue.[1760]

Antigen-specific immunosuppressive agents disable specific targets within the immune system. For example, after specific antigen activation, the responding T cells expand and express IL-2 receptors on their surface. Lymphokine toxin coupled to IL-2 binds and specifically removes this population. Monoclonal antibodies are also available that are specific for the IL-2 receptor. Their presence prevents T cells from proliferating in response to IL-2.[403] Agents that block CD28-mediated T-cell costimulatory signals inhibit T cell activation and induce a state of antigen-specific unresponsiveness in both in vitro and in vivo experiments.[406,407] Dendritic cells (ordinarily highly potent activators of naive T cells) that are transfected with CD95 ligand cDNA, called "killer DCs," deliver death signals, not activation signals, to T cells after antigen-specific interaction.[408] Direct inhibition of complement-mediated responses using modified C3 has been reported.[409] Additionally, in mild cases of leprosy the bacterium can induce an antigen-specific immunosuppression against *M. leprae* antigens only. This is perhaps due to a lack of costimulatory signals (interference with cytokine secretion), activation of suppressor T cells, or disturbances in TH1/TH2 cell activities.[1437]

In traditional organ transplantation work, immunological tolerance[410] to the histocompatibility antigens on the transplant can be induced by the use of tolerogenic antibodies[411] or other agents, called tolerogens[412] or antigen-specific tolerization therapy.[413,414] For example, several small donor blood transfusions to the recipient prior to transplantation are observed to improve graft retention,[415-417] and pretransplant implantation of donor bone marrow has induced donor-specific tolerance.[1438] Mitomycin-C-treated spleen cells from a donor rat, when injected preoperatively into a recipient rat, induce immune unresponsiveness when the recipient subsequently receives a cardiac allograft from the donor.[418] Anergic antigen-specific CD4 T cells can inhibit T cells restricted by a different MHC class II molecule. The anergic T cells act as suppressor cells by competing for the membrane of the antigen-presenting cell and the locally-produced IL-2. Induction of tolerance to a single alloantigen could serve to regulate the immune response to an allograft carrying several MHC (and minor antigen) differences.[419] The body can also learn to accept foreign material as "self" by placing the material to be tolerated into the thymus,[5872] where cells that recognize it will be inactivated or killed, or by using Starzl's trick[5873] of transplanting the graft along with immune cells that have the specificity of the graft (in his case, bone marrow from the organ donor), such that, again, cells attacking the graft are themselves attacked. The liver is also known to have a certain degree of "intrinsic tolerogenicity".[1438]

By the late 1990s, strategies were being sought to induce specific tolerance to allogeneic biological transplants without affecting other immune functions. The "veto effect"[372-378] permits one such technique,[378] wherein, for example, CD8 T cells suppress responses of MHC-restricted T-lymphocyte precursors to antigens expressed by those CD8 veto cells. Veto inhibition normally cannot provide complete tolerance to allogeneic grafts since it only operates on CD8-expressing cell populations. But Staerz, Qi and colleagues[379] have produced a hybrid antibody (Hab) combining a monoclonal antibody for a class I MHC molecule with a soluble CD8 molecule, which can specifically and effectively transfer veto inhibition to different stimulator cell populations, thus promising to selectively and completely tolerize graft-specific cytotoxic T lymphocytes without affecting normal immune responses. Another Hab combines CD4 and an anti-MHC class II antibody, which binds to class II molecules bringing CD4 accessory molecules to the surface of class II-bearing stimulator cells. CD4 T cells with specificity to Hab-coated stimulator cells cannot engage their CD4 molecules and are no longer activated.[380] There is also evidence that retrovirus-infected cells possibly may employ a veto-like mechanism to evade immune T-cell recognition.[381]

A more valuable approach from the standpoint of nanomedicine is to reduce the immunogenicity of the implant itself, before it is implanted. Traditionally, much of this work involves the "camouflaging" of graft cells. For example, Scott and Murad[420] used coatings of nonimmunogenic long-chain polymers such as methoxypoly(ethylene glycol) (mPEG) to globally camouflage the surface of foreign cells. This effectively attenuated antibody to surface epitopes and decreased the inherent immunogenicity of foreign, even xenogeneic, cells. Pegylated red blood cells (RBCs) lost ABO blood group reactivity, anti-blood group antibody binding was profoundly decreased, and pegylated sheep RBCs were ineffectively phagocytosed by human monocytes, unlike untreated sheep RBCs[421] — with no significant detrimental effects on RBC structure or function.[422] Pegylation of antigen presenting cells and T lymphocytes prevented recognition of foreign class II MHC molecules and prevented T cell proliferation in response to foreign MHC molecules.[420] Loss of peripheral blood mononuclear cell (PBMC) proliferation was not due either to mPEG-induced cytotoxicity, since viability was normal, or to cellular anergy, because phytohemagglutinin (PHA)-stimulated mPEG-PBMC demonstrated normal proliferative responses. Addition of exogenous interleukin (IL)-2 also had no proliferative effect, which suggested that the mPEG-modified T cells were not antigen primed.[423] Similar experiments by Stuhlmeier and Lin[424] on pegylated endothelial cells showed that mPEG inhibits binding of several antibodies, LPS, and the cytokine TNF-α to the cells.

Some natural human cell types stimulate a stronger immune response than others if foreign members are put into the body. Strong immune response comes from leukocytes and endothelial cells.[514] A weak or no immune response comes from keratinocytes, smooth muscle cells, and fibroblasts.[514] Fetal cells may exhibit immune tolerance because of the expression of nonclassical HLA-G molecules at their surface.[2165]

Nanorobot architects must take care to avoid designs that might inadvertently trigger or facilitate an autoimmune response. Autoimmune disease (Chapter 23) is the consequence of an immune response against self-antigens that results in the damage and eventual dysfunction of organs that become targeted by the immune system. In most cases the triggering event is unknown, although for decades an infectious cause has been postulated to explain the development of autoimmunity. According to the "molecular mimicry" hypothesis,[1153-1156] infectious agents (or other exogenous substances) may trigger an immune response against autoantigens when a susceptible host acquires an infection with a pathogen that has antigens that are immunologically similar to certain host antigens but differ sufficiently to induce an immune response when presented to T cells. The tolerance to autoantigens breaks down, and the otherwise pathogen-specific immune response that is generated cross-reacts with host tissues to cause tissue damage and disease. If a medical nanomachine is designed with organic components that are epitopically similar to components of the natural human body, then an autoimmune attack against those natural human components could also be directed against the nanorobots. Other medical nanorobots that present both human and viral[2548] (or bacterial) components on their exterior blood-contacting surfaces could facilitate autoimmune sensitization of a human patient by providing a previously nonexistent immunological bridge between pathogenic and human epitopes.

Alternatively, resemblance between bacterial antigens and host (or even nanorobot-surface-displayed) epitopes, also called molecular mimicry, could weaken the immune response to that bacterium by inducing a certain degree of immune system tolerance to the pathogen. This is a potential negative "side effect" of nanorobotic treatment that may be avoidable using good design.

Antigenic disguise is another simple camouflage tactic found in nature.[1437] Pathogens may hide their unique antigens from opsonizing antibodies or complement by coating themselves with host proteins such as fibrin, fibronectin, or immunoglobulins. For example, *S. aureus* produces cell-bound coagulase,[1723] which binds to fibrinogen[1724-1726] and prothrombin[1725-1727] and activates it to form staphylothrombin, causing fibrin to clot and to deposit on the cell surface.[1725] This may immunologically disguise the bacterium so that its natural immunogenicity is not recognized as a target for an immune response.[1437] Protein A produced by *S. aureus*,[1728] and the analogous Protein G produced by *Streptococcus pyogenes*,[1729,1730] bind the Fc- or Fab-regions of immunoglobulins, thus coating the bacterium with antibodies and canceling their opsonizing ability. As yet another example, the fibronectin coat of *Treponema pallidum*[1731] may provide an immunological disguise for these bacteria.[1437] Microbes can also simulate mammalian complex carbohydrates at cell surfaces to use as immune masks — for example, N-acetyl heparosan,[2333] colominic acid, and fructosyl chondroitin analog in *E. coli*,[2334] LeX in *H. pylori*,[2334] and hyaluronic acid in some bacteria.[2335]

15.2.3.5 Immune Privilege

Immune privilege,[425-434] first described 130 years ago,[435] protects tissue grafted to certain sites from rejection. Medawar's original explanation for this phenomenon[436] — that immune privilege was just immune ignorance, with privileged sites isolated behind blood-tissue barriers lacking lymphatic drainage, and with antigenic material (trapped within these isolated sites) remaining invisible to the immune system — is now known to be incorrect. It has since been found that foreign tissues in privileged sites could eventually evoke antigen-specific systemic immunity[437] and that certain privileged sites (such as the testis) had extensive efferent lymphatic pathways.[438] Rather than immune ignorance, the systemic immune apparatus recognizes antigens in privileged sites and cooperates to create and sustain a graft-friendly environment.[439] Medical nanorobot engineers may be able to borrow some of nature's techniques and convince the body's immune system that resident nanorobots or implanted nanorobotic organs possess immune privilege and thus should not be attacked.

There are two distinct loci of immune privilege: (1) privileged sites (the best example being the fetus) and (2) privileged tissues. Immune-privileged sites and tissues include[439] the eye (anterior chamber, cornea, and retina),[434] brain,[428,789] hair follicles,[790,791] cartilages, liver,[426,429] adrenal cortex, uterus (pregnant) and placenta,[468] ovary and testis,[425,427,456] prostate,[438] and tumors.[433,441] Immune privilege is biologically necessary for the success of pregnancy.[489] Immune privilege in the anterior chamber of the eye is critical to the avoidance of stromal keratitis, a blinding disease of the cornea accompanying ocular infection with HSV-1. In mice, the incidence and severity of HSV-1 keratitis rises dramatically in eyes where privilege has been lost.[490] Orthotopic corneal allografts are the most successful of all solid-organ transplants in humans because the eye is a privileged site and the cornea is a privileged tissue.[446] Corneal grafts placed in eyes that have lost immune privilege suffer acute rejection.[491]

Immune-privileged sites are regions of the body where allogeneic or xenogeneic grafts of foreign tissue enjoy prolonged, even indefinite, survival relative to nonprivileged sites. These are regions in the body where the immune system appears not to function.[440] Infectious organisms or tumor cells inserted into immune-privileged sites do not elicit destructive or protective immunity.[441,442] The eye is an example of a privileged site, where even minor episodes of inflammation could result in impaired vision or even blindness if the inflammation proceeds unchecked.[440] HSV-1 virus injected directly into the anterior chamber of mouse eyes induced an immediate infiltration of neutrophils and lymphocytes, but extensive apoptosis (Section 10.4.1.1) was observed in infiltrating immune cells 24 hours after infection in animals having functional CD95 (aka. Fas or APO-1) receptors and CD95L (aka. FasL) ligand expression.[440] By expressing CD95L, the eye directly kills activated immune cells that might invade the globe and destroy vision.[440] CD95L expression in the testis (another privileged site) may perform a similar function.[443,444] As summarized by Streilein,[439] privileged sites incorporate multiple additional features allowing them to accept foreign grafts. These features include: (1) blood-tissue barriers (for eye, brain); (2) absence of efferent lymphatics (eye); (3) direct tissue fluid drainage into the blood (eye, brain); (4) functional integrity of the spleen (eye);[445] (5) establishment of a potent immunosuppressive microenvironment[446] containing growth factors such as TGF-β (eye, brain, placenta, testis)[447] and neuropeptides (eye);[448,449] and (6) soluble and membrane-bound inhibitors of complement activation and fixation (anterior chamber of eye).[450-451] Antigenic materials placed in privileged sites evoke a state of deviant systemic immunity in which the usual mediators of immunogenic inflammation (e.g., delayed hypersensitivity T cells, complement-fixing antibodies) are curtailed, and other mediators

(e.g., cytotoxic T cells, noncomplement-fixing IgG antibodies) are enhanced.[452-454] For example, antigen injected into the eye is picked up locally by intraocular dendritic cells, which then migrate via the blood to the splenic white pulp where antigen-specific regulatory and effector T cells are activated.[439] At least four pathways are known by which immune privilege can lead to T-cell tolerance:[455] clonal deletion,[470] clonal anergy, immune deviation,[437,442,447,449] and T-cell suppression.[453]

Immune-privileged tissues resist immune rejection when grafted into conventional (nonprivileged) sites. For example, constitutive expression of CD95L on the Sertoli cells of a testis graft triggers apoptosis in the recipient's CD95+ antigen-activated T cells that are challenging the graft.[456] Myoblasts (muscle cells) genetically engineered to express FasL can protect neighboring transplanted islet cells by inducing apoptosis in visiting T cells for more than 80 days in mice,[2350] although the altered myoblasts evidently stimulate an inflammatory response that eventually destroys them.[2351] CD95L-coated tissues (eye, testis, tumor cells) generally stay free of patrolling immune cells. However, Chen et al[457] have noted that while surface-expressed CD95L triggers apoptosis in T lymphocytes,[458-461] it also stimulates neutrophils and other polymorphonuclear leukocytes. This stimulation may then be inhibited by the local presence of TGF-β — together, CD95L and TGF-β promote lymphocyte clonal deletion and suppress inflammation.[457] Privileged tissues also are often characterized[439] by intratissue structural barriers such as extensive tight junctions among parenchymal cells (Sertoli cells, retinal pigment epithelium); elaborate surface expression of hyaluronic acid (placenta, trabecular meshwork of the eye); reduced or absent expression of MHC class I and class II molecules (brain, eye, placenta); expression of class Ib molecules (placenta);[433,462] release of class I molecules (liver);[463] secretion of immunosuppressive cytokines (eye)[464-466] and corticosteroids (gonads); and fetal-like fibroblasts (gingival oral mucosa).[467]

Another instance of immune-privileged cells is the embryo, whose developing cells in the placenta manufacture an enzyme known as indoleamine 2,3-dioxygenase (IDO). IDO destroys tryptophan, an amino acid needed by maternal T cells (human cells cannot make their own tryptophan). This localized cell-induced nutrient depletion is believed to suppress the activity of maternal T cells that would otherwise make their way through the placenta and attack the fetal blood supply.[468] Other studies have shown that certain macrophages, induced to express IDO in response to interferon-γ from activating T cells, inhibit T cell proliferation in vitro by rapidly consuming tryptophan.[469-471] Amniotic membrane, a related privileged tissue that is fetal in origin and multipotential, lies between mother and baby and reacts with neither. It can be transplanted between species and still survive without the need for immunosuppression. In experimental studies, human amnion has been used to resurface rabbit knee joints[472-474] and can be useful in ocular[475-481] and other[482-488] transplantation procedures. Fibroblasts, which do not constitutively express HLA class II molecules, cannot induce the formation of required helper T cells and thus stimulate no rejection response when transplanted between hosts.[514] Human stem cells were originally believed to provoke no immunogenic reaction because they are not differentiated. However, recent results by Drukker et al[5718] found very low but consistent expression of MHC class I molecules even on undifferentiated human embryonic stem cells. As the cells differentiated, they produced higher levels of the proteins — probably high enough to trigger an immune reaction[5719] and to be rejected upon transplantation.[5718] (Even though embryonic stem cells aren't invisible to the immune system, these cells could be genetically engineered so as not to express MHC proteins, or nuclear transfer techniques might be used to create genetically matched stem cells for individual patients.[5719])

15.2.3.6 Immune Evasion

Certain parasites also display a form of immune privilege that is more properly termed "immune evasion",[492-497,2348] which might also be borrowed for medical nanorobot design. For example, live adult blood fluke (schistosomiasis) worms produce no lesions and rarely cause symptoms[498] or allergic reactions.[495] Schistosome parasites, despite being multicellular organisms up to several millimeters in length, can survive in the bloodstream of mammalian hosts for decades[496] even in the face of an ongoing antiparasite immune response by the infected host.[492] The developmental and adult stages of the parasite are mostly invisible to the immune system.[496] In vitro, bound complement is localized to infoldings of the parasite's tegument and not on its free surfaces.[499] Adult worms possess surface molecules bearing alternative pathway complement activation sites (Section 15.2.3.2), but these sites are masked by adsorbed host components in vivo.[499] Adsorbed host serum components can also inhibit specific antigen-antibody interactions at the parasite's surface, suggesting a degree of specificity in what the parasite adsorbs from the host[500] — adult worms can adsorb heterospecific[501] and homospecific[502] antibody onto their tegumental surfaces. Antibody bound to worm tegumental antigen causes shedding of the bound complex in ~20 minutes at 37°C.* [503] Soluble adult worm antigen preparation (SWAP) triggers release of cytokine IL-10 from peripheral blood mononuclear cells from both healthy and infected individuals,[505] and the IL-10 then suppresses lymphoproliferative responses to SWAP by 90-100%.[504] T cell proliferative hyporesponsiveness,[505,506] nonspecific T-cell immunodepression[507] and modulation of immune responses[508] are well known in chronic schistosomiasis.

The human body does not recognize the adult worms as foreign material because, although purified schistosomal tegumental protein is potently immunogenic,[509] the adult parasites can remake their surfaces constantly and cover them with native molecules taken from the human host.[510] This covering may include material borrowed from host red cells,[511] neutrophils,[512] LDLs,[513] and other sources.[503] Surface turnover is mostly slow. Immunoradiometric assays show that host erythrocyte antigen is lost from adult worm tegument with a half-life of up to 45 hours in vitro and ~5 days in vivo.[493] The component of adult surface cell lipid bilayer with the fastest turnover is phosphatidylcholine and is due to deacylation/reacylation, not to the sloughing of membranes.[497] Thus a relatively stable adult schistosome surface membrane escapes immune recognition and damage by employing active processes which result in reduced surface antigenicity[495] and the development of a tegument intrinsically resistant to immune damage[492] — a potentially useful example for medical nanorobotics. C. Haberzettl suggests that early simple therapeutic nanorobots might incorporate an "onion-skin" design, with separate concentric layers serving distinct purposes (e.g., organ targeting, cytopenetration, intracellular transport, etc.) and being sloughed off or absorbed in sequence, as their specific purpose is completed.

With an appropriate design, nanorobots could alter their antigenic signature (Section 5.3.6) fast enough to avoid antibodies from being raised at all. Some microbes already employ a related strategy. K. Todar (from whose discussion[1437] the next seven paragraphs draw

** Some bacteria also shed bound antigen-antibody immune complexes.[1737]*

heavily) points out that a similar example of immune evasion is displayed by *Borrelia recurrentis*, a spirochete that causes the human disease relapsing fever.[1746,1747] Explains Todar:[1437] "The disease is characterized by episodes of fever which relapse (come and go) for a period of weeks or months. After infection, the bacteria multiply in tissues and cause a febrile illness until the onset of an immune response a week or so later. Bacteria then disappear from the blood because of antibody mediated phagocytosis, lysis, and agglutination, and then the fever falls. Then an antigenically distinct mutant arises in the infected individual, multiplies, and in 4-10 days reappears in the blood and there is another febrile attack. The immune system is stimulated and responds by conquering the new antigenic variant, but the cycle continues. There may be up to 10 febrile episodes before final recovery. With each attack, a new antigenic variant of the bacterium appears and a new set of antibodies is formed in the host." This bacterium can change its antigenic signature during the course of an infection in a single host.[1437,2544] Antigenic variation[1736] usually results from site-specific inversions or gene conversions or gene rearrangements in the DNA of the microbes. Antigenic variation is also found in *Plasmodium*,[1740,1741] in trypanosomes that can switch between the transcription of one of an estimated 1000 variant surface glycoprotein genes,[1750] and in other parasites.[1742]

Many pathogenic bacteria exist in nature as multiple antigenic types or serotypes, meaning that they are variant strains of the same pathogenic species.[1437] For example, there are over 1800 known serotypes of *Salmonella typhimurium* based on differences in cell wall (O) antigens or flagellar (H) antigens.[1735] There are more than 80 different antigenic types of *Streptococcus pyogenes* based on M-proteins on the cell surface,[1734] and over 100 strains of *Streptococcus pneumoniae* depending on their capsular polysaccharide antigens. Based on minor differences in surface structure chemistry there are multiple serotypes of *Vibrio cholerae*, *Staphylococcus aureus*, *Escherichia coli*, *Neisseria gonorrhoeae*, and an assortment of other bacterial pathogens. Antigenic variation is prevalent among pathogenic viruses as well.

Neisseria gonorrhoeae can change fimbral antigens during the course of an infection.[1437] During initial stages of an infection, adherence to epithelial cells of the cervix or urethra is mediated by pili (fibriae). Equally efficient attachment to phagocytes would be undesirable. Rapid switching on and off of the genes controlling pili is therefore necessary at different stages of the infection, and *N. gonorrhoeae* is capable of undergoing this type of "pili switching" or phase variation.[1732,1733] Genetically controlled changes in outer membrane proteins also occur in the course of an infection. This finely controlled expression of the genes for pili and surface proteins changes the adherence pattern to different host cells, increases resistance to cervical proteases, increases resistance to phagocytosis and immune lysis, and is presumably necessary for successful infection.[1437]

Another mode of evasion is available to nanorobots resident in locations where components of the immune system cannot easily reach. Some pathogens persist on the luminal surfaces of the gastrointestinal tract, the urinary tract, the oral cavity, or in the lumen of salivary gland, the mammary gland, or kidney tubule.[1437] If there is no host cell destruction, the pathogen may avoid inducing an inflammatory response because sensitized lymphocytes or circulating antibodies cannot reach the site to eliminate the infection. Secretory IgA could react with surface antigens on bacterial cells, but the complement sequence would be unlikely to be activated and the cells would not be destroyed.[1437]

There are at least two other immunological evasion strategies employed by microbial pathogens or tumor cells. However, these strategies may be inappropriate or inefficient for medical nanorobots, as explained below:

1. *Decoys*. The first method is to release surface antigens in soluble form into the surrounding tissue, which can "mop up" antibody before it reaches the bacterial surface. The use of soluble receptors as decoys by the Shope virus[2352] and by the poxviruses[2353-2355] is well known. As another example, soluble bacterial cell wall components are powerful antigens and complement activators that contribute in a major way to the pathology observed in meningitis and pneumonia.[1437] Protein A is produced by *S. aureus* and is normally bound to the staphylococcal cell surface, but may also be released in a soluble form which can then bind to the Fc region of IgG, thus agglutinating and partially inactivating the IgG.[1437] Malignant tumor cells can release large amounts of MIC, a major histocompatibility class I homolog, which apparently downregulates the NKG2D receptor found on most natural killer cells (NKC) and impairs the action of tumor-specific effector T cells.[5684]

2. *Enzymes*. The second method is to produce enzymes that destroy antibodies. For instance, body surface-dwelling bacteria[1738] such as *Neisseria gonorrhoeae*, *N. meningitidis*, *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *S. mutans* produce IgA proteases that inactivate secretory IgA on mucosal surfaces by cleaving the molecule at the hinge region, detaching the Fc region of the immunoglobulin.[1437,1760] *Candida* yeasts display similar activity.[1739]

If employed by medical nanorobots, both decoy and enzyme methods would require either onboard storage or manufacturing of protein molecules, thus adding to device complexity. These strategies would also require emissions of active biomolecules into the tissues, an inherently inferior and possibly more dangerous approach compared to methods that involve only surface modifications of the nanodevice.

Immune evasion is much simpler for medical nanorobots once they are inside a cell, since activation of intracellular class II molecules by engineered surfaces is unlikely. A similar trick is already used by many types of microorganisms. In the bacterial world,[1605] macrophages infected with *Brucella* (a coccobacillus), *Mycobacterium leprae*, or *Listeria* (a soil saprophyte) support bacterial growth while offering protection from immune responses.[1437] Other intracellular pathogens such as *Yersinia* (etiologic agent of the plague of the Middle Ages) and *Shigella* are residents of cells other than phagocytes or other antigen-presenting cells, so their antigens are not displayed on the surface of the infected cell.[1437] *Chlamydia pneumoniae* can be found inside monocytes[1748] and white blood cells.[1749] Benjamini et al[1760] point out that microbes capable of intracellular survival use several strategies to avoid being killed after phagocytosis: *M. tuberculosis* and *Chlamydia* block the fusion of lysosomes with the phagocytic vacuole; *H. capsulatum* interferes with acidification of the phagolysosomal vacuole; *Listeria monocytogenes* produces bacterial products that allow it to escape from the phagolysosomal vacuole to the cell cytoplasm (a more nutritionally favorable niche); *Shigella flexneri* apparently triggers apoptotic death of the phagocytic cell; and *Toxoplasma gondii* generates its own vacuole to remain isolated from host lysosomes and thus avoids triggering recognition of infected cells by the immune system.

Among the viral pathogens, herpes simplex virus can interfere with immune system recognition of infected cells through a mechanism that inhibits MHC class I molecule presentation on the infected cell and blocks its interaction with virally derived peptides.[1760]

Other techniques of immune evasion[2546] employed by viruses include: (1) interference with trafficking along the endocytic pathway; (2) interference with class I MHC biosynthesis in the ER (endoplasmic reticulum); (3) interference with cytosolic proteolysis of viral antigen; (4) diversion of the ER-targeted peptide transporter system; (5) retention and destruction of class I MHC molecules; (6) modification of MHC function after their delivery to the cell surface; (7) blocking transcription of MHC class II proteins; (8) distribution of inhibitory NK receptors at the surface to prevent NK cells from destroying the virus-infected cell; (9) negative cytokine regulation; and even (10) inhibition of apoptosis.

Among the protozoans, intracellular parasites are protected from the immune response while their life cycle is completed inside a cell, resulting in the release of more parasites into the host system along with the death of the host cell. One example is *Plasmodium*, a protozoan parasite that infects red blood cells and causes malaria. This disease presents in a cyclical fashion,[1743] coinciding with the life cycle of millions of parasites that are all in the same life phase simultaneously. Another example is *Leishmania*, a flagellate protozoan parasite that hides inside macrophages — the macrophage is unable to recognize the parasite within itself and is thus unable to destroy it.[1744,1745] Other intracellular protozoan parasites include *Toxoplasma*, *Cryptosporidium*, and *Pneumocystis*, which can cause transient or life-threatening illness, some treatable and some not. These examples provide further biological analogs to the nanorobotic cytocarriage (Section 9.4.7) approach.

It is worth noting that the potential ability of nanorobots to hide from the immune system by using variants of the techniques employed by pathogens for similar purpose does not imply that pathogens will correspondingly be able to evade detection by medical nanorobots. It is certainly true that the surfaces of intracellular pathogens that can infect motile phagocytic cells (e.g., the tuberculosis *Mycobacterium* or the bacterium *Listeria*, both of which can reside inside macrophages[4588]) are not accessible for direct probing by the antigen sensors of extracellular diagnostic or therapeutic nanorobots. But cell surface markers will usually reveal such infection, so surveillance nanorobots can check for the presence of such markers and thus deny intracellular pathogens a secure hiding place inside human cells. For instance, the membrane surface of macrophages infected by *Mycobacterium microti* is antigenically different from that of uninfected macrophages.[5263] *Listeria*-derived peptides are found acting as integral membrane proteins in the plasma membrane of infected macrophages,[5264] and other *Listeria*-infected antigen-presenting cells display hsp60 on their plasma membranes only when infected.[5265] As another example, conserved invariable regions of the antigenic variation protein,[5266-5268] of the outer surface proteins,[5269-5271] or of other surface-exposed proteins[5272,5273] of *Borrelia* can be targeted for detection as reliable pathogenic signatures, by medical nanorobots.

15.2.4 General and Nonspecific Inflammation

Inflammation[1837] is a nonspecific physiological response to various forms of tissue damage including trauma (Chapter 24), infection (Chapter 23), intrusion of foreign material (Section 15.4.3.5, Chapter 24), local cell death (Section 10.4.1.1), or as an adjunct to immune system (Section 15.2.3.3), tissue remodeling (Chapter 24), or neoplastic responses.[234] If vascular tissue has also been disrupted, then the complex process of blood coagulation (Section 15.2.5) may be superimposed on the inflammatory response, and if an infection is involved, the complement system (Section 15.2.3.2) may be activated.

The four classical clinical signs of inflammation, first reported by the ancient Roman medical writer Cornelius Celsus (Section 1.2.3.1), are redness (rubor), swelling (tumor), pain (dolor), and heat (calor). The magnitude of these initial events is related to the intensity and extent of the inflammatory stimulus, with cells involved in the inflammatory response (Section 15.4.3.1) producing more than 100 chemical mediators.

Redness or erythema reflects a higher local concentration of red blood cells in the vicinity of the inflammatory stimulus.[234] This occurs because the first responses to such stimuli are (1) a rapid vasodilation of local capillaries (changing their local aspect ratio, leading to an increase in blood entry into the capillary beds), (2) an increase in the permeability of vascular endothelial cell linings (causing a loss of plasma through the capillary walls), and (3) a tendency for platelets and erythrocytes to become "sticky" (leading to slower flow and sludging). Vasodilation arises from the activation of Hageman factor (coagulation factor XII; Section 15.2.5) through contact with collagen or foreign proteins,[234] biomedical polymers,[1838] or with glass,[1839] kaolin particles,[1857] or certain other insoluble negatively charged surfaces.[1840-1845] The intermediate contact activation of kallikrein, a polypeptide, leads to conversion of a group of additional molecules to kinins.[1846] Kinins are a group of strong vasoactive mediators that can affect blood pressure (e.g., induce hypotension), elevate blood flow throughout the body, increase the permeability of small blood capillaries, and stimulate pain receptors (see below).

Swelling or edema (see also Section 15.5.2.2) occurs in the vicinity of the inflammatory stimulus because the increased permeability of the capillary endothelium allows fluid to move into the surrounding tissue bed.[234] Normally the endothelium is tight, permitting only a slow flow of water and small molecules into the surrounding tissues that is drained by local lymphatic vessels (Section 8.2.1.3). This slow flow maintains a constant tissue volume and a 10-15 mmHg pressure differential between the arteriole ends of capillaries and the external tissue bed.[234] With increased vascular permeability, water and molecules such as plasma proteins and locally activated kinins enter tissues, causing them to distend or swell unless promptly balanced by increased lymphatic drainage.* However, local lymphatics may be constricted or blocked by the original trauma, or occluded by cell fragments or nanorobots (Section 15.5.2.2), or hydraulically compressed, and the elevated concentration of plasma proteins raises local osmotic pressure, tending to hold the fluid in place. In extreme cases, a fluid movement is blocked leading to the so-called "compartment syndrome"[5493] (sometimes related to anatomic barriers such as fascial planes[5494]) which, if not promptly relieved, results in cell death and tissue necrosis.[234]

Pain occurs proximal to the inflammatory stimulus in part because the local edema may activate local deep pain receptors, or nociceptors. Inflammatory pain, is experienced by patients as a throbbing sensation repetitively pulsed by the peaks in systolic pressure.[234] Kinins also produce pain by acting directly on nerve endings to induce both acute and persistent pain — the kinin B_2 receptor predominates in acute inflammatory pain, the B_1 receptor in persistent inflammation.[1846] Kinins may also be involved in the hyperalgesia associated with peripheral and central inflammatory insults to the CNS, and there are many interactions between kinins and other inflammatory mediators known to be involved in the genesis or maintenance of the accompanying hyperalgesia.[1847] Prostaglandins,

** Bradykinin, an end product of contact system activation (Section 15.2.5), is a tenfold more potent vasodilator than histamine.*

cytokines, neuropeptides, and 5-HT have been implicated in the process of activation or sensitization of nociceptors. There is evidence that some of these mediators have powerful and complex interactions with kinins in the inflammatory pain process.[1847] As a possible analog with hard-material nanorobots, there is at least one report[2086] of pain possibly caused by numerous small insoluble crystals in the renal tubules. Accordingly, care must be taken in nanorobot mission design to forestall nanorobot crystallization — crystal-like aggregates[5627] or van der Waals solids[5628] comprised of multiple individual nanorobots — which might form under certain conditions of dehydration or pH, especially among nanorobots purposely created to form space-filling aggregates (Section 5.2.5).

Heat in tissues near the site of inflammation is usually attributed to increased blood flows and to local disturbances of fluid flow in the presence of increased cellular metabolic activity by increasing numbers of cells. Pyrogens known to cause systemic fever (Section 15.2.7) might also be generated locally either by tissue necrosis or as a result of activation by bacterial or viral toxins (e.g., endotoxin) in the presence of infection.[234]

These early events in the general inflammatory response are largely chemical in origin.[234] Shortly afterwards, the affected tissue is invaded by a series of cells such as neutrophils, macrophages and fibroblasts. These cells are responsible for the removal of dead tissue, phagocytosis of foreign matter, damage repair (though sometimes creating additional damage), and tissue remodeling. The inflammatory cell response to foreign particles, and possibly to medical nanorobots, is described in Section 15.4.3.5.

Could medical nanorobots or nanoorgan surfaces trigger general inflammation in the human body? One early experiment[1848] to determine the inflammatory effects of various implant substances placed subdermally into rat paws found that an injection of 2-10 mg/cm^3 (10- to 20-micron particles at 10^5-10^6 particles/cm^3) of natural diamond powder suspension caused a slight increase in volume of the treated paw relative to the control paw. However, the edematous effect subsided after 30-60 minutes at both concentrations of injected diamond powder that were tried. This swelling could have been wholly caused by mechanical trauma of the injection, not the diamond powder. Another experiment[1849] at the same laboratory found that intraarticulate injection of diamond powder was not phlogistic (i.e., no erythematous or edematous changes) in rabbit bone joints and produced no inflammation. Diamond particles are traditionally regarded as biologically inert and noninflammatory for neutrophils[222,605,633,639] and are typically used as experimental null controls.[1849] CVD (chemical vapor deposition) diamond[521] and DLC (diamond-like carbon) diamond[587] surfaces elicit minimal or no inflammatory response, and atomically smooth diamond may perform even better. Diamond particles are said to have little or no surface charge[633,640] but unmodified graphene (Section 2.3.2) surfaces readily acquire negative charges in aqueous suspension.[689,690] Adamantane-based compounds exist which enhance or inhibit the inflammatory response.[5563] Experiments are therefore needed to determine if negatively charged fullerenes or diamondoid substances can contact-activate Hageman factor or kallikrein and trigger an inflammation reaction. Carbon nanotubes and spherical fullerenes generally appear to be noninflammatory.[2599,5227]

The inflammatory properties of other possible nanorobot materials appear positive. For instance, vitreous carbon is mildly inflammatory[801] to inert.[798] Pyrolytic carbon is mildly inflammatory[801,902] to inert.[802] Graphite is minimally inflammatory,[820,822,823] though 1-micron particles apparently stimulate some nitric oxide production in rat cells, a possible indicator of inflammatory response.[5227] Carbon fiber elicits no significant tissue inflammation[224,840] or foreign body reaction.[848] Experiments with sapphire have generally found no serious inflammation in dental soft tissues[1006,1018,1021,1031] or bony tissues,[974,1029,1046] or only mild reactions.[1032] However, there are a few exceptions[1030,1068] including brief acute inflammatory response in special cases[1050,1055] so the noninflammatory character of sapphire has not yet been definitively established.

On the more negative side, carbon black is sometimes found to elicit moderate inflammatory responses in various soft tissues[852,856,887] and the lungs,[769,889-891] though there are some contrary reports.[857,893] The performance of Teflon is mixed,[1343] depending on the form of the material used and the type of tissue in which it is implanted (Section 15.3.4). Inflammatory tissue reactions range from none,[1168,1171,1173,1195,1344] to mild,[1185,1189,1220,1376] moderate,[1191,1277,1350,1368,1391] or severe.[900,901,1364,1366] Teflon activates fourfold more kallikrein than Hageman factor.[1850] Further details on these materials are in Chapter 15.3. Various natural crystalline substances can produce crystal-induced inflammation without any requirement for particle-bound opsonins.[2322] Examples include monosodium urate crystals in gout,[2322] silica crystals in pulmonary tissue disease,[2323] calcium oxalate[2324] and calcium pyrophosphate dihydrate[2325] crystals in kidney disease and arthritis, and hydroxyapatite and related basic calcium phosphates[2326] in various crystal deposition diseases.

Since the general inflammatory reaction is chemically mediated, it may be possible to employ nanorobot surface-deployed molecular sorting rotors to selectively absorb kinins or other soluble activation factors such as HMGB1,[5505] thus short-circuiting the inflammatory process. Active semaphores consisting of bound proteases such as gelatinase A could be deployed at the nanorobot surface to cleave and degrade monocyte chemoattractant molecules[2173] or other chemokines, suppressing the cellular inflammatory response. Conversely, key inflammatory inhibitors could be locally released by nanorobots. For instance, Hageman factor contact activation inhibitors such as the 22.5-kD endothelial cell-secreted protein HMG-I,[1851] surface-immobilized unfractionated heparin,[1852] and C1 inhibitor[1843] would probably require lower release dosages than for aspirin or steroids, and therapeutic blockade of factor XII activation has been demonstrated.[1853] Prekallikrein MAbs (antibodies) have been raised that inhibit prekallikrein activation by Hageman factor[1854] and direct inhibitors of tissue kallikrein are known.[1858] One plasma protease inhibitor strongly inhibits both Hageman factor and kallikrein activation.[1855] Diclofenac sodium is a well-known nonsteroidal anti-inflammatory agent (NSAID) that competes with arachidonic acid for binding to cyclo-oxygenase, resulting in decreased formation of prostaglandins.[5564] A variety of antinociceptive agents have long been known.[5814-5819] The multivalent guanylhydrazone CNI-1493 inhibits macrophage activation, suppressing the acute inflammation reaction.[2593-2595] As yet another example, platelet activating factor (PAF) is a cytokine mediator of immediate hypersensitivity which produces inflammation. PAF is produced by many different kinds of stimulated cells such as basophils, endothelial cells, macrophages, monocytes, and neutrophils. It is 100-10,000 times more vasoactive than histamine and aggregates platelets at concentrations as low as 0.01 pmol/cm^3.[2003] Various PAF antagonists[2059-2062] and inhibitors[2062-2065] are known. These or related inhibitory molecules, if released or surface-displayed by medical nanorobots, may be useful in circumventing a general inflammatory response.

There is also a well-known nonspecific inflammatory response[5826] that often, though not always,[5827] causes[5828] or accompanies[5829] mechanical injury or irritation. For example, angiogenesis may be

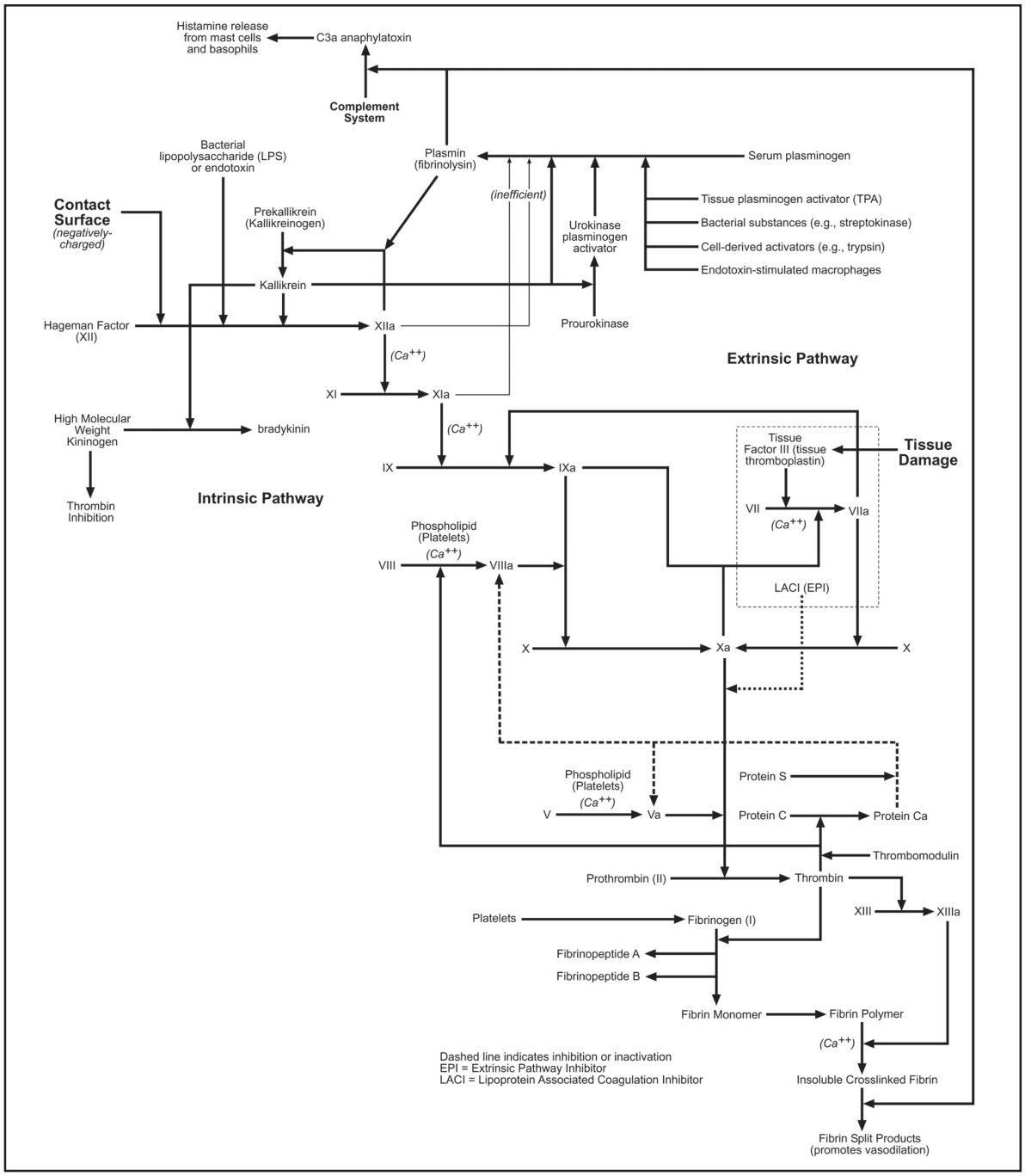

Fig. 15.10. The intrinsic and extrinsic coagulation pathways, with links to the kinin and complement systems (modified and redrawn from Duncan[1856], Schmaier[2321], and Trowbridge and Emiling[2331]).

induced by nonspecific inflammatory response to transmyocardial mechanical revascularization[5830] or needle puncture mechanical injury;[5831] nonspecific corneal inflammation has been reported in one case following a laser keratomileusis procedure;[5832] incision of the skin during vascular surgery can induce local nonspecific cellular inflammation;[5833] and inhalation of respirable fractions of fibrous glass particles by rats can produce a nonspecific inflammatory (macrophage) response similar to the effects of inhaling inert dusts.[5834] The possible induction of a nonspecific inflammatory response by properly designed and operated active mechanical surface components (e.g., sorting rotors, manipulatory appendages) of medical nanorobots seems avoidable but is an interesting issue that should be investigated further.

15.2.5 Coagulation and Thrombogenicity

Blood coagulation involves a complex series of reactions in which various proteins are enzymatically activated in a sequential manner, transforming liquid blood into a gel-like mass which is then stabilized to form a thrombus (clot) consisting of platelets, fibrin, and red cells. Mechanical blockage by fibrinogen clots helps prevent the spread of microbial invaders. The series of reactions (Figure 15.10) is classically divided into two pathways — extrinsic and intrinsic —

involving more than a dozen factors, that converge on a single common final pathway resulting in clot formation.[234,1753,1856,1859-1863]

The extrinsic pathway is initiated at the site of tissue injury with the release of tissue factor (factor III or tissue thromboplastin)[1864] which is found on the surfaces of many extravascular cells. In the presence of Ca^{++} ion, Factor III activates factor VII to VIIa which then activates factor X[1865-1867] to Xa, initiating the common final pathway.

The intrinsic pathway is initiated by activation of the contact factors by a negatively charged surface[1840-1845] — e.g., tissue material such as collagen on the exposed surface of a blood vessel, in vivo,[234] or glass[1839] or particulate material such as kaolin[1857] or urate crystals,[2327,2329] in vitro. The intrinsic pathway begins with human factor XII (FXII or Hageman factor), a serine protease produced by the liver that circulates in plasma as an 80-kD single-chain inactive zymogen. The zymogen is activated via (1) interaction with negatively charged surfaces, (2) bacterial LPS,[2332] or (3) via proteolytic cleavage by kallikrein (produced from prekallikrein by plasma kininogen[1860,2320,2321]). After this activation, the zymogen is proteolyzed by the kallikrein into a two-chain active protease, activated FXII (FXIIa).[1868] FXIIa can activate several plasma cascade systems[1853] including the contact system,[1843,1869-1871] fibrinolysis, and the complement system (Section 15.2.3.2) as well as the intrinsic pathway. FXIIa attacks prekallikrein to generate more kallikrein, setting up a positive feedback (amplification) control loop. FXIIa also activates contact factor XI to XIa in the presence of Ca^{++}, and the additional kallikrein releases bradykinin (a polypeptide with potent vasodilator and pain-producing action) from kininogen. Factor XIa, again in the presence either of Ca^{++} or of factor VIIa from the extrinsic system, activates factor IX to yield the serine protease factor IXa. Factor IXa then cleaves a bond in factor X[1865-1867] to produce the 2-chain serine protease, factor Xa, in the tenase complex (VIIIa, IXa, X and Ca^{++}) on the surface of activated platelets, initiating the common final pathway.

In the common final pathway, factor V[1872-1874] is activated to factor Va in the presence of Ca^{++} by trace amounts of thrombin.[1875-1878] Factor Va then interacts with Xa and platelet anionic phospholipids on the surface of activated platelets to convert prothrombin to thrombin, a serine protease of the trypsin family. This more abundant thrombin produces more Va from V and converts VIII to VIIIa, XI to XIa, and XIII to XIIIa. The last step in the sequence is the proteolytic cleavage of fibrinogen by thrombin (a 34 kD, ~4.6 nm diameter roughly spherical molecule[1879]), leading to the release of two fibrinopeptides, A and B, and the production of fibrin monomer. The fibrin monomers are polymerized and crosslinked by activated factor XIIIa in the presence of Ca^{++}, producing a stable insoluble polymer and a clot. After the clot has formed, it can later be dissolved during fibrinolysis: inactive plasminogen (90 kD) is cleavage-activated by tissue plasminogen activator (tPA) or urokinase to release a serine protease, plasmin, which can cleave the fibrin polymer.

For coagulation to occur, platelets must undergo adhesion and activation.[6043] The adhesion of platelets to exposed collagen in injured blood vessels is mediated by a bridging molecule called von Willebrand's factor[1880] that is secreted by endothelial cells into plasma. This prevents platelets from detaching under the high shearing stresses developed near vessel walls. The activation of normally quiescent platelets is a complex phenomenon that includes changes in cell shape, increased movement, aggregation, and release of the contents of their granules containing nucleotidyl phosphates, serotonin,[1881] various factors, enzymes and plasma proteins. The most potent activator of platelets in vivo is thrombin.[1882] Thrombin interacts with a receptor on the platelet plasma membrane, followed by transmembrane signaling and subsequent activation of the cell. Collagen[1883] is the other most important platelet activator. ADP can stimulate aggregation but not granule release.

In principle, the blood-contacting surfaces of a nanoorgan, or of nanorobots[22] in sufficient bloodstream numbers and concentrations, could activate platelets or either of the two coagulation pathways. That is, a poorly-chosen nanodevice exterior exhibiting negatively charged surfaces (Section 15.5.6.2) could contact-activate the intrinsic pathway, or careless mechanical actions by in vivo nanodevices could cause tissue injury to extravascular cells sufficient to invoke the extrinsic pathway. Careful choices of materials and of allowable mechanical motions (Chapter 15.5) should reduce or eliminate inherent nanodevice thrombogenicity and red cell hemolysis (Section 15.5.5.1.1). The fact that natural endothelium is nonthrombogenic[5961] provides an existence proof that such surfaces can exist, and strongly suggests that it should be possible to bioengineer[5962] or nanoengineer such surfaces from artificial materials, including active components providing metered emissions of useful antithrombogenic mediators;[5963] marrying natural endothelium to artificial surfaces,[5964] or "endothelialization," is well-known in vascular grafting.[5965-5971]

For example, DLC diamond-coated stents,[626,628,4723] heart valves[612] and other blood-contacting LVAD (left ventricular assist device) surfaces[596,613,1680] and substrates[597,660,4726,4730] generally show reduced thrombogenicity and weak or no platelet activation.[660,4726] Pyrolytic carbon (LTIC) may be somewhat thrombogenic during brief exposures to blood.[814] But LTIC is considered a fairly nonthrombogenic material (with relatively low platelet adherence[1680]) for long-term exposures to blood[808] such as in heart valves,[813] especially if very pure.[908] Fullerene thrombogenicity is unknown, though several forms of graphite are somewhat thrombogenic.[819,822] Carbon composites show at least short-term thromboresistance,[829] though with some surface accumulation of platelets.[830] Carbon black particles can produce prompt thrombocytopenia[875,884] along with cerebral thromboemboli,[884] possibly due to uncontrolled surface chemisorption effects. Platelets adhere less readily to Teflon after longer exposures[1202,1326] but their reactivity may be enhanced,[1159] which suggests that bulk Teflon is thrombogenic.[1192,1195,1317,1326] There is also contrary evidence,[1192,1209] possibly due to the many different forms of the material in use. Albumin-bound Teflon[1328,1330] and low-roughness surfaces[1315] may be moderately thromboresistant, but Teflon prostheses,[1370] catheters,[1375] and tubes[1189] have produced significant thromboses. Sapphire (alumina ceramic) has low thrombogenicity[1058-1060] and both platelet adhesion[977] and activation[1060] are low. Hemolysis (Section 15.5.5.1.1) is near-zero for diamond,[643,660,4726] graphite,[643] and alumina[643] powders, though Teflon patches used to repair atrial septum defects in the 1970s were sometimes mechanically hemolytic.[1347,1348]

Future experiments must determine if ordinary diamondoid surfaces will have to be supplemented with additional antithrombogenic coatings in order to achieve medical nanorobot mission objectives. If such coatings are required, one simple possibility is surface-immobilized heparin, a ~15 kD straight-chain anionic (acidic) mucopolysaccharide (glycosaminoglycan) that forms polymers of various lengths. Heparin, first discovered in 1916,[2364] is produced naturally by human liver mast cells and basophil leukocytes. It inhibits coagulation primarily by enhancing about ~1000 times the ability of antithrombin to inactivate a number of coagulation enzymes, including thrombin and activated factors X, XII, XI, and IX.[5489] Nanorobot exteriors could be "heparinized"[1884-1891]] and thereby rendered thromboresistant by immobilized heparin on

all blood-contacting surfaces at ~monolayer surface concentrations (e.g., 7-10 pmol/cm^2).[1891] Cellulose membranes coated with 3.6 pmol/cm^2 of endothelial-cell-surface heparin sulfate show complete inhibition of platelet adhesion.[1892] Albumin-heparin conjugate coated surfaces also display anticoagulant activity[1893] — pre-adhered endothelial cells proliferating on this coating significantly reduce the number of platelets which subsequently adhere to the surface, and other immobilized heparin conjugates have also given promising results.[1894] Unfortunately, heparin can have undesirable side effects such as binding with platelet factor 4, which then induces associated antibody production leading to thrombocytopenia,[2366,2367] so a synthetic heparin-like analog may need to be engineered with properties similar to low molecular weight heparin (e.g., enoxiparin[5495]) which decreases risk[5489] of HITT (heparin-induced thrombosis) syndrome.[5496] Coatings of hydrophilic acrylic copolymers with salicylic acid residues have also given good antithrombogenic behavior in animal studies,[1895] and hirudin-thrombin complex adsorbed on glass bead surface did not stimulate fibrinogen activation.[1896] Polyethylene electret film has even been studied for its athrombogenic properties.[1897]

If satisfactory passive nonthrombogenic surfaces cannot be found, nanorobots might employ any of at least four active strategies to prevent iatrogenic coagulation:

1. *Local Factor Depletion*. Factor X (56 kD) and factor V (330 kD) are the only two coagulation factors whose removal would interrupt both intrinsic and extrinsic pathways prior to the deposition of fibrin. Conveniently, these two factors have among the lowest blood concentrations of any of the factors — 0.005 mg/cm^3 (~50 molecules/micron^3) and 0.005-0.012 mg/cm^3 (9-20 molecules/micron^3), respectively (Appendix B), though factor X is the preferred target because factor V is also present in platelets. The diffusion limit of 56 kD molecules having diffusion coefficient ~8 x 10^{-11} m^2/sec (Table 3.3), if present at a concentration of ~10 molecules/micron^3, is ~10^4 molecules/sec delivered to the surface of a spherical nanorobot 1 micron in radius (Section 3.2.2). Nanorobot surface-deployed sorting rotors (Section 3.4.2) could selectively deplete factors X and V from serum at the rate of ~10 molecules/sec-rotor (Section 4.2.3), eliminating coagulability in a hematologically isolated local environment or greatly reducing coagulability if fresh blood is continuously replenishing the factor supply. Interestingly, an experiment using gold-coated polyurethane film chemisorbed with any of three different peptides found that the film acted as a thrombin scavenger, absorbing thrombin with high affinity and selectively removing it from plasma,[1898] a crude analog of the more sophisticated procedure described above.

2. *Global Factor Depletion*. Comprehensive management of the entire bloodstream inventory of coagulation factor molecules with whole-body real-time control also appears feasible nanorobotically, unlike contemporary heparin or warfarin anti-coagulation agents. There are ~10^{17} molecules each of factor X and factor V present in free form in the whole blood volume.* A population of 10^{12} bloodstream-resident 10-micron^3 nanorobots each having 10^4 sorting rotors on its exterior surface would require ~10 sec to remove ~90% of the entire serum inventory of either factor. (The removal rate is restricted by the maximum diffusion limit.) Each molecule would receive some minor chemical modification that inactivates it before it is released back into solution, to preclude the need for onboard storage. Prothrombin (72 kD, ~800 molecules/micron^3 in serum; Appendix B) could also be selectively depleted from serum, either locally or globally, before it can be cleaved to make activated thrombin. Even thrombin itself (34 kD, ~0.3 molecules/micron^3 basal[1899] to ~700-900 molecules/micron^3 thrombotic[1900]) could be nanorobotically depleted, chemically modified, and then released. Note that this method is unsuitable if the patient is bleeding and requires prompt hemostasis, except possibly for therapeutic nanorobots deployed in conjunction with clottocytes[22] (Chapter 24). Factor depletion seems most appropriate as a temporary measure to avoid nanorobot-induced thrombogenesis in hematologically intact patients.

3. *Inhibitor Release*. Instead of depleting coagulation factors, nanorobots could release coagulation inhibitors[2318,2319] during the nanomedical mission, either locally or globally, and then retrieve these molecules before exiting the body. The simplest approach is to inhibit thrombin, the cornerstone molecule of the coagulation cascade. There are four naturally occurring thrombin inhibitors found in normal plasma[1753] — antithrombin III (potentiated by acidic proteoglycans such as heparin), α_2-macroglobulin, heparin cofactor II, and α_1-antitrypsin (α_1-antiproteinase). Various other thrombin inhibitors are also known[1907-1910,1914-1920] including most especially the hirudins.[1909-1913] There are a number of factor X inhibitors, including the coumarin drugs (e.g., warfarin[1935-1937]), low-molecular-weight (4-6.5 kD) heparins[1901-1903] such as a heparin pentasaccharide with purely anti-factor Xa activity,[1904,1905] and vast numbers of other alternatives[1921-1935,2318,2319] including heparin mimetics[2365] that avoid heparin's unwanted side effects. For example, synthetic factor Xa inhibitor FX-2212 inhibits Xa activity by 50% at a serum concentration of 272 nM (164 molecules/micron^3) in vitro.[1927] Both indirect[1938,1939] and direct[1940-1949] inhibitors of factor V or Va have been reported,[1950] and prothrombin activation inhibitors are known.[1951-1957] Inhibitory monoclonal antibodies[3962] have also been raised against several of the coagulation proteins.

   Nanorobots could also release any of a number of platelet inhibitors to prevent coagulation. Platelet adhesion inhibitors are well known.[1958-1961,1968] Persantine,[382] prostacyclin,[1962] ibuprofen,[1962] and even nitric oxide[1963] have a demonstrable effect on platelet deposition. Platelets can be prevented from adhering using an RGD (Arg-Gly-Asp) tripeptide-containing peptide that acts as an antagonist for the fibrinogen receptor on platelet surfaces,[1964,1965] e.g., when administered at ~0.6 ng/sec per cm^3 of blood in live dogs.[1964] Platelet activation inhibitors are also well known[1966-1969] and include nitric oxide,[1970] prostacyclin,[1971] kininogens,[2321] and artificial peptides.[1972] Platelet degranulation inhibitors have been investigated.[1973-1978] Platelet aggregation inhibitors include kininogens[2321] and a wide

** The presence of Ca^{++} ion is a crucial ingredient in at least six enzymatic steps of the coagulation cascade. Reducing Ca^{++} to minimal levels near the nanorobot would effectively prevent coagulation in the local vicinity, or greatly reduce it if there is exogenous replenishment. The normal concentration of serum or extracellular Ca^{++} is quite high compared to coagulation factors, ~10^6 ions/micron^3 (Section 10.4.2.1). Still, 10^4 surface-resident Ca^{++} sorting rotors per nanorobot could remove ~10^{10} ions/sec (Section 3.4.2) from the local environment, thus depleting the nearest 10,000 micron^3 of plasma of all Ca^{++} ions. Those 10^{10} ions could then be stored in ~5% of the internal volume of a 10-micron^3 nanorobot. A bloodstream population of ~0.5 trillion of such nanorobots could reduce serum Ca^{++} concentration to <1% of normal in ~1 sec. If chelated (e.g., citrated) and released, the Ca^{++} would be temporarily unavailable to the coagulation cascade because the ion is tightly bound, although citrate is rapidly metabolized by the body, freeing the Ca^{++}. J. Rootenberg cautions that mission design should include analysis of whether these local actions might induce trans-cellular stasis reactions. R. Bradbury notes that chelating serum Ca^{++} would likely disrupt many biological processes, and might even induce release of mitochondrial Ca^{++} stores; use of EGTA might provide longer-term chemical sequestration of Ca^{++}.*

range of anti-aggregating drugs[1968,1979-1985] such as aspirin,[1986] clopidogrel,[1987] ticlopidine,[1988,1989] crotalin (inhibitory dose ~10^{-6} gm/cm^3 or ~100 molecules/micron^3 in mouse serum[1990]), adamantane derivatives,[5572] and potent natural aggregation inhibitors such as prostacyclin.[1991] One potential difficulty with this approach is that most of the enzyme cascade reactions take place in complexes on surfaces, and the spatial arrangement of clotting factors[1992] may prevent the inactivation of factors by nanorobot-released inhibitors, proteolytic enzymes, or specific antibodies unless those molecules are applied locally. (A. Kumar notes that global neutralization of clotting factors could increase the risk of petechiae and microbleeds for the duration of the nanorobotic mission, possibly producing further complications for the patient such as loss of blood volume or edema.)

4. *Regulatory Control*. The coagulation system is a complicated cascade of enzymatic reactions. Feedback mechanisms provide a delicate balance of activation and inhibition at each point in the cascade. Fibrin clots are constantly being laid down and dissolved in a state of dynamic equilibrium. Medical nanorobots may cautiously intervene in, and possibly manipulate, this dynamic control process. For example, protein C and protein S are two vitamin K-dependent coagulation proteins that provide a vital control mechanism in the cascade. Protein C is activated to Ca (activated protein C or APC) by thrombin (with thrombomodulin). But then this activated protein Ca (with cofactor protein S) inactivates the activated factors Va and VIIIa by proteolytic degradation,[1993,1994] which in turn inhibits the formation of thrombin via factor Xa. Protein S is itself cleaved and inactivated by factor Xa[1995] and has Ca-independent anticoagulant activity,[1999] and of course there is also a protein C inhibitor.[2000] A deficiency of either C or S is associated with venous thromboembolism. It is possible that an artificial surplus of protein Ca[2001,2002] and protein S could significantly brake the coagulation process. (Natural protein Ca circulates at 3-5 mg/liter[1996] or ~30 molecules/micron^3 in human blood with a half-life of ~1000 sec.[1997]) Similarly, a factor XIIa inhibitor[1998] might inhibit the intrinsic pathway from the top; tissue pathway factor inhibitor (TPFI) might interrupt the extrinsic pathway in some instances;[1864,1922] and so forth. The medical nanorobot designer should verify that no chemical substance displayed or emitted by the nanorobot will mimic the structure or activity of natural thrombotic stimulators or key coagulation factors such as tissue thromboplastin, factor Xa, or thrombin.

The possible risk of nanorobot-induced bleeding is discussed in Section 15.6.2.

15.2.6 Allergic and Other Sensitivity Reactions

This Section briefly considers possible unwanted reactions that might be triggered by the presence of medical nanorobots or nanodevices inside the human body, including allergic hypersensitivity (Section 15.2.6.1), "sternutation" or sneezing (Section 15.2.6.2), nausea and vomiting (Section 15.2.6.3), and shock (Section 15.2.6.4).

15.2.6.1 Allergic Reactions (Hypersensitivity)

An allergic reaction or "hypersensitivity" is the most common disorder of immunity, affecting ~20% of the U.S. population. This reaction is an acquired and abnormal immune system response to a substance, called an allergen, that normally does not cause a reaction. An allergy requires an initial exposure to an allergen, which produces sensitization to it. Subsequent contact with the allergen then results in a broad range of inflammatory responses. Common allergic conditions or symptoms include eczema or atopic* dermatitis, allergic rhinitis, bronchial asthma, urticaria (hives) and food allergy. Allergens may be introduced by skin contact (e.g., cosmetics, jewelry), ingestion (e.g., food), inhalation (e.g., pollen), or injection (e.g., drugs). Most allergic reactions are mediated by IgE antibodies (Section 15.2.3.3). Hypersensitivity reactions may be trivial, resulting in a rash, or serious, causing potentially lethal anaphylactic shock. Could nanorobots become allergens and provoke an allergic reaction?

Allergic reactions are usually classified by the type of tissue damage that they cause. Some allergic reactions produce more than one type of tissue damage, and other reactions involve antigen-specific lymphocytes rather than antibodies. The four recognized types of allergic reaction are:

Type I: Anaphylaxis. Anaphylaxis is the most extreme systemic form of immediate-type hypersensitivity in which the antigen-antibody complex binds to mast cell and basophils, causing their degranulation and release of histamine, leukotrienes and prostaglandins responsible for hypotension, bronchoconstriction and edema.[5489] Anaphylaxis occurs when a specific allergen combines and cross-links IgE** affixed to basophils in the circulation and to mast cells in the tissues to induce a major mast cell response,[2052] as for instance in the reaction to ragweed pollen, or in allergic bronchial asthma. The primary function of mast cells — which reside in connective tissue just below epithelial surfaces, in serous cavities, and around blood vessels — is to synthesize and store histamine (a strong vasodilator and bronchoconstrictor), serotonin, bradykinin, and other mediators of inflammation such as neutrophil and eosinophil chemotactic factors, in intracellular granules. During the mast cell response, the cells release these stored substances. This causes flushing, urticaria, asthma, angioedema, change in smooth muscle tone, increased secretion of thickened mucus, lower blood pressure, changes in cardiac contractility, and local recruitment of leukocytes. Major systemic reactions can be life-threatening and may involve vomiting, severe bronchial obstruction and vasodilation, increased venule permeability and diminished blood volume, laryngeal or pulmonary edema, and cyanosis. Another major systemic reaction is shock (i.e., circulatory collapse), a systemic response which is secondary to profound vasodilation and rapid decrease in systemic blood pressure. Shock can also involve a limited, localized reaction. For instance, complement-derived anaphylatoxins can stimulate intravascular neutrophil aggregation and embolization to the pulmonary microvasculature, where neutrophil products including elastase and free radicals may cause the condition of shock lung.[955] Symptoms begin within 2 hours of exposure to allergen. Clinical examples of IgE-mediated anaphylaxis include reactions to serum proteins, venoms and insect stings, enzymes, vaccines, allergen extracts, hormones, seminal plasma, foods, polysaccharides and drugs.[2052]

** An "atopic" allergy differs from normal hypersensitivity reaction in that there exists a genetic predisposition for the reaction in the patient's histocompatibility genes. Atopic diseases typically produce IgE antibodies to harmless inhalants such as pollens, molds, animal danders and dust mites. Hay fever and asthma (~20% of the population[2005]) are two of the most common inherited allergies.*

*** Non-IgE-mediated anaphylaxis-like reactions, called anaphylactoid reactions, may occur (1) by activation of complement (e.g., during transfusions in IgA-deficient patients), leading to generation of C3a and C5a anaphylatoxins (Section 15.2.3.2); (2) by arachidonate mediated pathways (e.g., aspirin or nonsteroidal anti-inflammatory agents); (3) by direct mast cell-releasing agents (e.g., opiates); or (4) by physical stimuli or exercise.[2052] Anaphylactoid reaction may occur at first exposure to an allergen, unlike anaphylaxis.*

Type II: Cytotoxic Reactions. These are antigen-antibody reactions mediated by IgG and IgM at cell surfaces that result in the lysis of blood cells (red cells, white cells, and platelets) due to the release of complement. Clinical examples include the body's reaction to transfusion with incompatible blood cells (producing hemolytic transfusion reaction with symptoms of fever, chills, headache, hypotension, and even vascular collapse in severe cases); erythroblastosis fetalis; and Goodpasture's syndrome.

Type III. Immune Complex Reactions. These are antigen-antibody reactions mediated by IgG and IgM in fluid spaces. The reactions produce toxic antigen-immunoglobulin complexes that circulate in the blood. There, the complexes cause damage by adhering to blood vessel walls and initiating an inflammatory response (vasculitis). Serum sickness, characterized by fever, joint and muscle pain, lymphadenopathy and urticaria, can occur in sensitized patients who are receiving penicillins, sulfonamides, or animal-derived antitoxins. Localized immune complex reactions (Arthus reactions) can damage organs, joints, and other structures.

Type IV. Delayed-Type Hypersensitivity (DTH) or Cell-Mediated Immunity (CMI) Reactions. These are reactions between antigens and sensitized antigen-specific T lymphocytes, not antibodies. The reaction subsequently releases inflammatory substances, toxic substances, and lymphokines that attract other white cells. Clinical examples include tuberculosis, transplant rejection, and contact dermatitis in response to common allergens such as rubber in elastic materials, chromium in leather, and nickel in costume jewelry (which alter skin protein self-antigens to create new foreign antigens).

As of 2002, a comprehensive picture of the precise characteristics of allergenic molecules[2009,5042,5043] had not yet emerged in the field of molecular "allergology".[5044] Most allergens are 15-40 kD acidic proteins or glycoproteins,[2006,2007] or other chemicals.[2008] Many of the known food allergens are homologous to pathogenesis-related (PR) proteins[2009] — proteins induced by pathogens, wounding, or certain environmental stresses. Many non-PR allergens[2009] belong to other protein families such as α-amylase and trypsin inhibitors from cereal seeds, profilins from fruits, vegetables and pollen,[2010] and proteases from fruits. Food allergens typically have molecular weights from 10-70 kD.[2011] These allergens induce the production of antigen-specific IgE and are stable molecules resistant to processing, cooking and digestion.[2011] Non-food allergens may cross react with food allergens.[2012,2013] For example, latex-allergic patients are also sensitive to a broad class of plant proteins called patatins found in potatoes and bananas.[2013]

Nonprotein "allergens" (a term usually reserved for IgE reactions) may include nickel,[2014-2018,2021-2026] chromium,[2022-2027] cobalt,[2022-2024,2033] gold,[2024,2030-2032] palladium ions,[2019-2021,2024] and other metals and metal-containing substances;[2015,2026-2029] acrylic compounds,[2034,2035] epoxies,[2036] hydrocarbons[824,2037] and Teflon implants;[1188] and a few mineral substances such as aluminum silicate,[2038] crystals of zirconium silicate and clay minerals,[2039] at least one tricalcium phosphate ceramic,[1048] and possibly silica dust[2040] (silica is a well-known antigenic adjuvant).* On the other hand, synthetic porous ceramic (Triosite),[2041,2042] at least one bioactive glass-ceramic,[2043] hydroxyapatite ceramic,[1048] alumina ceramic[1048,2028,2044] and graphite[824,2045] are considered nonallergenic. Ceramic coatings are used to eliminate metal allergies on implant surfaces,[2046,2047] and hypersensitivity to oral ceramic is reported only rarely.[2048-2051] Particles of carbon black can have a significant adjuvant effect on systemic specific IgE response to conventional protein allergens,[867] and a few rare cases have been reported of allergic reaction to India ink particles used in endoscopic colonic tattooing.[855] There is one report[5026] that intraperitoneal injection of Teflon particles in mice can have an adjuvant effect, elevating serum levels of allergen-specific antibodies IgE and IgG2a. There are no reports in the literature of allergenicity for diamond (cf. possible contact dermatitis by adamantane derivatives[5569]), sapphire, fullerenes, or other probable diamondoid nanorobot exterior materials. Such allergenicity appears unlikely, but experiments should be done to positively confirm this expectation. Intriguingly, the possibility of a purely crystallographic allergenic sensitivity is suggested by tests of cellular allergic reactions to zircon crystals, as assessed by variation in arachidonic acid metabolite production in mouse macrophages[2044] — the tests were negative for crystals of quadratic zircon but positive for crystals of monoclinic zircon.

Medical nanorobot designers must first attempt to ensure that no surface component (including any organic biocompatibility-related coatings) or chemical emission of a nanomedical device can serve as a human allergen, or can elicit any of the above four allergic reactions. If this cannot be reliably accomplished in all cases, other approaches may be available to eliminate the unwanted allergic response. For example, tryptases,[2053] the predominant proteins of human mast cells (~6-19 pg/cell[2053]), have been implicated as pathogenic mediators of allergic and inflammatory conditions, most notably asthma.[2054] Although tryptases are distinguished from other serine proteases in being resistant to most proteinaceous inhibitors,[2054] several classes of tryptase inhibitors have recently been found[2056-2058] which inhibit enzyme activity after enzyme release from cells. However, since the amount of tryptase that could be released from mast cells might overwhelm nanorobot-released tryptase inhibitors (because any free enzyme can activate many molecules of substrate), mast cell tryptase-release inhibitors[2055,5796-5800] that might reduce or even prevent enzyme release from mast cells might be more useful in the present context. In principle, these or similar inhibitors could be rapidly dispensed by medical nanorobots or secreted by dedicated internal nanorobotic organs, instantly quenching the allergic response.

The traditional treatment of choice for anaphylaxis is an injection of epinephrine (0.183 kD), a potent vasoconstrictor and sympathomimetic, in a therapeutic dose of ~6×10^{-8} gm/cm^3 or ~200 molecules/micron^3 in whole blood.[382,5497] One 0.3-mg whole-body dose (~10^{18} molecules) could be delivered in ~1 second by 3 billion 10-micron^3 bloodborne nanorobots each using only 1% of internal volume for drug storage and ~300 sorting rotors on the nanorobot exterior. Of course, epinephrine has severe systemic consequences and can cause cardiac arrest or a stroke if not properly monitored.

To prevent common symptoms of allergic rhinitis, the usual approach is to target histamine directly, perhaps using cetirizine,[2066] a fast-acting histamine-blocker drug, or any of a large number of other antihistamine H1 receptor antagonists that inhibit histamine release from mast cells and/or basophils, such as ambroxol,[2067] CGP 41251,[2068] chlorpheniramine maleate,[382] epinastine,[2069] loratadine,[2070,2071] or oxatomide.[2055] Of course, most antihistamine drugs have widely varying undesired or adverse side effects. Hence a superior approach may be to use nanorobotically-embedded molecular sorting rotors (Section 3.4.2) to rapidly absorb, chemically neutralize, and then release the primary inflammatory mediator molecules such as histamine, tryptase, serotonin, and so forth. For maximum effectiveness, rotor binding sites should ideally be more numerous and possess greater binding affinity than the natural mediator receptors, and the rotors should be positioned to intercept

** Most of these substances do not cause IgE reactions, most of the time. For instance, nickel allergy is usually contact dermatitis, a Type IV reaction that does not involve IgE.*

the mediators as close as possible to the site of their release. Even patients who are experiencing a strong allergic reaction have been found to have serum levels[2072] of only >1 ng/cm^3 of plasma histamine (0.111 kD, >5 molecules/micron^3) and >15 ng/cm^3 of total tryptase (144 kD, >0.08 molecule/micron^3), largely because of rapid degradation by the body when not bound to the intended natural receptors. Such small amounts may be handled relatively quickly by a modest number of bloodstream-resident medical nanorobots. One sorting rotor can transfer ~5 molecules/sec of histamine from a ~1 ng/cm^3 serum concentration (Section 3.4.2), so a single nanorobot with 10,000 surface rotors could clear ~1000 micron^3/sec of serum of ~99% of its histamine content. (Histamine is most plentiful in nasal secretions, ~2000-7000 ng/cm^3,[2073] but the rate of extraction from solution by sorting rotors can increase almost in direct proportion to solute concentration.)

15.2.6.2 Sternutogenesis

Could the presence of inhaled or perambulating medical nanorobots in the nasal passages induce sternutation (sneezing)? A sneeze involves dozens of muscles in the face, chest and abdomen, all operating in a correct sequence that has been hardwired in the brain and spinal cord.[2290,2291] The sequence is mediated by the trigeminal nerve, particularly the anterior ethmoidal, posterior nasal, and infraorbital nerve branches.[2292] Most of the branches of the trigeminal nerve end in the facial skin where they carry messages serving the sense of touch (including temperature and pain), but some branches end in the nasal mucosa just below the surface.[2290] The nasal mucosa is densely innervated by small-diameter myelinated sensory nerve fibers[2293] ending in receptors[2294] located in and under the epithelium.[2295,2296] Some nerve endings are chemically sensitive and respond to irritating odors to trigger a sneeze.[2290,2295] Other types of nerve ending respond to touch or mechanical stimulation. Irritation of the nasal passages excites nerve impulses that travel through the trigeminal ganglion to a set of neurons collectively known as the sneezing center in the lateral medulla,[2297] located in the lower brainstem (medulla oblongata). The sneeze reflex in humans occurs in two phases.[2298] During the nasal phase, the sneezing center sends impulses along the facial nerve back to the nasal passages and face, causing the nasal passages to secrete fluid and become congested, and the eyes to water. During the subsequent respiratory phase, the sneezing center sends impulses to respiratory muscles via the spinal cord, causing the characteristic deep inspiration and forceful expiration of air.[2299]

Many stimuli can trigger a sneeze,[2299] including nasal infections, allergies (e.g., pollens and molds), cold air and humidity, chemical irritants[2311] such as spices[2300] (mean level 0.15 mg/m^3)[2301] or ammonia,[2290] newspaper dust,[2302] 2- to 10-micron oil mists at 0.1-0.3 mg/m^3 (~10^6 particles/m^3),[2303] exposure to bright sunlight (autosomal-dominant photic sneeze reflex[2304] affecting 18-35% of the population[2305]), overeating, sexual excitement, hair pulling or eyebrow plucking, shivering, repetitive electrical stimulation,[2306,2307] catheter-delivered air puffs to the superior nasal meatus,[2308] or a needle inserted into the orbital cavity.[2309] Sneezing can be a purely allergic reaction, accompanied by histamine and neuropeptide release[2310-2312] that can be locally suppressed using drugs like NSAIDs or Azelastine.[2313] However, nanorobots should be designed to be chemically and allergenically inert, so the most likely source of nanorobot sternutatogenicity is mechanical stimulation (c.f., a nylon fiber applied to the nasal mucosa[2314]). The most likely source of such stimulation in a nanomedical context is the physical motions of nanorobots moving across the surfaces of the nasal passages.

Precise measurements of the threshold stimulus needed to activate nasal mechanosensors have not yet been reported. However, the minimum detectable skin pressure, which occurs on tongue and fingertip, is ~2000 N/m^2 (Section 9.5.2), and intranasal pressure during sneezing is ~600 N/m^2 in adults[2315] and ~700 N/m^2 in premature newborns.[2316] Mechanical stimulation of cat nasal membrane at 20 Hz with a peak-to-peak displacement of 500 microns evoked the sneeze reflex.[2317] Assuming the area compressibility modulus for this membrane is ~1 N/m (Section 9.4.3.2.1), the required displacement pressure was ~2000 N/m^2. Assuming ~1000 N/m^2 as the activation threshold for mechanically-stimulated sneezing (based on the aforementioned pressure values), and assuming the minimum value for mucus viscosity (Table 9.4), Eqn. 9.73 suggests that the viscous motive forces required to propel a spherical 1-micron diameter nanorobot through the mucus at a speed of ~1 cm/sec or slower (force <~1 nN, power <~10 pW power) should be insufficient to trigger the sneeze reflex. Thicker nasal mucus would demand slower locomotion to hold applied forces below the assumed threshold limit for sneezing, especially since nasal inflammation undoubtedly makes these reflexes more sensitive.[5821] These questions can be resolved by simple laboratory experiments.

15.2.6.3 Nauseogenesis and Emetogenesis

Can the mere presence of nanorobots in the human body provoke nausea or vomiting (emesis)?[2426-2433] Vomiting is one of the most complex motor functions performed by humans. Emesis is a sequential interaction between viscera, the central nervous system, and somatic muscles that results in the expulsion of intraluminal contents from the proximal small intestine and stomach.[2422] Nausea and the act of vomiting are controlled by a region in the medulla that coordinates the respiratory and vasomotor centers and the vagus nervous innervation of the gastrointestinal tract.[2421] This "vomiting center"[2424,2427] may be stimulated by four different sources of afferent input from:

1. afferent vagal nerve fibers, rich in serotonin 5-hydroxytryptamine ($5HT_3$) receptors, and splanchnic nerve fibers in the gastrointestinal viscera that may be stimulated by biliary distention, gastrointestinal distention, mucosal or peritoneal irritation, or infections.[2421] Noxious enteric contents initiate the emetic reflex through the activity of vagal and sympathetic afferent nerve fibers that reach to the brainstem.[2422] More specifically, vomiting can be induced (a) via irritation of the gastric mucosa by the alkaloid emetine in ipecac syrup,[2434] copper sulfate,[2435] mercury,[2436] lye,[2437] or bile reflux;[2438] (b) via gastrointestinal mucosal irritation by iron salts,[2439] various laxatives[2440] and pesticides,[2441] mechanical irritation[2442] or duodenal[2443] or urinary[2444,2445] obstruction, and by bile duct perforation;[2446] (c) via peritoneal irritation associated with post-anesthetic residual tissue stretching[2447] or colonic perforation,[2448] acute pancreatitis,[2449,2450] or various drugs and other chemicals;[2451-2453] or even (d) via coronary artery occlusion.[2433] Emetogenic mechanoreceptors and chemoreceptors have been found in the stomach, jejunum and ileum.[2433]

   Properly designed medical nanorobots should not externally display or emit nauseogenic or emetogenic molecules. Massive numbers of medical nanorobots simultaneously physically traversing or cooperatively manipulating the intestinal walls (Sections 8.2.3 and 15.5.1.4, Chapter 26) could in principle produce sufficient mechanical irritation or tissue stretching to elicit emetogenesis. However, esophageal and intestinal shear forces

of >~1 N/m^2 due to the normal passage of chyme or feces (Section 9.4.3.3) are not commonly nauseogenic. A cubic (~300 micron)^3 intestinal nanorobot applying ~100 nN of lateral towing force (similar in size and strength to an amoeba; Section 9.4.3.7) also applies ~1 N/m^2 shear force, which likewise should not induce emesis. Amebiasis involving 12- to 50-micron motile trophozoites in the large bowel produces vomiting only in cases of severe dysenteric colitis,[498] and it is not clear whether the cause of the vomiting is the number and movement of amoebae or some other factor. The presence and movements of tens of trillions (Section 8.5.1) of motile micron-sized commensal bacteria in the human colon is not normally nauseogenic.

2. the vestibular system, having fibers with high concentrations of histamine H_1 and muscarinic cholinergic receptors, which may be stimulated by motion,[2454,2455] sensory conflict,[2456] or infections.[2421,2422] Purposeful mechanical manipulations of the human vestibular (Section 7.4.6.2) or auditory (Section 7.4.6.3) sensory apparatuses by medical nanodevices could be nauseogenic or induce vertigo.[2464] These symptoms are unpleasant but not life-threatening. Nevertheless, nanorobot missions should be designed to avoid these outcomes or else the patient may require administration of the belladonna alkaloid scopolamine (a traditional prophylactic treatment for motion sickness[5498]) or other agents such as meclizine (an antihistamine with anticholinergic properties).[2422]

3. higher central nervous system centers, including disorders of the central nervous system (e.g., elevated intracranial pressure caused by tumors,[2457-2460] closed head injuries,[2461] migraine and epilepsy,[2461] or even intracranial amoebic invasions[2462]) or certain sights, smells, taste aversions, or emotional experiences that may induce vomiting.[2421] For example, patients receiving chemotherapy may develop vomiting in anticipation of chemotherapy; sedatives such as benzodiazepines are antiemetic for patients with anticipatory or psychogenic vomiting.[2421] Normally the presence of therapeutic nanorobots inside the human body will not be directly detectable by the human senses, but the in vivo administration of nanodevices might still elicit psychogenic emesis in worried patients who are anticipating receiving nanorobots (Chapter 17).

4. the chemoreceptor trigger zone (CTZ),[2423-2426] rich in receptors for serotonin 5-HT_3, dopamine D_2, histamine and opioids, and located outside the blood-brain barrier in the area postrema of the medulla, whose chemoreceptors may be stimulated[2421,2422,2463] by drugs and chemotherapeutic agents,[2464-2469] opioids and anesthetic agents,[2472] circulating toxins or other humoral agents, hepatic amoebic invasions,[2473] hypoxia,[2474] uremia,[2475] chlorine fumes,[2476] acidosis, and radiation therapy.[2425] Barring poorly planned releases of nauseogenic effluents, medical nanorobots should not activate the CTZ.

In the highly unlikely event that nanorobots and their missions cannot be designed to be completely non-nauseogenic, many antiemetics are available.[2469-2471] Antihistamines are weakly antiemetic for "vomiting center"-mediated emesis.[2421] Blockade by serotonin 5-HT_3 receptor antagonists (e.g., ondansetron[2477] and tropisetron[2467]), dopamine antagonists[2478,2479] (e.g., metoclopramide[2479]), and NK1[2480] antagonists is well known. Phenothiazines and related compounds specifically block CTZ-mediated vomiting.[2424]

Nausea is the conscious recognition of excitation of an area in the medulla associated with the vomiting center.[5489] The sensation of nausea apparently involves the cerebral cortex,[2430] and the "vomiting center" is actually a distributed control system[2428-2430] perhaps including a central pattern generator[2461,2481] comprised of several distinct neural clusters or pathways. So most efficiently, a small number of specialized nanorobots could be stationed within (1) the vomiting center located in the nucleus tractus solitarius,[2482] (2) the brain stem between the obex and the retrofacial nucleus,[2430] (3) the medullary midline,[2429] (4) the area postrema,[2483] (5) the parabrachial nucleus,[5909] and (6) certain higher brain centers.[2430] These precisely positioned specialized nanorobots could then directly control or completely extinguish all emesis-related neuron signal traffic by means previously described (Sections 4.8.6, 7.4.2.6, and 7.4.5.4), thus directly preventing nausea and vomiting.

15.2.6.4 Nanoid Shock

Could the presence of medical nanorobots inside the human body produce shock? Shock is a life-threatening medical emergency in which blood pressure is too low to sustain life, due to inadequate pumping action of the heart or excessive vasodilation.[361] Shock may be caused by a wide variety of conditions including dehydration, drug reaction, hemorrhage, infection, myocardial infarction, poisoning, or trauma. There appear to be only three general classes of shock response that could be directly triggered by medical nanorobots. These three responses may collectively be termed "nanoid shock":

1. *Anaphylactic Shock*. (See Section 15.2.6.1) Anaphylactic shock from complement activation (Section 15.2.3.2) is another possibility.

2. *Septic Shock*. Septic shock[2074-2076] is usually (though not always[2524]) caused by Gram-negative bacterial endotoxin (e.g., lipopolysaccharide or LPS) components of the cell wall that are released into the bloodstream when a microbe is destroyed or lysed. Endotoxins can activate Hageman factor, which can in turn activate the complement system, the bradykinin system (bradykinin release produces vasodilation, increased vascular permeability and blood volume depletion), the coagulation cascade, and the fibrinolytic system.[2077] Nanorobots with external surface-bound moieties or which emit chemical substances that have molecular homology with endotoxins (either of which can probably be avoided in a good nanomedical design) might elicit an analogous septic shock. The adverse effects of bacterial endotoxin are mediated by various active substances such as tumor necrosis factor (TNF) or cachectin, a cytokine produced by macrophages and other mononuclear cells (Section 15.2.7). If necessary, the nanorobot fleet could selectively absorb[2078] and neutralize those mediating substances, or release, say, TNF-specific antibodies,[2079] antagonists,[2080] inhibitors,[2081] decoys,[2084] or synthesis inhibitors[2082] to eliminate the risk of septic shock.

   For example, with minor additions, phagocytic nanorobots called microbivores[2762] (Chapter 23) could be used to combat toxemia, the distribution throughout the body of poisonous products of bacteria growing in a focal or local site, and other biochemical sequelae of sepsis. For instance, *E. coli*-induced septicemic shock in vervet monkeys occurred at 425 x 10^6 CFU/ml and LPS endotoxin rose from normal at 0.076 ng/ml to a maximum of 1.130 ng/ml blood concentration.[5499] In another study,

endotoxin levels during a Gram-negative bacterial infection rose from 0.2 to 2 ng/ml in pig blood.[5500] Eliminating a bloodstream concentration of ~2 ng/ml of ~8 kD LPS endotoxin[5501] would require the extraction and enzymatic digestion of ~8 x 10^{14} LPS molecules from the ~5400 cm^3 human blood compartment, a mere ~800 LPS molecules per nanorobot assuming a single terabot dose (10^{12} devices) of modified microbivores.

The high mortality associated with Gram-negative sepsis is due in large measure to the patient's reaction to LPS, which induces the production of cytokines such as IL-1β and IL-6 which leads to an uncontrolled inflammatory reaction resulting in tissue damage and organ failure.[5502] Small quantities (~ng/ml) of LPS are released by living and growing bacteria (see previous paragraph), but the killing of bacteria using traditional antibiotic regimens often liberates large quantities of additional LPS, potentially up to ~10^5 ng/ml.[5502] Such massive releases as occur with the use of antibiotics will not accompany the use of microbivores,[2762] because all bacterial components (including all cell-wall LPS) are internalized and fully digested into harmless nonantigenic molecules prior to discharge from the device. And of course nanorobots will themselves contain no LPS. Microbivores thus represent a complete antimicrobial therapy without increasing the risk of sepsis or septic shock. (Note that while Gram-positive organisms can also induce cytokine production, 100- to 1000-fold more Gram-positive bacteria are needed to induce the same concentration of cytokines as are induced by Gram-negative bacteria.[5502])

If the patient presents with a septic condition before the microbivores are introduced, a substantial preexisting concentration of inflammatory cytokines will likely be present and must be extracted from the blood in concert with the principal antibacterial microbivore treatment. Unwanted cytokine molecules may be rapidly and systemically extracted from the blood using a modest dose of respirocyte-class nanodevices,[3573] a combination-treatment approach previously suggested elsewhere.[2762,5503] Specifically, a 1-terabot intravenous dose of micron-size pharmacytes (Section 10.4.1.4, Chapter 19) each having ~10^5 cytokine-specific molecular sorting rotors and ~0.5 $micron^3$ of onboard storage capacity could reduce the blood concentration of ~20 kD IL-1β and IL-6 cytokines from LPS-elevated levels of ~100 ng/ml[5502] (~3 x 10^{-9} molecules/nm^3) down to normal serum levels of ~10 pg/ml[2163] (~3 x 10^{-13} molecules/nm^3) after only ~200 sec of diffusion-limited pumping, using just ~0.1% of the available onboard storage volume. (Extracting an additional ~10^5 ng/ml of LPS from the bloodstream would take a similar amount of time and would use ~100% of the available onboard storage volume.) Cytokines that have exited the circulation must be removed by other means.

3. *Mechanical Shock*. Traumatic shock may occur in cases of acute intestinal obstruction, crush injuries, perforation or rupture of viscera or blood vessels, pneumothorax, nerve injury due to contusion of highly sensitive parts (e.g., testicle, solar plexus, eye, urethra), gastrointestinal strangulation (e.g., hernias, intestinal intussusception or volvulus), or visceral torsion (e.g., of ovary, testicle).[2004] Traumatic shock toxin (a thrombogenic aminophospholipid) occurs only on the cytosolic layer of cell membranes and is liberated by cell destruction, causing disseminated intravascular coagulation.[2083] Such mechanical traumas should be rare in the context of individual nanorobot locomotion and manipulation activities in vivo, but mechanical shock could result from poorly-planned large-scale coordinated transtissue nanorobot fleet movements (Chapter 14), from vascular blockage due to nanorobotic-induced emboli caused by "traffic-jam" control-failure effects (Chapter 12), or from incautious nanosurgical techniques (Chapter 12). These causes should be avoided in medical nanorobot mission design.

15.2.7 Nanopyrexia

Human core temperature (Section 8.4.1.1) is tightly regulated through the preoptic nucleus of the anterior hypothalamus[2090] to a mean "set point" of 37°C with circadian variations around this mean rarely exceeding 0.6°C,[2091] although set point is lowered 0.5-1.0°C in mammals on calorie restriction diets.[5930-5932] An array of thermoregulatory mechanisms[2092] ensures that the hypothalamic thermal set point temperature is maintained to within a natural "load error" of 0.2-0.5°C.[2093] Thermal deviations exceeding the load error provoke a natural counteractive response to restore core temperature back to the set point.

Abnormal elevation of systemic body temperature (pyrexia) can occur in one of two ways: hyperthermia or fever.[2094]

In hyperthermia,[2095] thermal control mechanisms are overwhelmed, so that heat production exceeds heat dissipation. Hyperthermia may develop during periods of intense physical exertion (Section 6.5.2), dehydration, immersion in hot fluids (Section 8.4.1.2), or from waste heat thrown off by energy-consuming nanorobots in vivo (Sections 6.5.2-3). In each case the body's thermoregulatory mechanisms are fully engaged, attempting to cope with the departure from homeostasis. In some situations, thermoregulatory disorders such as heatstroke, hot flashes,[5357-5361] hypothalamic insult (caused by drugs, infection or tumor), malignant hyperthermia, or thyroid storm, can cause extreme pyrexia with temperature rising to 41.1°C or higher.[2096] Protein denaturation begins at ~42°C, and heating blood above 47°C rapidly produces visible damage to erythrocytes.[2097] Heat-damaged cells show morphologic changes, increases in osmotic and mechanical fragility, and are removed rapidly after reinjection into the circulation.[2098] Similarly, an increase of ~6.5-10°C in tooth pulp temperature for >30-45 seconds can permanently damage the pulp.[2099] If nanorobots are the cause of hyperthermia, it is because local or systemic thermogenic limits (Section 6.5.2) are being exceeded. Obeying these operational limits avoids the problem.

In fever, the second cause of pyrexia, the hypothalamic thermal set point is shifted higher by the action of circulating pyrogenic cytokines, causing intact peripheral mechanisms to conserve and generate heat until the body temperature increases to the elevated set point.[5489] Fever is a natural self-defense mechanism (produced by substrate cycling in skeletal muscle) intended to make the host less hospitable to microscopic invaders. The intact control mechanisms of thermoregulation act to raise body temperature up to the new set point, then maintain the elevated systemic temperature. Thus fever is not equivalent to an elevated core temperature. Rather, it represents an elevated set point.[2084] Fever is triggered by the release of endogenous pyrogenic cytokines (fever-producing substances) from cells of the immune system into the bloodstream. Mononuclear phagocytes are the main source of endogenous pyrogens, and a variety of these substances,[2096] categorized as monokines and lymphokines, or collectively, as cytokines, also mediate the acute-phase response to infection and inflammation. Pyrogenic cytokines act as hormones in that they are carried by the circulation from the local inflammatory site of production to the central nervous system. There they bind with high affinity to 80 kD

receptors present on vascular endothelial cells within the hypothalamus. This elicits phospholipases, which in turn cause release of arachidonic acids from membrane phospholipids. As a result, prostaglandin levels rise, resetting the hypothalamic regulatory center to a new set point. The cytokines may also interact directly with neural tissues.[2084]

The most important of the pyrogenic cytokines are interleukin-1 (IL-1), tumor necrosis factor (TNF), interleukin-6 (IL-6), interferon alpha, beta and gamma, interleukin-8 (IL-8), macrophage inflammatory protein (MIP-1α, MIP-1β), and possibly[2100] platelet-derived growth factor (PDGF).

IL-1 (17.4 kD) comes mainly from monocytes and macrophages, though it can also be produced by neutrophils, B and T cells, endothelial cells, and virtually all other nucleated cells.[2094] IL-1 production may be stimulated by the presence of microorganisms, exposure to endotoxin and other bacterial toxins or microbial products, phagocytosis, antigen-antibody immune complexes, and various forms of tissue injury.[2094] IL-1 induces additional IL-1 production[2101] and additional IL-1 receptor expression on certain target cells.[2102] IL-1 stimulates immune cells thus enhancing host defense mechanisms. The cytokine stimulates lactoferrin release by neutrophils (e.g., neutrophils have ~1700 IL-1 receptors per cell[2103]), which reduces serum iron levels during many bacterial infections, thus retarding bacterial growth. (IL-1 also acts on the central nervous system to induce sleep[2104] and has numerous other helpful and deleterious biologic properties.)

TNF is another pyrogenic cytokine that acts directly on the hypothalamus to elevate the thermal set point. It also causes fever by inducing IL-1 production. LPS-activated macrophages are the main source of TNF, along with monocytes and NK cells as well as antigen-stimulated T-cells and activated mast cells. TNF production is stimulated most potently by endotoxin, but also by certain parasites, viruses, enterotoxins (including toxic-shock syndrome toxin-1), and IL-1.[2105] Peak serum levels occur in 90 minutes, but TNF is cleared from the circulation in ~3 hours.[2094] TNF binds to different receptors than IL-1. These different receptors are found in the CNS, on vascular endothelium, adipose tissue, and on liver, kidney and lung tissues.[2094] TNF has other biological properties besides pyrogenicity, including increasing resistance to infection,[2106] inhibition of ACTH release,[2107] induction of sleep,[2104] and mediation of septic shock[2108] (Section 15.2.6.4). TNF is a mediator of both natural and acquired immunity as well as specific responses and acute inflammation.[5491]

Can nanorobots act as pyrogens, inducing systemic fever (nanopyrexia[5503])? Any external nanorobot organic coatings (Section 15.2.2) should be verified as nonpyrogenic. For example, phagocytosed latex particles do not stimulate pyrogen production in macrophages.[2129] But fever occurs in about one-third of all hospital patients, 67% of these due to infection[2109] but 12-18% due to "fever of unknown origin" or FUO[2110] that is nonetheless almost certainly biochemically mediated. FUO is usually ascribed to infections, neoplasms, collagen vascular disease, granulomatous diseases (including starch peritonitis,[2404] a febrile granulomatous response to starch introduced on surgical gloves), chronic liver disease and IBD (irritable bowel disease), pulmonary emboli[2111] and atelectasis[2406,2407] (but compare Engoren[2405]), and sometimes certain drugs[2112,2113,2409-2411] such as Dilantin.[2411] Fever can also be produced by mechanical tissue disturbance such as a thoracic esophageal perforation,[2085] knee and hip arthroplasty,[2401-2403] excision of Teflon particulate masses,[1282] or shock wave lithotripsy,[2087-2089] confirming the need for cautious nanosurgery (Chapter 12).

S. Flitman also notes the significance of Shapiro Syndrome, a spontaneous recurrent hypothermia and hyperhidrosis usually associated with agenesis of the corpus callosum[5910-5912] but also with hypothalamic lesions[5913] and lipomas.[5914] Dopaminergic denervation of the hypothalamic thermoregulatory center has also produced hyperthermia or "reverse Shapiro Syndrome",[5915] and Flitman has observed this effect in a patient with hypothalamic damage due to encephalitis, producing a fever long after the normalization of CSF pleocytosis (and hence the eradication of acute infection). The relevance to nanomedicine is that nanorobots passing through, or taking up residence in, the corpus callosum or hypothalamus must tread lightly to avoid inducing hypo- or hyperthermia, as this seems to occur with even a mild infiltration of the preoptic nucleus, according to Flitman.

As of 2002, there were no reports of pyrogenicity for anticipated nanorobot simple building materials such as diamond, fullerenes, or graphite. Carbon powder has been used in nasal provocation tests without eliciting fever,[2114] though there are rare cases of fever from amorphous carbon particles in India ink[856] and from inhaled or ingested hydrocarbons.[2408] With rare exception,[2115] bulk Teflon appears nonpyrogenic in vivo[2116-2118] — although perfluorocarbon emulsion can cause cutaneous flushing and fever at low doses[2119] (see also Section 7.2.1.1 and Chapter 22), and "polymer fume fever"[1683,2120,2121] or "Teflon fever"[1388] is the result when Teflon combustion products are inhaled. No pyrogenicity of monocrystal sapphire has been reported. However, there is one case of fever possibly caused by alumina powder inhalation.[2122] And while ceramics appear generally to be nonpyrogenic,[2123] macrophages exposed to particulate alumina ceramic release TNF, increasingly with size and concentration of particles.[1074]

Other particulates are less inert. Metal fume fever (due to zinc oxide inhalation) is well known[2124-2126] and excess trace elements such as copper and zinc can induce fever.[2127] Phagocytosed silica crystals elicit pyrogen production[2128,2129] and silicotic materials can produce fever.[2131-2133] Various low-solubility substances that crystallize in the human body can trigger fever once the crystals have formed. For example, monosodium urate monohydrate crystals,[2128-2130] which are deposited in synovial fluid during gout, cause fever[2134,2135] and stimulate IL-1,[2128] TNFalpha,[2136] and IL-6[2130] production in monocytes or synoviocytes. The smaller 10- to 40-micron crystals are less pyrogenic than the larger aggregates.[2128] Calcium pyrophosphate dihydrate (CPPD) deposited in the fibrocartilage during chondrocalcinosis (aka. CPPD crystal deposition disease) is pyrogenic,[2137-2143] and CPPD crystals increase IL-6 production by monocytes and synoviocytes in vitro.[2130] Fever has been reported from nephrolithiasis (kidney stones),[2144] from crystalluria[2145] with calcium oxalate or phosphate in urolithiasis (bladder stones),[2146,2147] from calcified lymph-node stones in broncholithiasis,[2148] from calcified salivary gland stones in sialolithiasis,[2149] and from precipitated crystals in the pulmonary microvasculature in a patient receiving total parenteral nutrition.[2150] Cholesterol crystals deposited as gallstones during cholelithiasis may be pyrogenic,[2151-2153] as are cholesterol crystal emboli in the blood.[2154] A systematic assessment of pyrogenicity should be undertaken for all crystalline and ceramic materials likely to be employed (whether singly or in combination) in the construction of medical nanorobots.

If inherent nanodevice surface pyrogenicity cannot be avoided, the pyrogenic pathway is readily controlled by in vivo medical nanorobots because only a small number of critical mediators are involved. For instance, the cytokine IL-4 suppresses production of the endogenous pyrogens IL-1, TNF and IL-6.[2155] NSAID

prostaglandin inhibitors like aspirin or ibuprofen are also effective antipyretic agents that block prostaglandin synthase (cyclooxygenase) enzyme activity and thus block the production of prostaglandins. Antagonists of the IL-1 receptor have been identified.[2156-2160] Glucocorticoids inhibit the production of IL-1, TNF and IL-6.[2161] Other inhibitors of TNF are known (Section 15.2.7) such as the anti-TNF monoclonal antibody Etanercept,[2412,2413] currently used in rheumatoid arthritis patients with excellent results. Nonsteroidal anti-inflammatory antipyretic drugs are employed for treatment of gout and other crystal-induced arthropathies.[2162] Additionally, many endogenous antipyretics that limit the rise in body temperature have been identified,[5045] including arginine vasopressin, glucocorticoids, melanocortins (e.g., alpha-MSH), TNF (under certain circumstances), IL-10, and most recently, cytochrome P-450.[5045,5046] Nanorobots may release these or similar inhibitors, antagonists, or down-regulators in a targeted fashion to interrupt the pyrogenic pathway. Alternatively, they may use molecular sorting rotors to selectively absorb the endogenous pyrogens, chemically modify them, and then release them back into the body in a harmless inactivated form.

For example, typical bloodstream concentrations are ~10 pg/cm^3 for IL-1β[2163] and ~100 pg/cm^3 for TNF,[1074] or ~0.0003-0.003 molecules/micron^3 assuming a molecular weight of ~17.4 kD for either molecule.[2084] If there are 2-20 x 10^{12} molecules of these cytokines in the entire circulation, then a fleet of 0.1-1 trillion nanorobots each with 10,000 sorting rotors on its surface (extracting ~0.001 molecules/rotor-sec) can reduce bloodstream IL-1 or TNF concentrations by ~90-99% in ~2-20 seconds. Selective absorption of prostaglandins, present in blood plasma at ~400 pg/cm^3 (Appendix B), might also serve to "manually" reduce the hypothalamic thermal set point. One other possible approach, adopted by certain *Vaccinia* virus strains,[2347] is to suppress the fever response by releasing soluble IL-1 receptors that bind to IL-1, thus inhibiting this normal pathway.

It is possible that perfectly biocompatible-surfaced nanorobots cannot be designed, or that necessary additional anti-pyrogenic functions cannot be added to nanorobotic devices already hard-pressed for onboard space. Although not ideal, in such cases a collection of different nanodevices could be deployed to implement a given treatment. Some devices would attend to the primary therapeutic goal while others would attend to the management of the unwanted biological responses, crudely analogous to drug combinations in current medical practice such as demerol plus vistaril[2414-2416] or combinations of chemotherapeutics and anti-emetics.[2417-2420] Mechanisms of tachyphylaxis[5891] could also be investigated for possible relevance.

The impact of nanorobots and nanorobotic organs on the thermophysical properties and thermoregulatory mechanisms of the human body is briefly discussed in Section 15.3.8.

15.2.8 Nanorobot Mutagenicity and Carcinogenicity

Another key aspect of biocompatibility is whether implanted nanorobotic organs, or in vivo medical nanorobots,[33] can induce undesirable genetic changes as a side effect of their presence or activities inside the human body. Such undesirable changes might take many forms. For instance, mutagenicity[2176,2178] is the production of inheritable coding flaws in chromosomes that otherwise may retain much genetic functionality. (All carcinogens are mutagens but not vice versa — a mutation may be lethal to a cell, may prevent cellular replication, or may not affect metabolic or growth processes sufficiently to produce malignant behavior.[234]) Genotoxicity[2179,2180] is a more serious injury to the chromosomes of the cell, such that when the cell divides, fragments of chromosomes and micronuclei remain in the cytoplasm. Teratogenicity[2181-2183] is the ability of a foreign material (or a fetotoxic agent) to induce or increase the risk of developing abnormal structures in an embryo, or birth defects. Carcinogenicity is the ability to produce or increase the risk of developing cancer — materials may be directly carcinogenic or may potentiate other agents.[234] Tumorigenic materials tend to induce neoplastic transformations, especially malignant tumors.

Direct experimental exploration of the carcinogenicity of likely nanorobot building materials has barely begun, but information available to date appears guardedly optimistic. For example, diamond (DLC) coatings exhibit low mutagenicity toward human fibroblasts in vitro.[659] There are no reports of diamond carcinogenicity or tumorigenesis. Alumina (sapphire) produces no mutagenic or carcinogenic effects on cultured human osteoblasts[1104] or when used as a blood-contacting material in a centrifugal blood pump.[1058-1060] While aluminum ion that leaches from sapphire at the highest plausible concentrations (~10^{-5} M; Section 15.3.5.6) might inhibit eukaryotic transcription,[2235] experiments suggest that the mutagenicity, carcinogenicity, and teratogenicity of aluminum is low[2236] and the association between aluminum and Alzheimer's has become doubtful.[5504] (S. Flitman notes that the original basis for the association is now believed to be laboratory error (e.g., "brains in buckets absorbed high concentrations prior to analysis"), and that Alzheimer's is not a disease induced by mutagenicity but rather is a protein-accumulation disorder with an inheritable predilection (ApoE, APP, PS1, PS2).) Teflon particles appear to be non-carcinogenic,[1237,1249,1311,1385] even though tetrafluoroethylene (a monomer used in Teflon manufacture) is hepatocarcinogenic after long-term inhalation by mice.[1385] There are no reports of carcinogenicity from pyrolytic carbon, graphite, or India ink in humans. In rodents, the inhalation of carbon black particles can produce pulmonary neoplasms[888] and lung carcinoma,[760,761] and particle-elicited macrophages and neutrophils can exert a mutagenic effect in vitro, on rat epithelial cells.[889]

The possible carcinogenicity of fullerenes was suggested more than a decade ago[698,917] but even by 1998 the risk was no longer considered serious.[669] Pure C_{60} and C_{70} molecules do not intercalate into DNA (which might promote cancer) when mouse skin is exposed to them,[698] though water-miscible fullerene carboxylic acid can cleave G-selective DNA chains.[922] No mutagenicity or genotoxicity of C_{60} as fullerol is observed in prokaryotic cells and only slight genotoxicity is seen in eukaryotic cells at the highest concentrations.[696,697] C_{60} dissolved in polyvinylpyrrolidone is mutagenic for several *Salmonella* strains due to singlet oxygen formation[681] — pure C_{60} is a known singlet oxygen generating agent,[919] and singlet oxygen is known to be genotoxic.[2237] Repeated epidermal administration of fullerenes for up to 24 weeks resulted in neither benign nor malignant tumor formation in mice, although promotion with a phorbol ester produced benign skin tumors.[698] Some C_{60} derivatives have actually shown promise as anti-cancer[1090-1092] or anti-tumor[684,922] agents. Carcinogenicity studies of rolled graphene sheets such as carbon nanotubes remain to be done (Section 15.3.2.1).

There are four types of carcinogenesis[234] which may be relevant in medical nanorobotics:

1. *Chemical Carcinogenesis*. Chemical carcinogenicity is actually a somewhat uncommon property of materials. An exhaustive literature search on 6000 of the most likely chemical candidates found only 1000 (17%) identified as possible carcinogens.[234]

The classic study by Innes et al[2184] found that fewer than 10% of 120 pesticides and toxic industrial chemicals tested were carcinogenic. Even this study was criticized as being too pessimistic because testing toxic potential carcinogens at high dosages may artificially accentuate their activity by inducing increased rates of cell division.[2185] Medical nanorobots normally will have chemically-inert nonleachable surfaces, but designers should ensure that all possible nanorobot effluents are noncarcinogenic. Potential nanorobot effluents may be prescreened during design using existing computational toxicology techniques.[2174-2177]

2. *Nonspecific Carcinogenesis*. Neoplasms can arise in response to chronic irritation, leading to chronic inflammation and granulomatous reaction to implants (Section 15.4.3.5). Chemicals,[2186] foreign bodies,[2187] infection and mechanical trauma[2188] can produce this type of neoplastic transformation which is characterized by replication infidelity — i.e., a cell that produces a daughter cell not identical to its parent, as in, for example, the formation of hyperplastic expansive scars known as nonmalignant keloids.[234] These benign lesions can occasionally, and apparently spontaneously, transform into malignant neoplasms such as fibrous histiocytomas.[2189-2192]

3. *Ex Cyto Foreign Body Carcinogenesis*. In the 1950s it was discovered that many agents not previously thought to be carcinogenic produced dramatic neoplasm incidence rates in rodents when implanted in solid form rather than injected or fed in soluble or dispersed form. This effect is called foreign body (FB) carcinogenesis,[2193-2202] solid-state carcinogenesis,[2203,2204] or the Oppenheimer effect.[2205,2206] The induction of neoplasms increases with the size of the implant and with decreasing inflammatory response (i.e., well-tolerated materials are, in the long run, better FB carcinogens). The risk of transformation is influenced by the micron-scale surface morphology of the implant.[5822] Risk is reduced on surfaces with porosity of average diameter above 220 nm; materials with distributed porosity of cellular dimensions are less carcinogenic in rodents than smooth nonporous material.[234,2197] Nonperforated polymer films induce subcutaneous sarcomas in mice and rats, but implanted foreign bodies with other shapes (e.g., perforated or minced films, or filters with 450-nm pores[2197]) or with roughened surfaces[2194] are weakly or non-carcinogenic except when total foreign-body surface area exceeds ~1 mm^2.[2202] In vitro experiments by Boone et al[2196] and in vivo experiments by Brand[2193] studied the effects of attachment of mouse fibroblasts to polycarbonate plates. Cells implanted after an in vitro exposure produced transplantable, undifferentiated sarcomas, leading these authors to conclude that the smooth surface of the plates acted as an FB carcinogen for at least initiation of tumorigenesis, independent of chemical composition. Brand[2193] cited six possible mechanistic origins of FB carcinogenesis, then concluded that: (a) disturbance of cellular growth regulation was most likely, based on the heritability of neoplastic behavior in the growing cell population, and (b) interruption of cellular contact or communication might also play a role in neoplasm expression and maturation (rather than neoplasm induction). It is now well established that smooth-surfaced foreign bodies, regardless of their chemical composition, will produce sarcomas when transplanted subcutaneously into rodents,[2196] and foreign-body sarcomatous growth in mice appears resistant to substances that normally inhibit neoplastic growth.[2199]

Is there any information that humans are also susceptible to ex cyto FB carcinogenesis? There is no evidence that a single incident of mechanical trauma can cause cancer.[2207] However, there are 28 known cases of tumors in humans associated with partial or total joint replacements, which occurred either fairly soon after implantation or a very long time (10-15 years) after implantation, the latter primarily as malignant fibrous histiocytomas.[234,2208] But all of these tumors were associated with stainless steel or cobalt-based alloy devices, perhaps due to elevated tissue concentrations of metals near the implant[234] — metal-on-metal devices can produce a 10- to 15-fold rise in circulating serum chromium.[2209] There are a few additional reports of possible remote-site tumors,[234,2210-2212] but other studies find such implant-related tumorigenicity to be very weak or nonexistent.[2213-2216] Some investigators[2217-2219] have therefore concluded that there is little clinical evidence for ex cyto FB carcinogenesis in humans, and that the Oppenheimer effect may be a consequence of the relatively primitive immune system of rodents in comparison to that of humans,[234] and of the lack of a telomere shortening inhibition pathway in mice that humans possess. But Black[234] urges caution because, in rare cases, sarcomas appear to have arisen on unabsorbable foreign bodies in man[2200-2202] — a category of foreign bodies that would definitely include diamondoid medical nanorobots and nanoorgans. Polarizable foreign particles have also been associated with cutaneous granulomas in three cases of systemic sarcoidosis.[2597] Nevertheless, A. Rao remains skeptical that, at least in the case of individual mobile nanorobots, "the brief time that nanorobots would reside within tissues would be enough to induce FBC."

4. *In Cyto Foreign Body Carcinogenesis*. Although FB carcinogenesis produced by materials external to cells appears to be rare in humans, solid materials in a form that can penetrate cells can be carcinogenic, a phenomenon originally known as the Stanton hypothesis.[2220] The best-known example is chrysotile asbestos,[2221-2223] first recognized as a human carcinogen only because it produced a relatively rare lung tumor.[2224] Subsequent studies of asbestos and related fibers in animal models revealed that mesothelioma could be induced by fibers <~0.25-1.5 microns in diameter and >~4-8 microns in length regardless of fiber composition.[2220,2227] Quantitatively, Stanton[2220] found that ~10^5 fibers of carcinogenic dimensions, embedded in the human body, yielded a ~10% probability of developing a tumor within 1 year; ~2 x 10^7 fibers raised the probability to 50%; and 10^9 fibers raised it to 90%. In vitro fiber cytotoxicity correlates well with fiber dimensions,[2225-2228] particularly the aspect ratio;[2228-2230] with fiber durability;[2225] and not with fiber bulk composition, but rather with the molecular nature of active surface properties which can also play a role in carcinogenic potency.[2225,2229] Stiff slender fibers such as mineral whiskers can penetrate cells and may produce mechanical[2231] or chemical[2232] damage to the nucleus and to chromosomes[2233] regardless of the material of which they are comprised. The likely mechanism is oxygen radical activity because antioxidant enzymes appear to protect cells against genotoxic damage induced by chrysotile fibers.[2234] This risk factor must be borne in mind when designing medical nanorobots (including all of their possible operational and failure-mode physical configurations) and any potentially detachable subsystems that may be of similar stiffness and size as the cytotoxic fibers.

CHAPTER 15.3

Biocompatibility of Nanomedical Materials

A great deal is already known about the biocompatibility of various materials that are likely to find extensive use in medical nanorobots. Chapter 15.3 includes a review of the experimentally-determined overall biocompatibility of diamond (Section 15.3.1), carbon fullerenes (Section 15.3.2), nondiamondoid carbon (Section 15.3.3), Teflon (Section 15.3.4), sapphire and alumina (Section 15.3.5), and other possible nanomedical materials including DNA and dendrimers (Section 15.3.6) and effluents (Section 15.3.7), and concluding with a discussion of nanorobotic thermocompatibility (Section 15.3.8).

15.3.1 Biocompatibility of Diamond

The exteriors of many individual medical nanorobots or nanorobot aggregates comprising nanoorgans (Chapter 14) may be made of diamond, so the biocompatibility of diamond surfaces[36] and particles is of considerable interest in nanomedicine.[20] Our analysis of the biocompatibility of diamond starts with a review of protein adsorption (Section 15.3.1.1) and cellular responses (Section 15.3.1.2) to diamond surfaces, followed by a survey of diamond-coated prostheses already proposed, developed, or in clinical use (Section 15.3.1.3) and experimental data on the biocompatibility of diamond particles (Section 15.3.1.4), and finally concludes with a brief summary of the chemical inertness of diamond (Section 15.3.1.5). The overall conclusion is that diamond appears to be extremely — indeed outstandingly — biocompatible with living cells. The hypothesis that atomically-precise diamond surfaces might possibly be engineered to be highly resistant to protein adsorption (though even the comparatively rough diamond surfaces and particles available today are already very biocompatible and chemically inert) is suggested by the data but is not yet thoroughly substantiated — it could be validated by studies showing, for example, a clear trend of lower protein adsorption with lower diamond rugosity.

15.3.1.1 Protein Adsorption on Diamond Surfaces

The first direct study of protein adsorption on diamond, done by Tang et al[521] in 1995, focused on fibrinogen (Section 15.2.2). Fibrinogen, a 340-kilodalton soluble plasma glycoprotein ~47.5 nm in length,[526] is the major surface protein to initiate coagulation[518,527-529] via platelet adhesion to fibrinogen, and inflammation including fibrosis[523-525] around implanted biomaterials. The adsorption and conformational state ("denaturation") of fibrinogen is commonly used as a biocompatibility indicator.[530] The amounts of "denatured" fibrinogen accumulated on surfaces correlates closely with the extent of biomaterial-mediated inflammation.[531]

Tang and colleagues[521] measured ~3.7 mg/m^2 (~6600 molecules/micron^2, or ~50% surface coverage) gross surface adsorption of human fibrinogen on chemical-vapor-deposited (CVD) diamond surfaces, after incubation of the plasma-coated diamond surface in a 20 μg/cm^3 fibrinogen solution (~0.1% of blood concentration; Appendix B) for 8 hours at room temperature. Much of this adsorbed fibrinogen was only loosely bound, however. A solution of sodium dodecyl sulfate was rinsed over the incubated CVD surface to remove the loosely-bound or elutable (non-denatured) fibrinogen. (Sodium dodecyl sulfate is an anionic detergent commonly used to solubilize proteins, e.g., a surfactant creating negative surface adhesion energy; Section 9.2.3. Although SDS is of course unavailable to wash biomaterials once implanted, the wash results nevertheless indicate the extent to which loosely bound proteins will eventually detach.) After the rinse, ~44% of the bound fibrinogen molecules detached, leaving ~2.1 mg/m^2 (~3700 molecules/micron^2) of spontaneously denatured fibrinogen still present on the CVD diamond surface.

CVD diamond[532-535] might not accurately represent the atomically-smooth flawless diamond surfaces which may characterize the typical MNT-manufactured medical nanorobot exterior. Far from being atomically smooth, CVD diamond films are amorphous and polycrystalline,[537] often with grain sizes up to 1-10 microns.[535,536] In Tang's experiment,[521] diamond wafers with two distinct sides were tested, as follows.

The nucleation side of the diamond wafers was grown in contact with a flat silicon substrate, which was then dissolved away by acid. The formation of SiC on such a substrate allows silicon to bond well with carbon during the growth process.[537] However, the presence of small amounts of surviving carbide in the nucleation diamond surface, or of concave nanoscale surface features recording the removal of SiC by etchant, could markedly alter the protein adsorbent characteristics of the diamond surface at the molecular level. Also, SiC is tolerated by cells up to 0.1 mg/cm^3 concentration but is cytotoxic at 1 mg/cm^3.[538] Furthermore, a contact profilometer measured the nucleation surface as having a rugosity of up to 250 nm, a roughness 100-1000 times greater than that which may be expected at the surfaces of the typical diamondoid medical nanodevice.

The growth side of the diamond wafers used in Tang's experiment was even rougher than the nucleation surfaces, so this surface was ground and polished but only to a rugosity of ~1 micron peak-to-valley. This is approximately the diameter of an entire bloodborne medical nanorobot and clearly not representative of an atomically-precise engineered medical nanodevice surface. There is no indication whether the grinding and polishing of the growth surface was done under oil (thus preserving a predominantly hydrogen-terminated, hence strongly hydrophobic, surface[539]), nor was there any evaluation of whether subsequent etching with H_2SO_4 and H_2O_2 might have produced carbonyl and hydroxyl conversions at the surface (thus possibly creating regions of hydrophilicity). Furthermore, diamond crystals are believed to polish by successive

repeated microcleavage along (111) cystallographic planes, which is why polishing is much easier in some directions than others.[539] Non-(111) surfaces, when mechanically polished, will always be rough and will consist of small domains of (111) surface canted at appropriate angles to the macroscopic orientation.[539] Residual asperities of ~5 nm have been reported even for exceptionally carefully polished surfaces.[540] The general conclusion is that the chemical and mechanical processes used in Tang's experiment seem unlikely to have produced a surface that is well characterized at the molecular level. Protein adhesion to near-atomically smooth diamond surfaces remains to be investigated experimentally.

Still, we can hypothesize that completely fibrinogenophobic surfaces might be engineered using atomically-smooth diamondoid materials, keeping in mind the important role of hydrophobic forces in surface denaturation (e.g., see Section 15.3.4.1). To do this will require a thorough molecular-level understanding (by 2002, not yet complete) of the adhesion and conformational properties of fibrinogen, as summarized below and in Section 15.2.2.

It has long been known that fibrinogen preferentially adsorbs on a hydrophobic surface, and albumin on a hydrophilic surface, during competitive binding.[541] One experiment[542] found 10,800 molecules/micron^2 of fibrinogen (~complete monolayer coverage) adsorbed on a hydrophobicized quartz surface (contact angle ~70°) after 30 seconds incubation with a 2.9-μM fibrinogen solution (~30% of physiological in human serum; Appendix B), but only 8400 molecules/micron^2 after a 60-second exposure of a hydrophilicized silicon surface (contact angle ~28°) to the same solution. Hydrophobic surfaces generally have higher adsorbence of adhesion proteins such as complement C3, fibronectin, and vitronectin, while hydrophilic surfaces have higher adsorption of albumin and immunoglobulin IgG.[543] (The fibrinogen molecule's own surface properties are very hydrophilic, changing to moderately hydrophobic as it converts to fibrin during coagulation.[544]) Fluorocarbon films (very hydrophobic) generally show high protein retention[1113-1114] (Section 15.3.4.1).

Surface functionality has been shown to influence protein-surface interactions.[1111-1113] Tang et al[531] found that surfaces having high concentrations of specific surface functionalities including -OH (hydrophilic), -NH_2 (hydrophilic), -CF_3 (hydrophobic), and siloxyl groups (hydrophobic) exhibited significant differences in both the adsorption and "denaturation" of adsorbed fibrinogen. But hydrophobicity alone did not dictate fibrinogen-surface interactions on these surfaces. Soaking in saline solution for 15 days increased oxygen incorporation in the -NH_2, siloxyl, and CF_3 rich films, and slightly decreased the oxygen content in the -OH rich films. After this soaking, the two hydrophilic films became somewhat less hydrophilic whereas the two hydrophobic films became somewhat more wettable.[531] These kinds of changes may be important for medical nanorobots expecting to remain in vivo for extended times. Rapoza and Horbett[545] observed rapid denaturation transitions, requiring <2 hours after adsorption on hydrophobic polymers containing no oxygen. More gradual conformation changes, occurring only after a time lag of 1-4 hours, were seen on hydrophobic polymers containing oxygen. Note that the existing literature discusses surface changes in response to short-term exposures. Little is known of the effects of long-term exposures lasting months or even years. Such exposures and their consequences should also be investigated because permanently implanted nanorobotic organs and nanorobots used for surveillance or early detection of disease could have very long mission durations.

Hydrophobicity and surface functionalities are accessible parameters well within the reach of diamondoid medical nanorobotic design. In general, the high surface energy of natural diamond makes it extremely hydrophobic.[547-549,658] Yoder[550] reports that ocean barnacles do not attach to diamond. However, a diamond surface may have any of several different crystal planes exposed. These planes may be passivated with any of a number of passivating atoms or molecules, all of which may affect the hydrophobicity of the surface. For example, a hydrogen-terminated (111) crystallographic surface with each H bonded to a single C looks like a hydrocarbon (e.g., like oil) and is not wetted.[539] On the other hand, oxygenation of a diamond surface (e.g., by heating to >250 °C in an O_2 atmosphere, or by ion bombardment) promotes formation of hydrophilic surface groups[552] with a complicated surface chemistry,[553,554] including a significant proportion of carbonyl (C=O) groups.[554] The outer faces of natural hydrophobic diamond may be terminated partly by hydrogen and partly by bridging oxygen (C-O-C).[539] Aging such surfaces in water for several weeks can change them to hydrophilic behavior,[554] possibly indicating conversion to hydroxyl (-OH) groups. Hansen[551,552] suggests that the small amount of oxygen on the atmospherically equilibrated polished surface is present largely as -OH groups because surface wettability appears insensitive to pH values below pH 11. Fe^{+++} (and Al^{+++} to a much lesser extent) can form surface complexes with these hydroxyl groups, whereas Na^+, Ca^{++}, and Cr^{+++} cannot. Complete atomic-scale positional and compositional control of the diamond-passivation layer on the exteriors of medical nanorobots should permit the engineering of adhesion-protein-selective surfaces of appropriate hydrophobicity, hydrophilicity, or adsorptivity (Section 15.2.2). For instance, it is well known that hydrophobic surfaces can be progressively hydrophilized via selective ion implantation[939] or RF plasma treatment.[1111-1113] Hosotani[555] has created an intraocular lens coated with diamond-like carbon film that is more hydrophobic and oleophilic than an uncoated lens.

Under aqueous conditions, surface-dependent structural deformation or spreading of the adsorbed fibrinogen molecule is larger on positively-charged surfaces than on negatively-charged implant surfaces — specifically, the molecular length and the D and E domain widths of fibrinogen are increased, while the corresponding molecular heights are decreased.[556] As an insulator, diamond in water generally does not present a highly charged surface.[633,639,640] But surface charge also lies within the purview of diamondoid nanorobot design (Section 15.5.6). For example, a hydrogen-terminated diamond surface has negative electron affinity.[557,558] Since hydrogen is less electronegative[559] than carbon, the surface externally appears to be a weak array of positive point charges* at molecular contact distances, arising from surface dipoles as polarized covalent bonds would be expected to produce.[558] On the other hand, the oxygenated diamond (100) surface has a positive electron affinity[560] as does the fluorinated (111) surface. (Methods for selectively fluorinating diamond surfaces have also been investigated.[561]) Both oxygen and fluorine are more electronegative[559] than carbon, so either surface would externally appear to be an array of negative point charges at molecular contact distances. The controlled coating of a diamond

** E. Pinkhassik points out that the difference in electronegativity between carbon and hydrogen is very small (2.5 and 2.1, respectively, on the Pauling scale, or 2.746 and 2.592, respectively, on the more modern Sanderson scale[5843]), while the difference between carbon and oxygen, or between carbon and fluorine, is much larger — e.g., 2.5/2.746 for C, 3.5/3.654 for O, and 4/4.0 for F. The C-H dipole is very weak, so a surface coated with C-H groups with carbon being in sp^3 hybridization can hardly be considered an array of positive point charges. In fact, the polarizability of the C-H bond may be more significant than the partial point charge. On the other hand, C-O and C-F dipoles are strong, and the partial point negative charges are likely to be larger.*

surface with atoms with different electronegativity might provide fine control of the electron affinity while maintaining chemical inertness of the diamond surface. Diamond glucose sensors employed in diabetic blood analysis use heavily boron-doped diamond as one electrode. On the other electrode, glucose oxidase enzyme (a protein) is immobilized on the diamond surface by electrochemical deposition, or is "wired" directly to the diamond electrode by covalent bonding to the electrode surface.[655]

Other blood proteins also must be tested for their adsorptivity to diamond. For example, one study[583,4723] of protein adsorption on diamond-like carbon (DLC) coatings (Section 15.3.1.2) found that DLC exposed to bovine serum albumin (BSA) at a concentration of 5 mg/cm^3 (~10% of physiological for human serum albumin) adsorbs 20 times less BSA than SiO_2 or TiO_2 control surfaces. Phytis L.D.A., the sponsor of this study[583,4723] and the only manufacturer of a DLC-coated stent, claims that "diamond-like coated surfaces showed only minimal adhesion of proteins at the surface; those adhesions are reversible and do not result in denaturations of protein."

15.3.1.2 Cell Response to Diamond Surfaces

Cellular interactions that occur at the tissue-implant interface are another important determinant of biocompatibility.[521,584-586] For example, neutrophils, the most abundant white cells in human blood, will directly adhere to protein-coated implant surfaces, leading to inflammatory responses.

The first pioneering study of cellular response to diamond surfaces was completed by Thomson and colleagues[587] in 1991, using tissue culture plates with diamond-like carbon (DLC) coatings 0.4 microns thick. DLC is an amorphous hydrocarbon polymer with carbon bonding largely of the diamond type instead of the usual graphitic bonding,[588] thus has many of the useful properties of diamond.[589] (The varying ratio of diamond type (sp^3) carbons to graphite type (sp^2) carbons in DLC may account for some differences in behavior exhibited by different DLCs.) DLC can be deposited near room temperature.[590] Mouse fibroblasts grown on the DLC coatings for 7 days showed no significant release of lactate dehydrogenase (an enzyme that catalyzes lactate oxidation, often released into the blood when tissue is damaged) compared to control cells. This demonstrated that there was no loss of cell integrity due to the DLC coatings. Mouse peritoneal macrophages similarly cultured on DLC also showed no significant excess release of lactate dehydrogenase or of the lysosomal enzyme β-N-acetyl-D-glucosaminidase (an enzyme known to be released from macrophages during inflammation). Morphological examination revealed no physical damage to either fibroblasts or macrophages. This confirmed the biochemical indication that there was no toxicity and that no inflammatory reaction was elicited in vitro. Follow-up studies in 1994-95 found that murine macrophages, human fibroblasts, and human osteoblast-like cells grown on DLC coatings on a variety of substrates exhibited normal cellular growth and morphology with no in vitro cytotoxicity.[591,650] In 2001, the same research group[4722] cultured two osteoblast-like cell lines on DLC-coated plates for 72 hours and found no adverse effects on these cells, as measured by the production of three osteoblast-specific marker proteins (alkaline phosphatase, osteocalcin, and type I collagen).

Other experiments have largely confirmed these results. For instance, human hematopoietic myeloblastic ML-1 cells and human embryo kidney cells proliferated continuously on DLC film with very high viability and no toxicity.[592] Scanning electron microscopy used to investigate the morphological behavior of osteoblasts found that these cells attached, spread and proliferated normally without apparent impairment of cell physiology when placed on DLC or amorphous carbon nitride films, whereas cells placed on silicon were able to attach but not to spread.[593] Human osteogenic sarcoma T385 cells and 1BR3 fibroblasts cultured on DLC-coated wells also showed DLC to be biocompatible.[594] The cytotoxicity study of DLC coatings by Parker and colleagues,[595] employing the Kenacid Blue cytotoxicity test in vitro with 3T3-L1 mouse fibroblasts, found normal cell growth on diamond surfaces. Other tests by this team of the biocompatibility of "amorphous carbon hydrogen" using a standard cell line showed that such films are nontoxic to cells, appear to increase cell attachment, and afford normal cell growth rates.[649] Dion et al[596-598] looked at general cytotoxicity and hemocompatibility of DLC surface with 3T3 Balb/c cloned cells. Human endothelial cells isolated from placenta were also investigated as a model for differentiating cells. No negative effects due to DLC coatings were observed on the viability of cells, all of which showed normal metabolic activities. O'Leary and colleagues[654] evaluated cytotoxicity and cell adhesion of murine fibroblasts on saddle field source deposited DLC (containing less than 1% hydrogen) coating a titanium alloy surface, and found normal cell adhesion, density, and spreading on DLC. Other studies of DLC biocompatibility[656-659,1680,5689,5690] have shown equally promising results.

In a study previously described (Section 15.3.1.1), Tang et al[521] examined the attachment of neutrophils to plasma-preincubated ~1 cm^2 350-micron-thick CVD diamond wafers. Incubation for 1 hour with purified human neutrophils at 2 x 10^6 cm^{-3} produced an attachment rate of ~4 x 10^9 cells/m^2 (~0.004 cells/micron^2), about the same as for 316 stainless steel and 40% lower than for titanium, two common and well-tolerated implant materials. SEM photographs of CVD diamond wafers implanted intraperitoneally in live mice for 1 week revealed minimal inflammatory response. Interestingly, on the rougher "polished" (~1-micron features) surface, a small number of spread and fused macrophages 10-13 microns in diameter were present, indicating that some activation had occurred. However, on the smoother "unpolished" (<0.25-micron features) surface, samples were partially covered by round, non-spread (non-activated) cells, 4-7 microns in diameter, which had formed no obvious pseudopodia or cell bridges. Tang noted that "the morphology of unpolished surfaces of CVD diamond could be responsible for preventing the activation of surface-adherent cells [but] the mechanism for this differential response of phagocytic cells...is not yet understood." If surface rugosity,[599,676,677,776] topography,[600-602] or crystalline structure[603] can account for the differential response, then it is perhaps possible that atomically-precise diamondoid surfaces with <1 nm features — constituting much of the external surfaces of medical nanorobots and nanoorgans — could be rendered adequately macrophage-resistant (Section 15.4.3.6).

In 2002, Linder et al[4721] found that: (1) the adhesion of primary human monocytes to DLC-coated glass coverslips is not significantly enhanced in comparison to uncoated coverslips, (2) the actin and microtubule cytoskeletons of mature human macrophages show normal development on DLC, and (3) growth on DLC does not affect the activation status of human macrophages, as judged by polarization of the cell body. The researchers concluded that "it is unlikely that contact with a diamond-like carbon coated surface in the human body will elicit inflammatory signals by these cells."

Finally, Jones et al[660,4726] deposited DLC coatings (by plasma-assisted CVD) and other coatings on titanium substrate and tested their hemocompatibility, thrombogenicity, and interactions with rabbit blood platelets. The DLC coatings produced no hemolytic effect, platelet activation, or tendency towards thrombus

formation. Platelet spreading correlated with the surface energy of the coatings (typically ~40 mJ/m^2 for DLC[4730]) with the lowest spreading for DLC.[4726] In general, platelet adhesion is reduced both by increased surface wettability and by the presence of platelet adhesion inhibiting proteins such as kininogen[756] which could be made available at nanorobot surfaces if required. Platelet adhesion to DLC or polycrystalline diamond surfaces has been measured experimentally as ~0.007 platelets/micron^2 after a 5-minute exposure to fresh human blood flowing at a wall shear rate (Section 9.4.1.1) of 50 sec^{-1}.[1680]

Any small object made of hydrophobic material may insert into bilayer lipid membranes. Experimental data have not been reported for diamond due to the unavailability of appropriate-size particles, but once these particles are obtained the interactions of, say, diamond nanorods with membranes can be studied and will likely show the insertion. E. Pinkhassik notes that an inadequately-controlled individual diamondoid nanorobotic arm or its protrusions might spontaneously enter the membrane of some cells, analogous to the solvation wave drive for cytopenetration proposed in Section 9.4.5.3.

15.3.1.3 Biocompatibility of Diamond-Coated Prostheses

Diamond has been touted as "the biomaterial of the 21st century",[596] and many uses for diamond surfaces in biomedical applications[604,4724] have been proposed including coatings for artificial heart valves,[548,550,594] prosthetic devices,[549,550,657,659] joint replacements,[593,605,606,4729,5688] catheters and stents,[594] orthopedic pins,[547] the roots of false teeth,[547] dental instrument tips,[594] surgical scalpels and microtome blades,[548,549] and even the complete fabrication of artificial heart valves.[548] Diamond electrodes also are widely employed in biosensors.[4831-4836]

So far, the largest anticipated use of biomedical diamond is in orthopedics and articulated prostheses. Early in vivo experiments involving diamond-like carbon (DLC) coated orthopedic pins implanted in sheep demonstrated low diamond bioactivity,[546,547] and implants of DLC-coated zirconium placed in the tibiae of Wistar rats for 30 days showed good osseointegration at the tissue-implant interface.[607] Chemical vapor deposition (CVD) diamond coatings for artificial joints are said to have "low immunoreactivity",[535] and in vitro testing of possible intra-articular diamond wear particles finds these particles "comparatively harmless".[605,608] DLC coatings deposited onto austenitic stainless steel hip implants and tested for cytotoxicity, cell adhesion (human fibroblasts) and mutagenicity in vitro showed good biocompatibility, as did in vivo tests of DLC-coated stainless steel cylinders 4 mm wide inserted into cortical bone and muscular tissue of sheep.[659] Allen et al[4722] implanted DLC-coated cobalt-chromium cylinders in intramuscular locations in rats and transcortical sites in sheep, and all implants were well tolerated as determined upon specimen retrieval 90 days after surgery. This indicates that DLC coatings are biocompatible both in vitro and in vivo, in musculoskeletal systems. Other DLC-type coatings for bone implants have also shown good biocompatibility[4727] and toughness — abrasive wear on amorphous diamond "is negligible compared with conventional hip joint materials".[4728]

Amorphous diamond coatings (80% sp^3 bonding fraction, 0.2-10 microns thick; sp^2/sp^3 film structure experimentally adjustable[4743]) deposited on stainless steel alloys via filtered pulsed-plasma arc discharge were found to be biocompatible causing no local tissue reactions. These coatings have been studied with the objective of attempting a total hip replacement.[609] Some DLC-coated metal prostheses have been implanted in humans[594] and the results appear promising.[608,657] For massive prostheses which are used to replace large segments of bone which are resected for bone tumors or for revision after failed standard prostheses, DLC coatings were tested and found to be the best of all surface finishes investigated.[610] Conformal coatings of DLC for geometrically complex mechanical structures to uniform thickness and quality[538] is challenging with current technology[5712-5714] but will become easy to do using the future techniques of positionally-controlled molecular manufacturing (Chapter 2).

Cardiac applications are another major area of active investigation of biomedical diamond coatings.[4731] In the late 1990s, all mechanical heart valves were still very thrombogenic, requiring mandatory high-dose warfarin treatment. But it was believed that DLC coatings[597] and plasma or glow discharge treatment (GDT) of mechanical valves[611] could reduce the extent of valve-related thrombogenesis by surface modification including (1) cleaning of organic and inorganic debris, (2) generating reactive and functional groups on the surface layers without affecting their bulk properties, and (3) making the surfaces more adherent to endothelial cells and albumin and less adherent to platelets, thus improving thromboresistivity.[611] A compact (~6 x 6 cm, 280 gm) centrifugal blood pump that was developed as an implantable left ventricular assist system (Chapter 22) has the entire blood-contacting surface coated with diamond-like carbon (DLC) to improve blood biocompatibility.[612] DLC or crystalline diamond coatings have often been recommended as the best possible coating material for blood-contacting LVAD surfaces.[596,613,1680]

Diamond-coated catheters have been proposed,[594] and their advantages would include lubricity, biocompatibility, low adhesion surface, impermeability and flexibility. DLC coatings generally adhere well to other catheter materials.[594] However, far more progress has been made in applying diamond coatings to stents (Section 15.5.3.2). Stents are used to prevent narrowing or closure of luminal systems and to ensure adequate flow through them.[614] They have been implanted in the coronary and peripheral arteries, in central veins, in the bronchi and the esophagus, and in the urethra and biliary duct.[594] Stents have traditionally been metallic because of the necessary mechanical requirements such as high expansibility with thin walls and high circumferential strength, but metal surfaces are thrombogenic.[620-623]. Corrosion resistance is dependent upon formation of a passive oxide film. If breached, metal ions are released, causing a foreign body inflammatory reaction[615-620] with a risk of tumor development.[624] The ideal stent should meet stringent requirements regarding thrombogenicity, biocompatibility and structure.[625]

Phytis L.D.A., a German stent-making company,* has developed a stainless-steel stent 60-80 microns thick that is entirely coated with a diamond-like layer which the company claims greatly reduces thrombogenicity and enhances biocompatibility.[626] The Phytis stent (Figure 15.11) is pressed into the intima of the blood vessel at high pressure (15-16 atm) during implantation, but is designed to reduce the cutting trauma[627] that normally takes place. Tests sponsored by the company showed that albumin adsorption was 20-fold less on the DLC coated stents than on SiO_2 and TiO_2 controls.[583] There was also a significant reduction of thrombogenic potential by the DLC stents compared to uncoated stents, which is further reduced for heparin-coated DLC stents.[628,4723] Other diamondlike stent coatings are also biocompatible.[4725,5711] DLC exhibits high flexibility compared with diamond as manifested in application in stent coatings where the cylindrical wired material expands to twice its diameter. This mechanical flexibility may be useful in the design of nanorobots.

** In December 2002, Phytis Corp.[5839] reported the "closing of our company branch" and characterized their business "as temporarily terminated."*

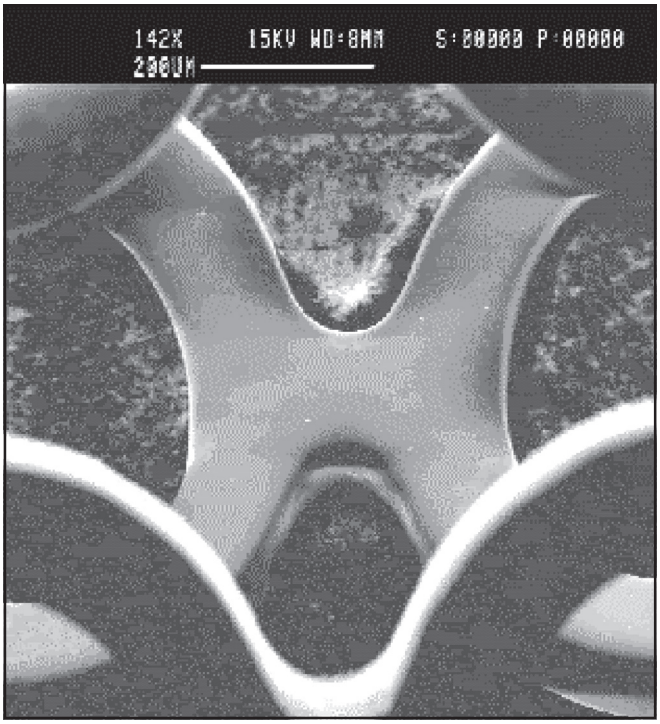

Fig. 15.11. The Phytis diamond stent, embedded in vascular intima.[4720]

Finally, an intraocular lens coated with a diamond-like carbon (DLC) film has been developed and its physical properties preliminarily investigated.[555]

It is important to reiterate that some nanomedical applications will demand a nonadhesive interface, while other applications will require complete tissue integration with the implant using biocompatible surfaces of engineered bioactivity, probably including atomically-precise nanostructured material surfaces that can promote and stabilize cell attachment.[629] Biocompatibility is highly application-specific — both adhesive and nonadhesive interfaces can be "biocompatible."

15.3.1.4 Biocompatibility of Diamond Particles

In biomaterials research, it has been found[630,631] that even though a bulk material may be well tolerated by the body, finely divided particles of the same material can often lead to severe and even carcinogenic complications in test animals. Differences in particle size influence histological reactions[644] and cytokine production.[645] Many nanomedical applications will involve "particle" sized diamondoid objects (e.g., micron-scale individual medical nanorobots) so it is of great interest to review the experimental data relating to the reactions of specific cells to the presence of diamond particles. We already know that finely divided carbon particles are well tolerated by the body[632] — the passive nature of carbon in tissue has been known since ancient times, and both charcoal and lampblack (roughly spherical 10-20 nm particles) have been used for ornamental and official tattoos[516] (Section 15.3.3.5). Diamond particles are also well tolerated by cells:

1. *Neutrophils*. A 1982 report of possible crystal-induced neutrophil activation[635-638] by 2- to 8-micron amorphous diamond crystals[634] was never confirmed. Indeed, to the contrary, diamond particles are traditionally regarded as biologically inert and noninflammatory.[633] For example, Hedenborg and Klockars[222] used 4- to 8-micron diamond dust as an inert control in their experimental work, and found that diamond dust did not stimulate the production of reactive oxygen metabolite by polymorphonuclear (PMN) leukocytes — a proposed pathway for chronic inflammation and tissue injury of the lung (Section 15.1.2). Tse and Phelps[633] found that 3-micron diamond dust crystals in a 2 mg/cm^3 concentration (~0.06% Nct; i.e., nanocrit, concentration in fluid, by volume, Section 9.4.1.4) were phagocytized by 21% of PMN cells (present at 7250 cells/mm^3 concentration) after 45 minutes, but no chemotactic activity was generated. Higson and Jones[639] exposed horse and pig neutrophils to urate, hydroxyapatite, pyrophosphate and brushite crystals (all implicated in joint inflammation) — which induced superoxide and peroxide generation in a concentration- and temperature-dependent fashion — but exposing the neutrophils to diamond crystals at 37 °C produced no effect. Yet another experiment[640] tested the ability of various crystals to stimulate phagocytosis, degranulation, and secretion of cell movement (motility) factors (CMFs) from polymorphonuclear leukocytes. The experiment found that hydroxyapatite (HA) crystals stimulated some enzyme release and CMF generation, and monosodium urate monohydrate (MSUM) crystals much more so. But 4- to 8-micron diamond crystal fragments in suspension up to ~0.2% Nct in culture, while clearly interacting with PMN leukocytes, did not stimulate degranulation, CMF production, or cell death even at high crystal concentrations. MSUM and HA particles are generally regarded as having atomically "rough" surfaces with a negative surface charge or Zeta potential, whereas diamond particles are considered relatively "smooth" with little or no surface charge.[633,640]
2. *Monocytes and Macrophages*. It has long been known that free carbon and diamond particles are ingested by cultured macrophages without harmful effects. For example, cells that have taken up large amounts of 2- to 4-micron diamond dust remain healthy for at least 30 hours, whereas cells succumb rapidly after ingesting silica.[652] Phosphatase enzyme discharged into diamond-containing phagosomes by adherent lysosomes did not escape into the cytoplasm or nucleus,[652] indicating that diamond does not damage these organelles (Section 15.5.7.2.4). In a more recent study,[641] 2- to 15-micron particles of diamond, silicon carbide (SiC), hydroxyapatite (HA) and polymethylmethacrylate (PMMA) were suspended in serum-free cultures of human monocytes at a concentration of 0.5 mg/cm^3 (~0.01% Nct in culture). All particles were phagocytosed, but while monocyte morphology changed after the ingestion of SiC and HA, there was no change after the ingestion of diamond, indicating no activation of the monocytes by the diamond. Interleukin-1β production was indistinguishable for control and diamond cultures, but increased 30-fold in the HA cultures, 38-fold in the cultures exposed to SiC, and in a similar range to HA and SiC for the PMMA. The authors[641] concluded that diamond particles in serum-free monocyte culture are inert, despite being phagocytosed, unlike most other particles. They offered several possible explanations for this: differences in opsonization, surface charge, or intracellular ion release.[646] Alternatively, different particles may be phagocytosed through different receptors on the monocyte surface. Macrophage responsiveness to diamond particles pre-exposed to protein-rich serum has not been extensively investigated, however.

3. *Fibroblasts*. Early studies in the 1950s[651] and 1960s[652] found that micron-size diamond dust particles did not induce fibrogenic activity. Schmidt et al[221] note that diamond dust is nonfibrogenic in human monocyte-macrophages found in the lungs. In other words, fibroblasts are not recruited by macrophages in response to the presence of diamond dust. Diamond dust of sizes <0.5 micron and 1-2 microns did not induce the release of thymocyte proliferation factor or fibroblast proliferation factor at diamond particle concentrations up to ~0.1 mg/cm^3 (~0.003% Nct in culture).[221] In another experiment,[642] synthetic hydroxyapatite crystals at a concentration of 50 μg/cm^3 in 1% and 10% serum stimulated 3H-thymidine uptake into quiescent canine synovial fibroblasts and human foreskin fibroblast cultures. Calcium pyrophosphate dihydrate crystals also stimulated uptake, as did calcium urate crystals markedly and sodium urate crystals more modestly. But 1- to 5-micron diamond crystals had no mitogenic effect on the fibroblasts at particle concentrations up to 0.4 mg/cm^3 (~0.01% Nct in culture).

4. *Other Cells*. The reactions of regenerating rabbit bone tissue to phagocytosable particles were studied[605] by dispersing various particles in hyaluronan and then introducing them into an implant-traversing canal, forming a bone harvest chamber. Tissue that entered the canal during the following 3 weeks was harvested. Particles of high density polyethylene, bone cement and chromium-cobalt injected in this fashion all provoked an inflammatory reaction in tissue entering the canal and caused a marked decrease in the amount of ingrown bone. But the phagocytosable 2- to 15-micron round-shaped diamond particles — introduced at a number density of ~60 million/cm^3 (~0.7% Nct in culture) — produced no decrease in bone formation and appeared "comparatively harmless...there was no obvious cellular reaction to these particles." Histologically, the diamond particles aggregated into clumps. Occasionally macrophages were seen nearby, but phagocytic cells remained few and dispersed, despite containing large amounts of ingested particulate diamond. There was no concentration of macrophages and giant cells such as is usually seen when PMMA or high-density polyethylene particles are implanted. Interestingly, 8- to 15-micron SiC particles also produced no inflammation or decrease in bone formation, even though the particles were "elongated splinters with sharp edges." Finally, neurologist Stephen S. Flitman [personal communication, 1999] notes that diamond has never been shown to be neurotoxic.

5. *Inflammation*. Tse and Phelps[633] found that 3-micron diamond crystals in a 10 mg/cm^3 concentration (~0.3% Nct injection fluid) injected into canine knee joints produced little evidence of inflammation — intra-articular pressure remained low, along with the local cell count. Diamond particles are generally considered noninflammatory relative to the complement system[1642] (Section 15.2.3.2), and produce no inflammation or edema in animal models.[1848,1849]

6. *Hemolysis*. Dion et al[643] observed no detectable hemolysis in vitro by various ceramic powders tested, including diamond, graphite and alumina, after 60 minutes of exposure to a powder concentration of ~0.5 gm per cm^3 of diluted blood (~14% Nct in vitro). The diamond powder in this experiment assayed ~1.25% impurities, mostly Zr.

7. *Other Biological Systems*. Diamond particles have been found to have an "adjuvant" effect on one fungus-based insecticide against beetles,[5228] probably due to the abrasive properties of these particles.

8. *Adamantanes*. Single-molecule units of diamond called adamantane ($C_{10}H_{16}$), when properly functionalized, possess useful pharmacological properties[5575] including antiviral[5513-5521] (including anti-HIV[5522-5524]) activity, antiparkinsonian and antidementia activity,[5525-5528] some anti-tumor activity[5529,5530,5565] though with toxicity problems at high dose,[5529] analgesic effects,[5568] and enhancement of immunotoxin activity.[5531] Interactions have been investigated between adamantanes and plasma proteins,[5532] cell adhesion proteins,[5533] enzymes,[5534-5543,5574] and receptors or channels;[5558-5560] with bacterial metabolism[5544,5565,5567] and viral assembly;[5571] and with polynuclear,[5545-5547] mononuclear,[5548-5552] and peripheral blood[5553] leukocytes. Lipid bilayer effects[5573] and cellular uptake[5566] of adamantane conjugates has been studied. Adamantane-based drugs such as amantadine[5554-5556] and tromantadine[5557] are nearly completely excreted unchanged in the urine, and typically no metabolites having a hydroxylated adamantane ring system can be detected.[5556] Of course, the properties of crystalline diamond are due to its molecular structure in which each carbon is in sp^3 hybridization and is bound to four other carbon atoms, and in n=1 adamantane, there is no single carbon that is bound to four other carbons. Polyadamantanes up to n=4 units have been chemically synthesized[5840] and polyadamantanes up to n=11 units have been identified, extracted, purified and crystallized from natural petroleum,[5841,5842] although the biomedical properties of these nanometer-sized diamond molecules have yet to be investigated.

15.3.1.5 Chemical Inertness of Diamond

A major benefit of diamondoid surfaces on medical nanorobots is that such surfaces should be extremely inert against attack by chemical substances at concentrations likely to be found inside the human body (Section 9.3.5.3.6). For example, in one study of a possible diamond-coated total hip replacement material,[609] 0.2- to 10-micron thick amorphous diamond (DLC) deposited on stainless steel alloys was found, after lengthy exposure to 10% HCl, to have corrosion rates reduced by a factor of ~15,000 compared to uncoated surfaces (see Section 15.3.3.6). No significant damage to the coatings was observed after 6 months. The Phytis diamond-like coated stainless steel stents showed almost zero release of chromium and nickel ions after 44-hour immersion in 1N HCl.[626] Diamondized stents incubated over 96 hours at 37 °C in human plasma released no detectable metal ions (e.g., nickel, chromium, molybdenum and manganese), as determined by Atomic Adsorption Spectroscopy (AAS) or by Inductively Coupled Plasma Mass Spectroscopy (ICP-MS).[626] Diamond-like carbon and diamond are both insoluble in reagents that dissolve graphite and other polymeric carbon structures.[599]

While diamond is believed to be very inert in tissues, further studies of bulk and particulate diamond biocompatibility with various tissues and organs are probably warranted, to supplement the traditional ADME and toxicology studies that the pharmaceutical industry might ordinarily consider in designing a clinical study for a new nanorobot.

Of course, medical nanorobot exteriors, while consisting mostly of diamondoid surfaces, may include various other materials (Section 15.3.6). The biocompatibility of internal nanorobot components and crush fragments of destroyed medical nanorobots is briefly addressed in Section 15.4.4.

15.3.2 Biocompatibility of Carbon Fullerenes and Nanotubes

Another potential building material for medical nanodevices is the graphene sheet comprising "buckyballs" (e.g., C_{60}) and "buckytubes" (e.g., carbon nanotubes), collectively known as the carbon fullerenes (Section 2.3.2). In principle, very large all-carbon cages could serve as containers for active nanomachinery, or graphene sheets could be worn as outer skins by atomically-diverse nanorobots or could compose the outer surfaces of nanorobot protuberances such as sensors or manipulators. In 1990, it was first announced that carbon-based fullerenes could be manufactured in macroscopic amounts.[916] Widespread experimentation began. By 1997, over 10,000 papers had appeared in the scientific literature describing the fullerene;[678] by late 2002, fullerene and nanotube biocompatibility had blossomed into a very active field of investigation — the interested researcher is urged to consult the most current literature for the latest results.

More than a decade after their initial discovery, the carbon fullerenes are being investigated for their bio-compatibility[681-751,4630-4636,5656,5657,6257] and biological applications.[679,2390,5230,5231] In general, the fullerenes have low cytotoxicity both in vitro[683,700,726,729,745,1095,5227] and in vivo.[719,720,745,1093,2599,5655] Few experiments on the biocompatibility of pure carbon nanotubes had been attempted by 2002,[2599] but there were a number of studies on the biocompatibility of pure C_{60} and related spheroidal fullerenes, as reviewed in Section 15.3.2.1. Of far greater immediate relevance to current medical applications of fullerene molecules are the many other fullerene biocompatibility studies that have examined C_{60} derivatives (Section 15.3.2.2). Derivatized fullerenes have much more importance in the near term especially given their possible many uses as pharmaceutical agents (Section 15.3.2.3).

15.3.2.1 Pure Carbon Fullerenes and Nanotubes

Because the fullerenes are condensed ring aromatic compounds with extended pi systems, concerns about their possible carcinogenic properties have been raised from time to time.[698,917] In regard to carbon nanotubes, inhalation toxicity has been the initial concern.[669,6060,6061] That's because carbon nanotubes are rigid cylinders >1 nm wide and up to 100 microns long that crudely resemble the shape of asbestos fibers that have been linked to cancer. The dangers of asbestos first emerged in the early 1960s, when studies linked exposure to these silicate fibers with mesothelioma — a rare cancer of the lining of the chest or abdomen (pleura, pericardium, or peritoneum) that's commonly fatal.[669] Asbestos fibers are small enough to be inhaled into the deep lung. Once embedded there, metals in the silicate fibers act as catalysts to create reactive oxygen compounds that go on to damage DNA and other vital cellular components. Asbestos expert Art Langer at the City University of New York's Brooklyn College has worried that carbon nanotubes may "reproduce properties [in asbestos] that we consider to be biologically relevant." Most notably, nanotubes are the right size to be inhaled. Their chemical stability means they are unlikely to be broken down very quickly by cells (hence could persist in the body), and their needlelike shape could damage tissue.[669] Morgan[6060] adds: "...the presence of long, extremely durable fibers in the lungs is worrisome. Nanotube ropes may indeed act like asbestos, and certainly if the nanotubes are wrapped up in something like PMMA they have a reasonably good chance of being damaging to the lung in moderate doses. But even if nanotubes are *not* damaging to the lung, we can't presently exclude a transport mechanism to a more sensitive organ elsewhere in the body. It makes sense to start the study of fullerene toxicology through inhalation studies. Concurrently, to get a better understanding of the mechanism of injury, we could study things like fiber durability in the lung, and lung cell protein production and macrophage sensitivity." In August 2002, Morgan[6060] announced that "we've recently come to an agreement with Dr. Joseph Brain, Harvard Department of Environmental Health, director of the Physiology program. He has agreed to study macrophage sensitivity and lung cell protein production in a mouse model, and will use nanotube material supplied by Dr. Edwards."

Chunming Niu, a chemist with Hyperion Catalysis International (Cambridge MA) that produces 300 kg/day of multiwalled carbon nanotubes (MWNTs), admits that this "certainly is a concern. We treat our nanotubes as highly toxic material." Rather than shipping nanotubes in powder form, Hyperion first incorporates the nanotubes into a plastic composite so that they cannot be inhaled.[669] As a precaution, many researchers who use carbon nanotubes in their work wear masks during procedures that could generate airborne plumes of the material.[5227]

Brooke Mossman, a pathologist at the University of Vermont College of Medicine, is reported as arguing that it is asbestos' ability to generate reactive oxygen compounds that makes it carcinogenic. Mossman says that the graphitic carbon structure of nanotubes is unlikely to react with cellular components to produce damaging byproducts: "We've worked with a lot of carbon-based fibers and powders and not seen any problems".[669] In 2001, Huczko et al[2599] at the Medical University of Warsaw conducted preliminary experiments to explore whether carbon nanotubes act in lung tissue the way asbestos does. Four weeks after subjecting guinea pigs to soot that did or didn't contain carbon nanotubes, pulmonary-function tests and inflammatory reactions (upon autopsy) were substantially identical between the groups. This led the researchers to conclude that "working with soot containing carbon nanotubes is unlikely to be associated with any health risk." Huczko[5655] also provides evidence that fullerenes have minimal risk of allergic reaction or skin irritation. However, Huczko's study[2599] evidently was performed without adequate controls and used techniques that have been abandoned by the EPA as not effectively evaluating the relevant criteria. Silvana Fiorito at the University of Montpellier in France found that 1-micron graphite particles stimulated rat cells to produce NO (nitric oxide, an indicator of immune response), but that neither carbon nanotubes nor fullerene cage molecules elicited NO production from these cells.[5227] Richard Smalley, the Rice University Nobelist and founder of Carbon Nanotechnologies Inc., was quoted in September 2002 as saying that an as-yet unreleased NASA study showed little cause for alarm over the biological safety of carbon nanotubes, though evidently one mouse tested died after receiving "vast amounts" of nanotubes in its lungs.[5716]

K.D. Ausman [personal communication, November 2002], Executive Director of Rice University's Center for Biological and Environmental Nanotechnology (CBEN), notes that in late 2002 the nanotube/asbestos comparison was still very much an open question, but that at least partial answers might be coming soon. Ausman notes that there appear to be two primary asbestos toxicity mechanisms.

The first toxicity mechanism involves the size and shape of the fibers, which prevents macrophages from engulfing the fibers and elicits a biochemical cascade that triggers the formation of scar tissue in the lungs. Given the current definitions of exposure limits (which include clearance rate in the denominator), no "safe" exposure limit can be set because these fibers are never cleared from the body. Says Ausman: "While nanotubes are much more rigid than asbestos fibers when normalized to aspect ratio, in practice they are not at all rigid individually because their aspect ratio is huge —

witness the remarkable curvature present in typical buckypapers. However, the tubes are frequently present as bundles or, depending on the sample, as multiwalled tubes. In those cases, the rigidity may be sufficient to see similar problems as seen with asbestos. The jury is still out, although there is a paper currently in peer review that sheds some light on this question."

The second toxicity mechanism of asbestos is due to very small amounts of bioavailable iron in the fibers which induces a type of cancer.[5793,5794] The most carcinogenic forms of asbestos, crocidolite and amosite, contain up to 27% iron by weight as part of their crystal structure, and these minerals can acquire more iron after being inhaled, forming asbestos bodies.[5794] Ausman notes that while nanotubes themselves are unlikely to produce a similar effect, nanotubes are traditionally made from metal catalysts, in many cases iron. "In typical samples, the metal content is huge compared to that of asbestos," he notes. "It is unknown how bioavailable it is, but again a paper that is in peer review should shed some light on this question."

The results of two studies — the NASA study and the DuPont study — focused on single-walled carbon nanotubes (SWNTs) were announced at an American Chemical Society meeting[6212,6213] in March 2003 as this book was going to press. According to one account,[6212] the NASA team[6214] exposed groups of mice to one of four substances: (1) newly made SWNTs mixed with tiny grains of the metal catalyst used in making the nanotubes, (2) SWNTs treated to remove the metals, (3) carbon black, or (4) quartz nanoparticles having well-characterized toxicity. The mouse lungs were instilled with a solution containing either 0.1 or 0.5 micrograms of material suspended in inactivated mouse serum. After 90 days, standard histological tests showed that all the particles made their way into the alveoli and most remained there intact. Even at the lower dose, the nanotubes (with or without metal particles) triggered granuloma formation surrounding the material, "a significant sign of toxicity." By comparison, the carbon black particles triggered little inflammation. In the second study at DuPont,[6215] SWNT-induced granuloma formation was similarly observed but the inflammation appeared to tail off after 90 days, and the group concluded that nanotubes were less toxic than the quartz dust. Both groups cautioned that conclusions about nanotube toxicity must wait until researchers learn more about how the animals' lung tissue reacts to airborne SWNT particles.[6248]

Almost all of the experimental studies to date have focused on the biocompatibility of C_{60} and related spheroidal fullerenes, rather than nanotubes. C_{60} (though easily destroyed by O_3 in the air even when shielded from UV and visible light[5508]) is present naturally in the environment,[5508-5512,6055-6058] being generated in trace amounts in virtually any sooty smoky flame, such as in forest fires, campfires and candle flames, and C_{60} has been discovered in meteorites,[5509] in space,[6056] and in carbon-rich shungite (a metamorphic Precambrian rock),[5510,6058] in more ancient formations dated back 1.85 billion years,[5511] and in rocks at the Cretaceous-Tertiary boundary.[5512,6057] (Carbon nanotubes might yet be found in nature.[6059]) Natural fullerene "concentrations have been exceedingly low and dose to humans, if any, have probably been trivial".[6060] Industrial toxicology reports show that pure C_{60} has virtually no inflammatory effect in mice and rats and does not elicit an immune response.[698] However, fullerenes readily adsorb molecular oxygen from air.[1604] Soon after bulk quantities of fullerenes became available for laboratory experimentation in the early 1990s, it was found that in the presence of light and oxygen, the C_{60} molecule could pass its superfluous excitation energy onto nearby oxygen molecules, creating a long-lived but very reactive form of oxygen called singlet oxygen.[680,681,918,919] It was quickly suggested that this could present potential health risks.[1099] Pure C_{60} is a singlet oxygen-generating agent. It yields singlet oxygen in very high amounts and is completely inert to photo-oxidative destruction.[682] One early experiment with macrophages observed little influence on the formation of reactive oxygen species by C_{60} but found that raw soot from fullerene production was oxidatively active with cells under the influence of light, though not cytotoxic.[683] (It also appears that C_{60} traps the chemical contaminant naphthalene much differently than soil,[6255] and Tomson et al[6256] are studying the impact and transport of carbon nanomaterials in the environment.)

Other experiments have since shown that C_{60} efficiently generates singlet oxygen when irradiated with light.[684] For example, when C_{60} was incorporated into rat liver microsomes in the form of its cyclodextrin complex and exposed to UV or visible light, it induced significant oxidative damage to lipids (e.g., lipid peroxidation as assayed by thiobarbituric acid reactive substances, lipid hydroperoxides, and conjugated dienes) and to proteins (e.g., assayed by protein carbonyls and loss of membrane-bound enzymes), predominantly due to the production of singlet oxygen.[685] Exposing C_{60} to laser pulses at 355 nm or 532 nm in the presence of O_2 produces large quantities of singlet oxygen. This occurs not by chemical reaction but by an energy transfer from the highly populated C_{60} triplet state to molecular oxygen.[919] K.D. Ausman notes that as the degree of derivitization increases for functionalized C_{60}, the efficiency of singlet oxygen sensitization goes down because the 1O2 sensitization goes through the C_{60} triplet state, and both the absorption cross-section at relevant wavelengths and the quantum yield of conversion to T1 drops. Light emission from carbon nanotubes was claimed to be observed in aromatic amine solvents,[4635] and Weisman and Smalley et al[5795] have found near-infrared emission from SWNTs. Photoinduced biochemical activity* has also been reported in fullerene carboxylic acid;[922] a "teflon ponytail" fullerene is an efficient sensitizer for (increasing) singlet oxygen formation in fluorous solvents;[4633] and porphyrin-fullerene hybrids have been synthesized.[4634]

On the other hand, when not in an excited state, C_{60} does not react with singlet molecular oxygen but quenches it slowly with a rate constant of $k_q \sim 5 \times 10^5$ / M-sec.[919] It is claimed that a single C_{60} molecule can absorb dozens of these reactive chemical species.[680] Water-soluble peptide (DL-alanine) and dipeptide (DL-alanyl-DL-alanine) derivatives of C_{60} are also known to quench pyrene fluorescence and erythrosine phosphorescence, both in water solution and in liposomes.[686] Charge transfer across C_{60}-doped bilayer lipid membranes has also been investigated by cyclic voltammetry to evaluate membrane suitability in practical biosensors,[687] and C_{70} can act both as a photosensitizer for electron transfer from a donor molecule and a mediator from electron transport across a lipid bilayer membrane.[688] Indeed, it was found that the steady-state photocurrent density obtained from the C_{70}-bilayer system was about 40 times higher, at comparable light intensities, than that of the carotene-porphyrinquinone system, previously the

** Some specific samples of single-walled carbon nanotubes (SWNTs) in air have emitted a loud pop and suddenly burst into flames when exposed to the light from an ordinary camera flash.[4697] According to Pulickel Ajayan of Rensselaer Polytechnic Institute, the initial popping noise is generated by the heating of the oxygen inside and between the nanotubes, which produces a shock wave that causes the carbon to oxidize, sparking combustion, when the temperature reaches 600-700° C. The explosion occurs because the black carbon nanotubes absorb light so efficiently that, when it is converted into heat, the heat cannot dissipate quickly enough across bunched-up tubes. MWNTs, unlike SWNTs, do not explode, and other nanotube researchers have taken flash photographs of SWNTs without triggering combustion.*

most efficient artificial system known in the early 1990s. The C_{70}-bilayer system has a quantum yield of about 0.04, while the stability (tens of minutes) and turnover number (10^3 electrons transported per C_{70} before decay) are 1-3 orders of magnitude greater than in other systems.[688]

Can fullerenes spontaneously traverse lipid bilayers? A simple C_{60} cage easily accepts electrons, acquiring a negative charge,[680] and nanotubes readily pick up negative charges in aqueous suspension.[689,690] The large electron affinity of fullerenes like C_{60} or C_{70} is well known.[691] Fullerenes exhibit enhanced electron-withdrawing character upon increase of their molecular size.[691] The negative charge of lipid bilayers (and most in vivo biological surfaces) might argue for fullerene objects to be slightly repelled from cell membranes. However, E. Pinkhassik notes that the negative charge of fullerenes is delocalized over a very wide surface and therefore should not be the decisive factor.

In general, hydrophobic molecules readily insert into the interior of the bilayer membrane, so we should expect fullerenes to insert into bilayers as well. Indeed, organic nanotubes with hydrophobic groups on their exterior surface are observed to spontaneously insert into lipid bilayers,[692] and C_{60} is highly hydrophobic.[693,725] Carboxylic acid C_{60} derivatives having polar character can readily enter lipid membranes,[745] and water-solubilized peptide (DL-alanine) and dipeptide (DL-alanyl-DL-alanine) derivatives of C_{60} can localize inside an artificial membrane, penetrate through the lipid bilayer of phosphatidylcholine liposomes, and perform activated transmembrane transport of bivalent metal ions.[686] The rapid uptake of radiolabeled C_{60} into human cells (~50% of C_{60} present in serum, within 6 hours[695]) does not result in acute toxicity and does not affect the proliferation rate of human keratinocytes or fibroblasts.[694,695] Open-ended carbon nanotubes that spontaneously inserted into cell membranes could promote cell lysis much like porins (Section 10.4.1.4), transmembrane siphons (Section 10.4.2.1), or the membrane attack complex (Section 15.2.3.2). Additional research will be required to identify all the parameters which may govern the spontaneous insertion of fullerenes into cell membranes.

E. Pinkhassik notes that the insertion of fullerenes into membranes can be directly relevant to nanorobot construction if one considers the danger of fullerene-based nanorobot appendages poking into cells. Accidental whole-nanorobot diffusion through bilayers is unlikely due to the large size of such a device, but an individual nanorobotic arm or its protrusions might potentially spontaneously enter the membrane of some cells. This issue could arise for graphene-based appendages or for any other hydrophobic material used in the construction of a small-diameter nanorobotic arm whose feature lengths exceed a half-membrane thickness, or about 3-5 nm (Section 8.5.3.2).

Another potential nanomedical concern is carcinogenicity.[698,917] Many organic substances that have aromatic ring systems, such as benzene, are carcinogens because a conjugated carbon ring has the appropriate size and shape to be intercalated into DNA, thus promoting cancer. But buckyballs appear to be too big and round to be incorporated into DNA,[680] as are buckytubes (essentially a curved array of such rings). So these should not present a problem as long as they remain intact. Preliminary experiments with mouse skin exposed to pure C_{60} and C_{70} confirm this expectation,[698] though more data is needed to increase confidence in the lack of carcinogenicity. The possible carcinogenic risks of nanotubes was discussed above.

Genotoxicity is defined as a serious injury to the chromosomes of the cell, such that when the cell divides, fragments of chromosomes and micronuclei remain in the cytoplasm. Experiments by Zakharenko and colleagues in 1994[696] and in 1997[697] examined the genotoxicity of C_{60} in prokaryotic cells (*E. coli*) and in eukaryotic cells (*Drosophila* somatic wing cells). No genotoxicity was observed at a C_{60} concentration of 0.45 $\mu g/cm^3$ in any of the cells, but at the highest fullerene concentration of 2.24 $\mu g/cm^3$ a slight genotoxic effect was observed in the eukaryotic cells.

A related concern is mutagenicity — the production of coding flaws in chromosomes that otherwise may retain much genetic functionality. Miyata et al[681,1092] found that C_{60} dissolved in polyvinylpyrrolidone was mutagenic for several *Salmonella* strains in the presence of rat liver microsomes when irradiated by visible light. Their results suggested that singlet oxygen was generated and that the mutagenicity was caused by the indirect action of singlet oxygen producing phospholipid peroxidation (principally of the linoleate fraction) in rat liver microsomes, leading to oxidative DNA damage (probably with the generation of radicals at the guanine bases only). However, a confusing factor in this study was their use of polyvinylpyrrolidone, a solvent known to cause liver cancer. Indeed, many studies of the biocompatibility of pure fullerenes have had to employ biologically harmful solvents, since naked fullerenes are not soluble in physiological saline. Teratogenicity (e.g., fetotoxicity; Section 15.2.8) of pure fullerenes has yet to be seriously investigated.

Cell and tissue biocompatibility experiments on pure fullerenes — principally C_{60} — have begun. In many situations, pure fullerenes are almost completely bioinactive.[5230] For example, the dermal toxicity of pure C_{60} was studied by applying a solution of C_{60} in benzene to mouse skin epidermis. A 200 mg topical dose produced no acute toxic effect on either DNA synthesis or ornithine decarboxylase activity over a 72-hour time course after treatment.[698] Repeated epidermal administration of fullerenes for up to 24 weeks (after initiation with a polycyclic aromatic hydrocarbon or PAH) resulted in neither benign nor malignant tumor formation. Promotion with a phorbol ester used as a positive control resulted in the formation of benign skin tumors.[698] In another study of the pharmacological effects of fullerenes on various tissues, pure C_{60} was applied to guinea pig trachea, right atria, ileum, and stomach (fundus) tissues, and to rat vas deferens and uterus.[699] A 4 μM (~3 $\mu g/cm^3$) dose had no direct effect in any tissue. A short-term repeated application of a 30 mg/kg dose of C_{60} for 4 weeks significantly reduced the potencies of acetylcholine in guinea pig ileum and its longitudinal muscle. C_{60} was found to have no direct or antagonistic properties toward drug receptors, though sub-chronic exposure decreased responsiveness. No effect on bacterial growth rates was found in 22 microbial strains exposed to C_{60} at doses of 43.2 $\mu g/cm^3$, and there was no cytotoxicity to human macrophage, leukocyte, or monocyte.[2383] (Therapeutic doses in rodent models are typically measured in μg.)

Besides the aforementioned work of Fiorito,[5227] by early 2002 the only direct study on carbon nanotube cytocompatibility was by Mattson et al[4820] who grew embryonic rat-brain neurons on multiwalled carbon nanotubes. They reported that on unmodified nanotubes, neurons extend only one or two neurites, which exhibit very few branches. In contrast, neurons grown on nanotubes coated with 4-hydroxynonenal (a bioactive molecule) elaborate multiple neurites which exhibit extensive branching.[4820] This result was said to "establish the feasibility of using nanotubes as substrates for nerve cell growth and as probes of neuronal function at the nanometer scale."

Other experiments have found some bioactivity,[5233] though usually only in functionalized fullerenes (Section 15.3.2.2). For instance, C_{60} solubilized with polyvinylpyrrolidone (PVP) in water was applied to the rat limb bud cell differentiation system and very strongly promoted cell differentiation (up to a 3.2-fold increase).[700] PVP alone inhibited the cell differentiation in proportion to its concentration, suggesting that a specific promoting action on chondrogenesis

may exist for C_{60}. In a test of the immune reactions of macrophages, raw soot from fullerene production and purified C_{60} were incubated with alveolar macrophages and macrophage-like cells. The effects of this treatment were compared to DQ12 quartz which is known to damage BAM and HL60M macrophages. Neither soot nor C_{60} were cytotoxic compared to quartz, but C_{60} did induce some chemotactic activity, although less than the soot or the quartz.[683] Nobuhisa Iwata et al[701] investigated the effects of C_{60} on the activities of glutathione S-transferase (GST), glutathione peroxidase (GSH-Px), and glutathione reductase (GR) enzymes in rodent and human liver. C_{60} inhibited GST activity toward trans-4-phenyl-3-buten-2-one in rat liver and toward ethacrynic acid in mouse liver, while activity toward other substrates was not affected. In human liver, C_{60} again inhibited GST activity toward ethacrynic acid and moderately inhibited GSH-Px and GR activities as well. Lin and Wu[702] conducted a study of platelet activation, using amine-terminated silane coupling agents to graft C_{60} molecules onto a polyurethane (PU) surface pretreated with oxygen plasma activation. Electron spectroscopy for chemical analysis (ESCA) analysis showed that the C_{60} molecules spontaneously attached via nucleophilic additions to the fullerene double bonds which fuse two six-membered rings. In vitro platelet adhesion assay subsequently demonstrated that the C_{60}-graft-PU activated more platelets than the nontreated PU control, though the researchers[702] admitted this might be due to "the few residual amine functional groups which are left over after the C_{60} grafting reaction."

Pure fullerenes are fairly chemically inert. They are stable substances in air or in solution and can be purified by sublimation without decomposition.[678] Unmodified fullerenes are virtually insoluble in water,[2566] suggesting a low reactivity with biological tissue.[680] They are only slightly soluble in ethanol but are much more soluble in aromatic solvents and in carbon disulfide,[695,910,920,921] with highest solubility in 1,2-dichlorobenzene.[2552,2566] Mustard-yellow aqueous suspensions of C_{60} have been prepared that do not settle out upon standing for more than 3 months. SEM examination of these suspensions shows the suspended particles are spherical clumps of C_{60} between 250-350 nm in diameter. There is some evidence for suspended-particle oxidation, to $C_{60}O$, after prolonged storage in air.[695] Pure C_{60} and C_{70} have also been solubilized by encapsulation inside hollow aggregates of block copolymers.[2547]

Intact pure fullerene surfaces are unlikely to be attacked by chemicals naturally present in the human body, although the possibility of a graphene surface being chemically attacked by short-lived reactive intermediates that form during metabolic processes cannot be entirely ruled out. There is just one unconfirmed (but somewhat dubious) report[2384] of the metabolization of C_{60} by a microbe — it is claimed that several species of fungi can grow in fullerenes as their sole source of carbon. Fullerenes can have numerous chemical groups attached to their surfaces via processes known variously as solubilization, conjugation, complexing, derivatization, or functionalization, typically using intermediary reactive chemical species not normally found inside the human body. Examples of chemical groups that have been added to C_{60} include hydroxyls (making water-soluble fullerols or fullerenols),[703-705] carboxylic acid,[922] proline,[706] polyamines,[707], amine-terminated silane,[702] aldehydes,[708] pyrrolidines[709,710] and poly(vinylpyrrolidone),[921] polyethylene glycol,[684] cyclodextrin,[909] cyclopropane,[711] lipid micelles and vesicles,[910] methanofullerenes[711] and lipidized methanofullerenes,[712] and even proteins[725,911] making water-soluble "fullereyl protein".[724,911] The C_{60} cage can reversibly accept up to 6 electrons under suitable conditions.[1100] Carbon nanotubes have been derivatized with, among other chemical groups, benzyne,[713,714] thionychloride and octadecylamine.[715] The variety of chemical modifications of fullerenes may warrant the study of interactions between the fullerene surface and the reactive species found in the human body.

With proper chemical treatment, C_{60} can have a stable orifice of fixed diameter opened up in its side, only allowing atoms smaller than a certain size to enter.[716,717] The open ends of ruptured carbon nanotubes, cut fullerene pipes, or ruptured fullerene surfaces would most likely be terminated with carboxylic acid groups if the cutting occurred in an acidic environment.[718] In non-acidic environments, hydroxyls, amines (basic), hydrocarbons (hydrophobic), or other terminating moieties could be present instead, producing alternative chemical reactivities near the break site.

C_{60} remains structurally intact (~99%) when exposed to a neutron flux of up to 1.5×10^{16} neutrons/m^2-sec.[1089]

15.3.2.2 Derivatized Carbon Fullerenes and Nanotubes

Most biocompatibility studies focus not on pure (insoluble) fullerenes but rather on solubilized C_{60} derivatives which may have potential utility as pharmaceutical agents. Tests have been devised to simplify fullerene biocompatibility testing, as for example methods of quantitative analysis of C_{60} in blood and tissues using high-performance liquid chromatographic assay.[719]

In general, water-soluble fullerene derivatives[5234] (and possibly their simple metabolites) are not acutely toxic even at 200-500 mg/kg doses in mice.[720] For instance, LD50 acute toxicity of fullerenol-1 for intraperitoneally-treated mice is ~1200 mg/kg.[721] In one study,[722] highly water-soluble polyalkylsulfonated C_{60} (FC4S) in 50 mg/cm^3 concentration was administered to rats. FC4S was completely nontoxic if given orally, but rats died within 30 hours after intraperitoneal injection with an enormous LD50 dose of 600 mg/kg of body weight — i.e., the drug is highly nontoxic at therapeutic concentrations. Intravenous or intraperitoneal injections in rats prompted immediate elimination through the kidney (the primary target organ in this study[722]), and induced phagolysosomal nephropathy in acute exposure rats and in surviving rats receiving 500 mg/kg intraperitoneally or 100 mg/kg intravenously (~0.1% Nct) — again, highly nontoxic. Toxicity of MSAD-C_{60} in rats is somewhat higher: 25 mg/kg administered by bolus intravenous injection in rats caused shortness of breath and violent movement, followed by death in 5 minutes,[734] though no toxicity was reported after intraperitoneal administration of 50 mg/kg-day for 6 days to mice.[1096] These compounds are believed not to be hemolytic.[734,921]

C_{60}- and C_{70}-derived fullerene carboxylic acids showed no photocytotoxicity toward Raji cells (B lymphocytes),[723] and intranigral infusion of carboxyfullerene appears to be nontoxic to the nigrostriatal dopaminergic system.[747] Nor are the derivatized fullerenes particularly mutagenic. One experiment[697] found no mutagenic effect in fullerol concentrations up to 2.46 mg/cm^3.

Small-molecule fullerenes are not normally recognized by the immune system and do not trigger the natural production of antibodies by themselves,[719,2516,4630] solubilized fullerenes can induce the production of specific antibodies,[724,725,2164,2387-2390] usually by interaction with the combining sites of IgG,[725] or can enhance IgG production as adjuvants.[5657] Immunization of mice with a water-soluble C_{60} derivative conjugated to bovine thyroglobulin yielded a population of fullerene-specific antibodies of the IgG isotype. This showed that the immune repertoire was diverse enough to recognize and process fullerenes as protein conjugates.[725] The antibody population also included a subpopulation that crossreacted with a C_{70} fullerene as determined by immune precipitation and ELISA (enzyme-linked immunoabsorbent assay) procedures. C_{60} conjugated with BSA produces polyclonal response in rabbits and monoclonal response in rats.[4630] It is speculated[725] that highly

hydrophobic fullerenes would be recognized by antibodies with hydrophobic amino acids in their binding sites, as has been reported for the combining site of an Fab' fragment of a monoclonal antibody specific for progesterone,[912,913] which is a highly apolar molecule of similar size to C_{60}. C_{60} and other fullerenes can also interact with donor $-NH_2$[914] and -SH[915] groups.

Antibodies raised to C_{60} in mice strongly bind to single-walled carbon nanotubes.[2386] There are several reports of antibodies being raised to single-walled carbon nanotubes,[2164,2385-2387] as for example a mutant of 1-10F-8A that targets single-walled carbon nanotubes.[4630] Computer simulations suggest that it may be possible to build antibodies which selectively bind to nanotubes of a specific diameter or chirality.[2164]

There are reports of fullerene compound interaction directly with biological receptors.[2390] For example, the Wilson group[2567] has prepared a fullerene-estrone hybrid compound that has estrogenic activity, binding to cytosolic estradiol receptor with K_d ~ 40 μM. Toniolo et al[693] has prepared a hydrophilic fullerene-based analog of peptide T which exhibits potent activity in a CD4 receptor-mediated human monocyte chemotaxis assay. Computer models have been used to assess the interaction of fullerenes with HIV protease,[735,2568] glutathione-S-transferase,[1092] DNA,[2569] and a peptide helix.[2570]

Solubilized fullerenes are bioactive[726] in tests with many different types of living cells. For instance, C_{60} fullerenol-1 inhibits the proliferative responses (transduction signals) of a number of cells, including rat aortic smooth muscle cells (at 10^{-6} - 10^{-2} M concentration), human coronary artery smooth muscle cells, and human CEM lymphocytes — possibly mediated through the inhibition of protein tyrosine kinase.[744] In another experiment, fullerenol-1 applied to rodent liver microsomes reduced monooxygenase activity and decreased cytochrome P450 and b5 contents at 500-1000 mg/kg doses, but had no effect at 10-100 mg/kg doses.[721] Added to rat liver mitochondria, fullerenol-1 decreases mitochondrial oxidative phosphorylation in vitro, producing a dose-dependent inhibition of ADP-induced uncoupling and significantly inhibiting mitochondrial Mg^{++}-ATPase activity with an IC50 level at 7.1 μM.[721] Highly water-soluble polyalkylsulfonated C_{60} (FC4S) in 50 mg/cm^3 concentration administered to rats suppresses liver cytochrome P-450-dependent monooxygenase activities but increases kidney cytochrome P-450-dependent monooxygenase activities.[722] C_{60} solubilized with polyvinylpyrrolidone (PVP) in water and incubated with mouse embryos in vitro potently inhibits cell differentiation and proliferation.[727]

Pharmacological effects of fullerenes on various tissues have been noted. For example, monomalonic acid C_{60} (MMA-C_{60}) was applied to endothelium-containing or denuded aorta of rabbit, trachea and ileum of guinea pig, and stomach (fundus), vas deferens and uterus of rat. At 10^{-5} M concentration, MMA-C_{60} was found to significantly reduce the endothelium-dependent relaxation induced by acetylcholine, but not to affect the agonist-induced contractile response of smooth muscle.[728] Dimalonic acid C_{60} at 10^{-5} M concentration inhibited endothelium (nitric oxide)-dependent agonist-induced relaxation through the production of superoxide.[729]

The biodistribution of fullerenes throughout body tissues, after they are introduced in vivo, has been studied. In one experiment,[720] a ^{14}C-labeled trimethylenemethane-based water-solubilized C_{60} fullerene was administered orally to rats. The compound was not efficiently absorbed and was excreted primarily in the feces. When injected intravenously, however, the compound distributed rapidly to various tissues with most of the material still retained in the body after one week, and with retention mostly in the liver (90%).[720] The substance also penetrated the blood-brain barrier. When administered intraperitoneally to pregnant mice at 50 mg/kg, PVP-solubilized C_{60} was clearly distributed into the yolk sac and embryos.[727] Microscopic evaluation revealed a harmful effect on conceptuses,[727] although the effects of underivatized C_{60} on embryogenesis were not reported. A biodistribution study of underivatized C_{60} in Swiss mice (4-5 mg/kg doses) found that >95% of the fullerene material was retained, mostly in the liver, probably unmetabolized.[705]

In 1999, Gonzalez and Wilson[731] tested a C_{60} fullerol (containing 16 hydroxyls) functionalized with an amide bis-phosphonate chemical group. This compound showed selective binding to the hydroxyapatite of bone (thus altering the mineral's usual crystal growth) which suggests that a rationally-designed molecule could be used to target bone tissue, possibly as an agent to address osteoporosis. Another study found that C_{60}-PEG conjugate injected intravenously into mice carrying a tumor mass in the back subcutis exhibited higher accumulation and more prolonged retention in the tumor tissue than in normal tissue.[684] However, the conjugate was excreted without being accumulated in any specific organ.[684] In vivo fullerene biodistribution studies of insoluble C_{60} and La@C_{60} suspensions* [719,1093] and water-soluble C_{60} derivatives[720,734,751] indicate a short residency in the blood pool with rapid localization and long-term residency in the liver (<1% clearance). One of these studies[751] demonstrated that fullerenes are not metabolized rapidly in vivo, although fullerene oxidation of C_{60} derivatives has been observed in vivo,[751] followed by selective absorption by liver cells.[732,1097] Although their acute toxicity is low at the ~mg/kg dose level,[705] water-soluble fullerenes are retained in the body for long periods which raises concerns about chronic toxic effects.

However, another biodistribution experiment by Wilson et al[705,730,1094] at Rice University found that solubilized C_{82} endohedral metallofullerenes — each containing a trapped radioactive holmium atom ($Ho_x@C_{82}(OH)_y$) — when introduced intravenously remain in the blood for about an hour with nearly total clearance from the blood shortly thereafter. These endohedral metallofullerenes localize in bone, spleen, kidneys, and liver, but with slow and steady clearance from all tissue (~20% after 5 days in rats) except bone, where fullerene concentration steadily increases with time. After 48 hours, metallofullerene concentration falls to 15% of injected dose (ID) in the liver, only slightly lower than the maximum of 24% ID for liver. Concentrations are only 3.6% ID (down from 7.6% ID max) in the kidney and 0.36% ID (down from 5.1% ID max) in the blood pool.[705] Accumulation in the brain is negligible.[705] After the first day, when 88.4% ID remains in rats, clearance is ~1.5% ID per day, with nearly equal amounts eliminated in the feces and urine.[705] Another biodistribution experiment[1093] involved a suspension of insoluble metallofullerene (La@C_{82}) injected directly into the heart of anesthetized rats. After 24 hours, >80% of the material still present in the body was located in the liver and blood pool, with some retention also in the brain.[1093]

Most recently, B.F. Erlanger's group[5880] injected carboxyfullerene and fluorescent-labeled antibodies targeted to naked fullerene to observe possible targeting to specific intracellular compartments of the fullerene-based agent in an animal model. They directly observed via fluorescence that the fullerene derivative had crossed the external cellular membrane and localized preferentially to the intracellular mitochondria. This seems to support "the potential use of fullerenes as drug delivery agents as their structure mimics that of clathrin known to mediate endocytosis."

** The nomenclature "X@C_{60}" is commonly used in fullerene chemistry to indicate that atom X is endohedrally trapped inside the closed C_{60} molecular cage.*

While fullerene molecules can exhibit a wide range of interactions, many of these interactions will not take place at the surfaces of medical nanorobots with graphene exteriors. E. Pinkhassik notes that "high mobility of relatively small buckyballs is responsible for many physiological actions observed by different researchers, and since the larger nanodevices will not be able to cross the membranes or easily get to active sites of proteins, they should be even more inert than their smaller counterparts."

15.3.2.3 Fullerene-Based Pharmaceuticals

By 2002, several major classes of fullerene-based pharmaceutical applications were under active investigation, most notably by the biotech company C Sixty,[5362] including:

1. *Antivirals*. Fullerenes have shown activity against HIV.[693,732-735,1096-1098] In 1993, MSAD-C_{60} was found effective against HIV-1 and HIV-2 with 50% effective concentration (EC50) averaging 6 x 10^{-6} M in acutely or chronically infected human lymphocytes, and with selective activity against HIV-1 protease.[732] MSAD-C_{60} was noncytotoxic up to 10^{-4} M in peripheral blood mononuclear cells and in H9, Vero, and CEM cells.[732] Following intravenous administration at 15 mg/kg of body weight, pharmacokinetic studies showed a half-life of 6.8 hours in the blood with distribution into the tissues. Binding studies showed the compound was >99% bound to plasma proteins.[734] MSAD-C_{60} is well tolerated in mice after IV administration up to 15 mg/kg, but a higher dose of 25 mg/kg produces shortness of breath and violent movement of rats, followed by death with 5 minutes of dosing.[734] By 1998, computational models for optimizing the binding of fullerene inhibitors of the HIV-1 protease led to the synthesis and testing of two C_{60}-derived ligands for the HIV protease active site that displayed ~50-fold increase in affinity compared to previously tested fullerene compounds.[735]

   By the late 1990s,[736] photodynamic reactions induced by singlet oxygen-generating agents were known to inactivate enveloped viruses.[682] Pure water-insoluble photosensitizer C_{60} could be used to mediate the inactivation of enveloped viruses. Buffered solutions containing C_{60} and Semliki Forest virus (SFV, *Togaviridae*) or vesicular stomatitis virus (VSV, *Rhabdoviridae*), when illuminated with visible light for up to 5 hours, resulted in a significant loss of infectivity. Viral inactivation was oxygen-dependent and equally efficient in solutions containing protein. C_{60} fulleropyrrolidone was also known to have antiviral activity.[737] A C_{60} molecule covalently linked to peptide T, like peptide T, displays potent human monocyte chemotaxis while weakly inhibiting HIV-1 protease.[693] C Sixty's anti-HIV fullerene compound $CSDF_1$ exhibits high water solubility (200 gm/liter), complete renal excretion, and a highly nontoxic LD50 of 800 mg/kg in rodents.[4630,5235] The drug appears effective even against highly resistant strains of the virus. The binding constant is ~nM for C Sixty's anti-HIV protease inhibitor;[4630] the company's anti-HIV drugs apparently have about one-tenth the toxicity of current HIV cocktails, and human trials start in 2003.[259]

2. *Antibacterials*. A water-soluble malonic acid derivative of C_{60} (carboxyfullerene) was protective in mice against *E. coli*-induced meningitis death in a dose-dependent manner, even when administered intraperitoneally as late as 9 hours after *E. coli* injection.[738] Fullerene-treated mice had less tumor necrosis factor alpha and less interleukin-1b production compared to the production levels for nontreated mice. *E. coli*-induced increases in blood-brain barrier permeability and inflammatory neutrophilic infiltration were also inhibited,[5876] suggesting that the C_{60} compound could be a useful therapeutic agent in some cases of bacterial meningitis.[738] Other fullerene-based inhibitors of *E. coli* growth have been investigated.[5236] Positively-charged water-soluble fullerene derivatives inhibit growth of *Mycobacterium tuberculosis* at ~0.005 mg/cm^3 concentrations.[2382] Carboxyfullerene directly inhibits in vitro growth of *Streptococcus pyogenes* and enhances bactericidal activity of neutrophils in mice in vivo,[5874] suggesting that the fullerene derivative "can be considered an antimicrobial agent for group A streptococcus infection." Subsequent work[5875] by this research group found that the antibacterial action of carboxyfullerene on Gram-positive bacteria is achieved by insertion into the cell wall and destruction of membrane integrity. Other studies[5877] have also found antibacterial activity of fullerene derivatives, and even of carbon nanotubes [U. Sagman, personal communication, December 2002].

3. *Tumor/Anti-Cancer Therapy*. A C_{60}-PEG conjugate irradiated by light strongly induced tumor necrosis without any damage to the overlying normal tissue,[684,2576] with complete cure achieved by a C_{60}-PEG dose of 0.424 mg/kg and irradiation power of 10^{11} J/m^2, making this and similar materials[5237] excellent candidates for photodynamic tumor therapy. In vitro cytotoxicity against the HeLa S3 cell line has been evaluated by studying the inhibited growth rate,[922] and some C_{60} derivatives have shown promise as anti-cancer agents.[1090-1092] Photodynamic activity of PEG-modified fullerene is reported against fibrosarcoma tumors in mice and on erythrocyte membrane.[2577,2578] Water-soluble $C_{60}(OH)_{24}$ has been shown (1) to strongly block microtubule assembly, (2) to inhibit cell growth via inhibition of mitotic spindle formation much like taxol, and (3) to affect the growth kinetics of human lymphocyte cultures and HEP-2 epidermal carcinoma cell cultures.[2571] Liposomes containing ~0.1 mM of solubilized C_{60} are reported to have anticancer effects on human cervical cancer cells.[2572] Other fullerene-based inhibitors of cancer cell[5236] and tumor[5237] growth have been investigated, and the first fullerene-based clinical treatment of a human patient with rectal adenocarcinoma was attempted by Andrievsky et al.[5238] Chemotherapeutic agents are also being attached to larger fullerene structures to be carried inside liposomes, that C Sixty calls "buckysomes."

4. *Anti-Apoptosis Agents*. C_{60} is a free-radical scavenger and can act as antagonist for ceramide-triggered (but not Fas-triggered) apoptosis.[739] Transforming growth factor-beta (TGF-β) induces apoptosis in normal hepatocytes and hepatoma cells, but carboxyfullerene blocks the apoptotic signaling of TGF-β in human hepatoma cells.[746] The antiapoptotic activity of C_{60} carboxyfullerene is correlated with its ability to eliminate TGF-β-generated reactive oxygen species,[746] and carboxyfullerene protects human keratinocytes from ultraviolet (UVB) damage[5878] "possibly via a mechanism interfering with the generation of reactive oxygen species from depolarized mitochondria." Carboxyfullerene also exerts some protection against oxidative stress-induced apoptosis in human peripheral blood mononuclear cells (PBMCs).[5879] Another water-soluble C_{60} derivative protects epithelial cells from substrate-restriction apoptosis by exerting a trophic effect on actin microfilaments, thus influencing cell adhesion ability.[740]

   More interesting are the neuron anti-apoptotic effects. In one experiment,[741] water-soluble C_{60} fullerenols decreased excitotoxic neuronal death following brief exposure to

N-methyl-D-aspartate (NMDA) (by 80%), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) (by 65%), or kainate (by 50%). The fullerenols also reduced neuronal apoptosis induced by serum deprivation.[741] (The fullerenols were not NMDA or AMPA/kainate receptor antagonists.) In a related experiment,[745] carboxylic acid C_{60} derivatives inhibited the excitotoxic death of cultured cortical neurons induced by exposure to NMDA, AMPA, or oxygen-glucose deprivation. One C_{60} derivative fully blocked even rapidly triggered NMDA receptor-mediated toxicity and reduced apoptotic neuronal death induced by either serum deprivation or exposure to amyloid beta peptide (Aβ1-42), the established cause of Alzheimer's disease.[5917] This suggested that polar carboxylic acid C_{60} derivatives might have attractive therapeutic properties in several acute or chronic degenerative diseases such as amyotrophic lateral sclerosis (ALS, or Lou Gehrig's disease).[745] In 2002, C Sixty had fullerene-based drugs to combat ALS and Parkinson's disease under development,[4630] with human trials expected to begin in 2003.[259]

5. *Antioxidants*. C_{60} derivatives[683,726,739,748,2583] including fullerenols,[741-744,2581] carboxyfullerene,[745-747,5875,5879] polyalkylsulfonated C_{60},[722] hexa(sulphobutyl)fullerene,[749] C_{60}-dimalonic acid[2582] and C_{62} bis(malonate)[1091] are known or suspected free-radical (oxygen-radical) scavengers. These derivatives often provide potent antioxidative action (e.g., preventing hydrogen peroxide- and cumene hydroperoxide-elicited cellular damage[742]) without increasing lipid peroxidation.[747] In experiments with mice, Dugan et al[741,745] found potent antioxidant properties in buckyballs (hundreds of times more powerful than Vitamin E) that could shield nerve cells from free radicals. C_{60} monomalonate selectively inhibited activity of the neuronal nitric oxide synthase (nNOS) isoform.[4631] C_{60} trisamine adducts also inhibited nNOS, but this was completely reversible by calmodulin, which suggests that these fullerene adducts are potent calmodulin antagonists at ~50 nM.[4632] Other fullerene-derived NOS inhibitors are known.[4636,5239] C_{60} molecules immobilized at a silicon surface also display anti-oxidant activity.[5240] The trimalonic acid derivative of fullerene (carboxyfullerene) is a water-soluble compound that has been found to be an effective antioxidant both in vivo and in vitro.[5875]

6. *DNA Cleavage*. Water-soluble fullerene carboxylic acid cleaves DNA fragments at guanine residues upon exposure to light.[922,2569,2574] Boutorine et al[2573] describe a fullerene-oligonucleotide that can bind single- or double-stranded DNA, and which also cleaves the strand(s) proximal to the fullerene moiety upon exposure to light. A C_{60} derivative linked to a gold surface and DNA was shown to bind and be cleaved with the gold-linked fullerene.[2575] Nakanishi et al[5232] also observed DNA cleavage by functionalized C_{60}.

7. *Other Applications*. Fullerenol-1 significantly attenuates noncholinergic (e.g., exsanguination-induced) airway constriction in guinea pigs.[743] It also produces a slight bronchial constricting action at high doses (2 mg/kg) when applied via intratracheal instillation.[743] Fullerene compounds have effects on nitric oxide[728] and acetylcholine[729] signaling pathways. Fullerene redox chemistry may be applicable to biosensor technologies.[2579,2580] In one experiment, a C_{60}-containing bilayer lipid membrane was shown to be a light-sensitive diode potentially useful in electrochemical biosensor devices.[2579] Favorable blood contact properties of surface-immobilized C_{60} have been reported.[2586] Paramagnetic malonodiamide C_{60} derivatives may be useful in making MRI contrast agents.[5241] C Sixty is also investigating possible drug-delivery "nanopills" consisting of two closed-end single-walled carbon nanotubes nested mouth-to-mouth, forming a capsule-like container.[4630,5242] More generally, the company[5362] is investigating the targeted therapeutic delivery of drugs or radioactive atoms enclosed in surface-functionalized fullerenes to specific tissues or diseased cells. In 2002 this research area was quite active and the interested reader should consult the literature for the most current results.

15.3.3 Biocompatibility of Nondiamondoid Carbon

Other nondiamondoid forms of carbon have been widely used as implant materials with some success, though none is expected to serve as well as diamond because their molecular surfaces are inherently more poorly defined. Prosthetic carbon materials have an extensive biocompatibility literature[904,955] whose summation is beyond the scope of this text, aside from the brief survey presented below. The most common classes of nanomedically-relevant biomedical carbons are glassy or vitreous carbon (Section 15.3.3.1), pyrolytic or low-temperature isotropic carbon (Section 15.3.3.2), graphite (Section 15.3.3.3), and carbon fiber composites (Section 15.3.3.4). Carbon black and India ink (Section 15.3.3.5) are commonly used as inert particulate diagnostic and cell-labeling agents. These surfaces are relevant both in their own right and also as imperfect analogs of sections of diamondoid nanorobot surfaces having aperiodic structures or high rugosity, or which may have partially graphitized. Interestingly, carbon substances can accelerate galvanic corrosion (Section 15.3.3.6) much like metals.

15.3.3.1 Vitreous or Glassy Carbon

Vitreous, polymeric or glassy carbon is a type of graphite formed by the decomposition of hydrocarbon gases on smooth surfaces (such as glazed porcelain) at temperatures above 650 °C. When examined by STM, this material shows atomic lattices with many relatively ordered defects and patchlike carbon crystallites with sizes of 3-15 nm.[792] The crystallites form surface domains that may differ in surface properties due to different orientations of the crystallites.[792]

Adsorption of serum proteins onto glassy carbon has been lightly studied. Amorphous carbon exposed to solutions of fibrinogen, to modified fibrinogen lacking the alpha chain protuberance, or to serum albumin, flowing at a shear rate of 135 sec^{-1}, adsorbed all 3 proteins to form a film.[793] During the adsorption process, individual fibrinogen molecules retained their trinodular structure and adsorbed randomly until a monolayer formed.[793] Adsorption of bovine serum albumin onto glassy carbon takes place in several steps. The structure of the adsorbed layers is different for various serum shear rates at the surface.[794] Kinetics of adsorption of serum albumin onto the surface of glassy carbon electrodes is highly accelerated by application of positive potential, suggesting an electrostatic interaction between the negatively charged albumin molecules and the positively polarized electrode.[795] In this study, adsorption of albumin was irreversible if the albumin solution was simply diluted; albumin formed a monomolecular layer on the electrode surface.[795] Glassy carbon electrodes are widely employed in biosensors.[4822-4830]

Microporous glassy carbon has good biocompatibility in rats.[796] Minimal tissue response is seen to the presence of glassy carbon, and glassy carbon bars aged in vivo for 5 months undergo no weakening.[797] Tissue reactivity to vitreous carbon was studied in dogs and the material was found to be quite inert. There were no inflammatory reactions or sensitivity changes in dog tissues and no unusual changes in the hemopoietic or enzyme systems.[798] Glassy

carbon implants placed intraorbitally in rabbits for up to 150 days produced no intolerance reaction or deviation of blood parameters, showing only a typical "foreign body" (Section 15.4.3.5) reaction.[4821]

Most studies have found good biocompatibility of glassy carbon implants in bone. For example, vitreous carbon inserted into the mandible and iliac crest of the rabbit pelvic bone for up to 1 year excited very little tissue reaction and did not appear to be degraded.[799] The material was well tolerated and showed no movement of known contaminants from the implants into the surrounding tissue.[782] In another experiment,[800] porous vitreous carbon cylinders were implanted intra-articularly into rabbits in the metaphysis of the femur opposite from the patella. There was new bone growth into the implants from the surrounding bone, with new bone in the pores reaching a maximum of 45% of pore volume after 12 weeks and no adverse tissue responses.[800] Only in one study did vitreous carbon implanted in rabbit mandibular tissues for 0.5-3 months elicit fibrous connective tissue capsule formation, multinucleated phagocytic cells, a mild inflammatory infiltrate, and reactive bone.[801]

Glassy carbon also appears biocompatible with teeth. In one experiment,[802]conical vitreous carbon endosteal implants were placed in premolar extraction sites in dogs and then allowed to heal for 2-8 weeks prior to restoration with a gold crown. Gingival tissues healed routinely and showed mild irritation similar to tissues adjacent to teeth, with normal sulcular depths. Bone formation was observed within grooves in the implant surface, providing retention and stabilization. Normal bone remodeling occurred adjacent to the implant sites. The resulting interlocking between tissues and implant appeared to function effectively as a bacterial seal. No inflammatory responses, foreign body reactions, or infections were observed. Glassy carbon is generally considered to have good biocompatibility,[904] despite the relatively high failure rate of vitreous carbon dental implants in humans[905] which seems largely due to mechanical factors such as brittleness.[903]

Glassy carbon materials placed in the middle ear have been less successful. Vitreous carbon implants in the mastoid bulla (middle ear) of gerbils for 1-13 months were well tolerated.[803] But 9 months after vitreous carbon and glazed carbon fiber reinforced carbon were placed in the middle ears of rats and guinea pigs, 40% of the implants had been extruded and 8% had elicited inflammatory responses which would undoubtedly result in extrusion, with only 52% of the implants remaining in situ.[804] Vitreous carbon ossicular chain prostheses implanted in the middle ear of rabbits during tympanoplastic procedures often produced extensive inflammation of the middle ear mucosa along with formation of an increasing fibrous capsule.[805] There was also a permanent foreign body reaction at the implant surface and missing formation of new bone or contact with bone.[805]

Vitreous carbon particles 11 microns in size implanted into the triceps surae muscle of Wistar rats produced no muscle tissue necrosis or exudative reaction during the acute phase (up to 1 week). During the chronic phase, the particles induced only a modest inflammatory infiltration of fibroblasts and phagocytes.[826]

15.3.3.2 Pyrolytic or Low Temperature Isotropic Carbon

Originally developed in the early 1960s by Gulf General Atomic as a coating for nuclear fuel rods,[938,1038-1040] pyrolytic carbon is formed in a fluidized bed by the pyrolysis of a gaseous hydrocarbon such as methane depositing carbon onto a preformed substrate such as polycrystalline graphite at 1000-1500 K.[903,955] Its strength and ability to absorb impact energy is ~4 times greater than that of glassy carbon.[903] Pyrolytic or low temperature isotropic carbon (LTIC) is characterized by a microporous, oxidized, high-energy hydrophobic and domain-mosaic structure.[806,906] LTIC examined by STM shows atomic lattices with many disordered defects, and patchlike carbon crystallites with sizes of 2-8 nm.[792] As with glassy carbon, the different orientations of the crystallites create surface domains that may differ in surface properties,[792] producing a poorly characterized molecular surface.

The pyrolytic carbon surface has strong interactions with adsorbed proteins[806] and even with DNA.[807] LTIC adsorbs and denatures all proteins without preference,[806] including albumin, fibrinogen, and some other small proteins. This is probably due to hydrophobic interactions, although the presence of air at the carbon-water interface can prevent surface denaturation of fibrinogen.[808] Protein adsorption has been directly visualized on LTIC,[809] and the steady state and time varying kinetics of fibrinogen and albumin protein adsorption onto ULTI[810] (see below) and LTIC[811-813] surfaces have been studied. For instance, the adsorption of human fibrinogen onto LTIC at pH 7.2 and 25 °C was 5.2 mg/m^2 (~9100 molecules/micron^2) and the net heat of protein sorption was measured as 3-4 x 10^6 Kcal/mole of adsorbed fibrinogen.[811] Tests for adsorption of bovine fibrinogen and human serum albumin (HSA) from buffered HSA solution found that both proteins are tenaciously bound to Pyrolite (an LTI pyrolytic carbon).[812] Note the authors: "The [high] thromboresistance of Pyrolite may be partly due to the lowered reactivity of the platelet binding domain, as well as a lessened ability of tightly bound fibrinogen to interact with platelets".[812] In general, the rate of protein adsorption is high, the surface concentration is large, and the surface strongly retains proteins such that they cannot be displaced by buffer or exchanged by proteins in solution.[806] Thus LTIC accomplishes its blood compatibility by establishing a passivating film of strongly adsorbed bland proteins which do not interact with platelets nor participate in blood coagulation.[806] The adsorption of albumin onto a pyrolytic carbon surface has been computationally simulated using molecular mechanics techniques.[4840]

For long-term exposures to blood, pyrolytic carbon is generally considered to be a relatively nonthrombogenic material.[808] This is one reason for its extensive use in artificial heart valves (Section 15.2.1.2). For example, in one experiment[813] mechanical heart valves with pyrolytic carbon surface were implanted in the mitral position of sheep without the administration of post-operative anticoagulants or antiplatelet agents for 2, 4, and 6 weeks, then were removed and examined by scanning electron microscopy. Surfaces appeared clean to the naked eye, but when observed by electron microscopy the surfaces were mottled, mainly by solitary platelets and aggregations, though only a few leukocytes or red blood cells were observed and there were no fibrin clots on the leaflets. The density of platelet deposition was higher in the vicinity of the pivots and near the edges of the leaflets, with the sizes of the platelet aggregations decreasing with longer duration. The outer surfaces of the pivot guards were covered by varying amounts of deposition composed of platelet aggregations and thrombi. There is some evidence that LTIC surfaces may be conditioned (e.g., reducing platelet retention) by adsorption of a passivating protein such as albumin.[810,926] Platelet adherence on LTIC is remarkably low compared to other implant materials, typically ~0.0043 platelets/micron^2 after a 5-minute exposure to fresh human blood flowing at a wall shear rate (Section 9.4.1.1) of 50 sec^{-1}.[1680]

For brief exposures to blood, however, this material is far from ideal. A comparison of the thrombogenicity of heart valve materials found that pyrolytic carbon disks implanted in the intrathoracic venae cavae of anesthetized sheep for only 2 hours elicited

significantly more thrombus formation than did titanium or cobalt-chromium disks, and more leukocyte adhesion than on pure titanium disks.[814] Recent investigations[908] of very pure heart-valve pyrolytic carbon suggests this material may have improved properties relative to traditional LTIC, which usually contains substantial amounts of silicon additive (up to 15% Si by weight) that was believed necessary to consistently achieve the hardness required for adequate wear resistance. (The silicon is present in the microstructure as discrete, lacey networks of silicon carbide particles.[955])

LTIC is generally biocompatible with cells. For example, porcine aortic endothelial cells were cultured on pure Dacron and on vapor-deposited pyrolytic carbon-coated Dacron vascular prostheses.[815] Cell adherence was unaffected, but cellular growth occurred only on carbon-coated Dacron. SEM images showed rounded adherent cells on Dacron but extensively spread cells on carbon-coated prostheses.[815] Similarly, an isotropic carbon coating on dental replicas implanted in dog mandibular arches showed good permucous acceptability (hard to obtain in other materials) and good anchorage to the surrounding bone.[816] LTIC dental implants in baboons found a good clinical response.[907] Most specimens showed a complete absence of bone resorption of the alveolar crest and an absence of epithelial cell migration or fibrous tissue formation at the implant-tissue interface. Pyrolytic carbon is also a biologically compatible material for arthroplasty of diseased finger joints.[817] In this study,[817] no adverse remodeling or resorption of bone was seen. 94% of the implants had evidence of osseointegration with sclerosis around the end and shaft of the prosthetic stems. A few instances of chronic inflammatory tissue were seen, but there was no evidence of intracellular particles or particulate synovitis.

Once again, however, the material is far from ideal. When LTI pyrolytic carbon transcortical (bone) implants were placed in the femora of mongrel dogs for 6 months, the bone formed a direct appositional interface with the LTI carbon. But the strength of appositional attachment was at least one order of magnitude weaker than bone growth attachment to porous titanium and carbon-coated porous titanium systems which were also tested.[818] (The presence of carbon coating enhanced bone ingrowth.[818]) As with glassy carbon, in at least one experiment[801] pyrolytic carbon or Pyrolite implanted in rabbit mandibular tissues for 0.5-3 months elicited fibrous connective tissue capsule formation, multinucleated phagocytic cells, a mild inflammatory infiltrate, and reactive bone. Thin capsules were also observed surrounding the ends of pyrolytic carbon catheters implanted intraperitoneally in dogs for 12 weeks.[895]

What about pyrolytic carbon particles? Helbing et al[902] tested 97.3% pure LTIC dust (2.7% graphite) of particle size <~ 1 micron by injecting the particles intravenously, intraperitoneally, and intra- and peri-articularly into 60-day-old Chbb-strain rats. There was a slight inflammatory reaction with an increase in neutrophils in the peritoneal fluid after 24 hours. Some carbon particles were phagocytosed by macrophages. After 12-24 weeks, some foreign body granulomas had formed around large aggregates of carbon particles, but the peritoneal surface was macroscopically shiny and smooth. No foreign-body giant cells were found in the knee joints and there was no evidence of acute inflammatory change. Joint cartilage remained completely unaltered after 6, 12, and 24 weeks. There was no evidence of foreign-body reaction in any of the parenchymal organs. The general conclusion was that tissue tolerance of LTI dust is excellent.[902]

Ultra-low-temperature isotropic (ULTI) carbon is a closely related material.[923] By the late 1970s, it became possible to deposit isotropic carbon coatings at nearly room temperature using a hybrid low-pressure vacuum process that does not require the object to be coated to be suspended in a fluidized bed. The steady state and time varying kinetics of protein adsorption of ULTI have been investigated. Flow exposures over ULTI-coated microporous membrane produced a uniform protein coating averaging 1.3 microns in thickness. Adsorption of human fibrinogen onto the ULTI was 53.5 mg/m^2 (~94,900 molecules/$micron^2$) and 14.4 mg/m^2 (~127,000 molecules/$micron^2$) of albumin, after a 1-hour exposure.[810] Albumin adsorption reaches equilibrium within 15 minutes, while fibrinogen levels are still increasing after 60 minutes, at which time the noncompetitive albumin/fibrinogen adsorption ratio reaches 0.27,[810] comparable to the 0.24 ratio achieved for LTIC.[925] In related experiments,[924] the response of ULTI carbon surfaced materials to ex vivo blood flow were evaluated over perfusion periods of 0.5-8 hours. At flow rates with low Reynolds numbers (Section 9.4.2.1), the carbon attracted fewer and less distorted cellular elements than uncoated microporous membranes and microchannels.[924]

Failure strength of ULTI carbon is ~7.5×10^7 N/m^2 (impact fracture energy 1.1×10^7 J/m^3), compared to 5.5×10^7 N/m^2 (6.6×10^6 J/m^3) for LTI carbon with Si, 4.5×10^7 N/m^2 (3.4×10^6 J/m^3) for pure LTIC, and 1.4×10^7 N/m^2 (7×10^5 J/m^3) for glassy carbon.[955] All these carbons have similar stiffness, with modulus of elasticity of $2.1\text{-}2.6 \times 10^{10}$ N/m^2,[955] in a range comparable to bone.

15.3.3.3 Graphite

Thrombosis on blood-exposed graphite-coated prostheses was first studied in the 1960s,[819] and in the 1970s it was found that graphite-based endoprostheses were generally nontoxic and produced no immunological reactions.[820] Glow discharge treatment to a graphite surface increases hydrophilicity, producing stronger adsorption of hydrophilic protein molecules and a more homogeneous distribution.[821] (See also Section 15.3.5.1.) Graphite began to be studied as an implant surface material in the 1990s, owing to its use in joints,[941] bone,[942,943] heart valves,[944] and as an electrode in biosensors.[945-949,4841-4845]

In the best study of bulk graphite biocompatibility to date, Eriksson and Nygren[822] investigated the initial reactions of graphite and gold with blood by short-time exposure to capillary blood and detection of surface-adsorbed plasma proteins and cells with an immunofluorescence technique. Antibodies specific to fibrinogen, complement factors C1q and C3c, prothrombin/thrombin, von Willebrand factor, and platelet- and leukocyte-membrane antigens were used. Fibrinogen was the most abundant plasma protein immobilized on either surface, and dense populations of platelets adhered to the protein layer. Complement factors and prothrombin/thrombin were found on the graphite surface, localized in fibrin clots or related to platelets. Platelets were activated (e.g., expression of selectin CD62) on both surfaces but more extensively on the gold surface. Activation of polymorphonuclear granulocytes (PMNGs), measured as the expression of integrin CD11b, was seen on both surfaces but with different kinetics. On the graphite surface the CD11b expression was only transient, whereas on gold it increased with time. The data suggest that graphite is more thrombogenic than gold, but is also less inflammatory.[822]

What about graphitic particles? Graphitosis from inhaled natural (impure) graphite dusts was mentioned in Section 15.1.2. But when rats were exposed to a single dose of synthetic (pure) graphite dust, particles were steadily cleared from the lungs.[823] Alveolar macrophages contained ingested particles throughout the entire 3-month experimental period.[823] At 100 mg/m^3 exposure, no pulmonary inflammation or macrophage activation was seen. A 500 mg/m^3 exposure produced transient inflammation and macrophage activation

for only about 24-48 hours.[823] Graphite is generally regarded as biologically inert. In one study,[824] for example, human airway epithelial cells cultured with charcoal and graphite particles did not stimulate production of IL-8 or GM-CSF (granulocyte-macrophage colony-stimulating factor).

Graphite particles have persistence in the dermis and as a result are often used as a pigment in tattoos.[825] In grade school this author accidentally stabbed his palm with a sharp pencil. Four decades later the resulting embedded graphite spot is still visible subepidermally with no evidence of inflammation or heavy fibrous encapsulation, though granulomas from this source are not unknown.[2513] Wear particles from graphite-based endoprostheses generally do not produce any severe inflammatory reactions.[820] In one experiment,[643] the hemolysis eventually initiated in vitro by various ceramic powders tested, including diamond, graphite and alumina, was almost zero.

Engineers contemplating the design of nanorobotic structures with graphitic exteriors should be aware that the growth of bacteria is often enhanced by the addition of carbon materials such as graphite or activated charcoal to the growth medium. Matsuhashi et al[827] have isolated bacterial strains that strictly require such carbon materials under the ordinarily lethal stress caused by high concentrations of salt. The organisms are Gram-positive, spore-forming, sugar-nonfermenting aerobic bacilli provisionally designated *Bacillus carbophilus Kasumi*. The growth- and germination-promoting effects of graphite and activated charcoal were demonstrated either quantitatively on agar plates containing fine crystals of the carbon materials mixed with a nonpermissive growth medium or qualitatively on agar plates on nonpermissive growth media half-covered with fine carbon particles. Further experiments[827] demonstrated a novel feature of the phenomenon: the ability to induce colony formation on the nonpermissive plate was transmissible through the air, as well as through plastic or glass barriers, via a mechanism which the researchers believe may involve transmission of physical signals regulating cell growth.

Chemically, graphite is insoluble in common solvents but is attacked by strong oxidizing agents such as mixtures of sulfuric acid with nitric acid, chromic acid, or chlorates, giving graphitic acids and finally mellitic acid, $C_6(COOH)_6$, whereas diamond is unaffected by such treatment.[783] Thin carbon films, when used as coatings on prosthetic devices, often serve as a barrier to gases and physiological fluids. The average gas permeability constant of 20-50 nm thick carbon films to room-temperature CO_2 was measured as 1.91 x 10^{-12} cm^3-cm/cm^2-sec-mmHg, a value comparable to or smaller than that of nuclear graphites which are considered to be impermeable to gases.[828] The heat of immersion evolved when graphite is brought into contact with solvent water has been measured for Graphon surface as 32.4 erg/cm^2,[2,927] vs. 66.7 erg/cm^2 for LTI carbon,[811] 203 erg/cm^2 for glass,[811] and 210 erg/cm^2 for amorphous silica.[928]

15.3.3.4 Carbon Fiber Composites

Although carbon fiber electrodes are in common use as biosensors[4847-4851] and related applications,[4852-4854] carbon fiber composites such as carbon fiber-reinforced carbon (CFRC) materials have a mixed record where biocompatibility is concerned.[4855] For example, in one experiment[829] a vascular prosthesis made of pyrolytic carbon fibers was implanted on the infrarenal aorta of growing pigs, then was removed up to 120 days after surgery. The carbon grafts showed thromboresistance of the inner surface at the time of implantation, development of a thin neointima with good viability, rapid and complete endothelialization of the flow surface, and solid anchorage to perigraft tissues. But another in vivo study[830] of carbon-carbon composites in contact with blood showed the accumulation of platelets on exposed surface material having any surface morphology, although platelet concentration in blood remained constant. Bulk structure of composites influences the adhesion mechanism of entrapped platelets (e.g., active adhesion vs. mechanical adhesion).

Carbon fiber patches inserted as prostheses into the dorsal lumbar fascia of rabbits initially had poor mechanical properties but developed good connective tissue response after several weeks.[831] In another study,[832] carbon fabric with 35- to 50-micron diameter fibers infiltrated with low temperature pyrolytic carbon produced a tightly woven porous structure with maximal pore size >200 microns; 30 days after percutaneous implantation in a calf, epidermal downgrowth was minimal. Later, a thin fibrous capsule surrounded the implant and mature connective tissue with accompanying blood vessels filled the pores of the fine trabecularized carbon layer, allowing a biocompatible connection between an artificial internal organ system and the external environment.[832]

Carbon fiber has often been tested as a prosthesis for ligaments because filamentous carbon is a known fibrogenic material, inducing the formation of replacement collagen.[833,934,935] In one early experiment that gave good results,[834] the biological reaction of tissues to carbon fiber ligament prostheses was examined in sheep knees. Connective tissue and bone grew into the prosthesis under physiological conditions at the insertion points in cancellous bone, and there was tissue ingrowth around the carbon fiber ligaments intra- and extra-articularly. Carbon fibers were reported to be a very good scaffolding and a permanent prosthesis for ligament replacement.

But other experiments gave poorer results. One study[835] found that carbon fiber used to reconstruct anterior cruciate ligament in the knee did not bond to bone nor did it induce the formation of new ligament. There was only a very minor fibroblastic response despite the presence of numerous particles of carbon fiber scattered throughout the knees.[835] In yet another study,[837] part of the patella ligament in rabbits was resected and replaced by carbon fiber implants. After residence times ranging from 1 week to 1 year, the carbon implants along with surrounding tissues and iliac lymph nodes were removed and examined by light- and transmission electron microscopy to determine whether the carbon fiber implant would be removed by phagocytosis and substituted by new ligament or some other adequate repair tissue. In this study, there was no indication of successful removal of carbon fibers by phagocytosis and the implant was surrounded by dense connective tissue like a scar. No vital dense or regular connective tissue was found in deep layers of the implant, even after 3 and 12 months, and no replacement of the carbon fiber implant by new ligament or tendon. A persistent foreign body reaction was observed, leading the authors to conclude that "it is very doubtful [that] good results with ligament and tendon replacement by carbon fiber implants can be expected in patients."

Similar results were obtained in humans. For example, carbon fiber ligaments implanted in human patients has evidenced a considerable foreign-body reaction to the carbon fibers and insufficient metaplasia of the allogenic material to connective tissue.[836] In another study,[838] more than a year after carbon fiber was used to reconstruct the lateral collateral ligament of a human knee, histological study suggested that the implant was unlikely ever to acquire the structure of a natural ligament. This was true even though the implant was biologically compatible and was deemed biomechanically sufficient as long as the entire tow of carbon fibers was preserved.[838]

Carbon fiber has been tested as a bone prosthesis with better outcomes, failing only rarely.[839] For instance, long-term middle-ear

implantation of carbon-carbon prostheses in guinea pigs produced no significant tissue destruction or inflammation, no digestion or erosion of the implants, and no passage of carbon particles into the reticuloendothelial system.[840] Carbon fiber-reinforced carbon implanted in holes drilled in rat femurs developed a thin layer of fibrous tissue bridging the gap between bone and implant for a period up to 8 weeks, but by 10 weeks bone was observed adjacent to the implant, giving firm fixation.[841] Another study[842] found that carbon-carbon cloth sandwich provided good osseocompatibility. The fiber-like surface texture gave a degree of bony attachment of greater strength than for titanium during 4-40 weeks post implantation.[842] In yet another experiment,[843] CFRC material with 30-micron pores was implanted as femoral transverse diaphyseal pins in rats. By 45 weeks, most specimens showed direct implant-bone contact over most of the interface although the interface was chemically abrupt with no cross-diffusion of ionic species. Implant pores were partially filled with tissue including fresh bone organized de novo deep within.

What about carbon fiber and carbon composite particulates? In inhalation experiments, no fibrosis, local reactive pulmonary inflammation, or other significant effects were observed in rats exposed to 7-micron thick, 20- to 60-micron long carbon fibers for 30 hours per week during a 16-week experiment at an average chamber concentration of 20 mg/m^3, although the inhaled particles were phagocytosed by alveolar macrophages.[224] Rats showed no fibrosis or other ill effects from inhaling 20 mg/m^3 (25 million fibers/m^3) of carbon fibers measuring 3.5 microns in diameter and 10-60 microns in length for 30 hours per week during a 16-week experiment.[765] Nonfibrous dust particles from pounded carbon fiber, inhaled by guinea pigs, were phagocytosed. Carbon fibers longer than 5 microns were still extracellular after 27 weeks and were uncoated; no pathological effects were observed.[223,844] In another experiment,[2584] a 5-day exposure to respirable carbon fibers at 50-120 gm/m^3 produced dose-dependent transient inflammatory responses in rat lungs, but no significant difference in the morphology or in vitro phagocytic capacities of macrophages were observed. Medical examination of carbon fiber production workers has revealed no adverse effects on the lungs.[225] However, one Russian animal study found slight pulmonary fibrosis and respiratory tract irritation from carbon fiber dust[226] and a Japanese study found morphological changes in rat lungs due to some kinds of carbon fibers.[762] One other study of several aerosolized carbon composites found some that showed little toxicity, but found others that were consistently toxic for alveolar macrophages and caused significant accumulations of airway cells and neutrophils in rat lungs.[845]

Carbon fiber particles can elicit a cellular response. In one experiment,[846] wear particles produced from Versigraft carbon when added to rabbit synovial cell culture induced significantly elevated collagenase and gelatinase enzyme production. 1 mg/kg particles injected into rabbit knees accumulated in the periarticular synovial folds and induced strong macrophage infiltration in the synovium.[846] In another study,[784] carbon fiber-reinforced carbon particles of up to 20 microns in diameter were phagocytosed when presented to in vitro cultures of murine macrophages. Larger particles were not phagocytosed but became surrounded by aggregations of macrophages, some of which migrated onto the particle surfaces.[784] Cells presented with a large excess of particles became rounded and detached from the substrate, and some underwent lysis.[784] In yet another experiment,[847] wear particles from carbon prosthetic materials were cultured with rabbit synovial fibroblasts. Internalized particles induced collagenase, but even carbon particles that remained extracellular provoked considerable collagenase synthesis. Synovicytes that contained no particles nevertheless produced collagenase when co-cultured with cells that did contain particles. This indicates that carbon fiber particle phagocytosis, besides inducing collagenase, also provokes the release of cell-activating factors which then activate other cells in the culture.[847]

The soft tissue response to long carbon fibers and carbon fiber microparticles is said to be excellent.[848,902] In general, carbon fibers are integrated by the organism without causing significant foreign body reaction (inflammation), with normal tissue growth around (and encasement of) the individual fibers.[848] There is, however, progressive rupturing of pure carbon fiber implants. The resulting carbon fiber microparticles are absorbed either by macrophages or by foreign body giant cells and are distributed throughout the body via the lymphatic system.[848] In one animal study,[826] particles from carbon fiber reinforced carbon of sizes 11 microns and 30 microns implanted into the triceps surae muscle of Wistar rats produced no muscle tissue necrosis or exudative reaction during the acute phase (~1 week). During the chronic phase (up to 52 weeks), the 11-micron particles induced only a modest inflammatory infiltration of fibroblasts and phagocytes while the 30-micron particles induced a much larger infiltration of fibroblasts, macrophages, and giant cells. The study by Helbing et al[902] found excellent tissue tolerance of <~8-micron particles of carbon-fiber reinforced carbon, in rats. In humans, the soft tissue response to carbon fiber was studied histologically one and a half years after being used to reconstruct the lateral collateral ligament of the human knee.[838] A remarkably consistent pattern was seen in the induced ligament. The basic pattern was a composite unit, consisting of a core of carbon fiber enveloped in a concentric manner by coherent layers of fibroblasts and collagen fibers. The new structure seemed to have been induced by continuous irritation caused by the physical structure of the carbon fibers.

Bones and joints seem to tolerate carbon fiber particles rather well. In one experiment,[849] carbon fiber fragments with a diameter of 7 microns and a length between 20-100 microns were injected in the medullary canal (in long bones) of 16 rabbits, and evaluated after periods of 2 and 12 weeks. There was phagocytosis of small carbon fiber fragments by macrophages, but only a minimal foreign body reaction to the intramedullary carbon fiber fragments. A small amount of fibrosis was observed around some carbon fibers along with a small amount of new bone formation with inclusion of carbon. Only a few carbon fragments were transported to the parenchymal organs, with no foreign body reaction.[849] In a similar study in humans,[835] carbon fiber wear particles scattered throughout the knees stimulated only a very minor fibroblastic response.

15.3.3.5 Amorphous Carbon Particles

It has already been noted that finely divided amorphous carbon particles generally are well tolerated by the body.[181,632,850] The essentially passive nature of carbon in human flesh has been known since ancient times, and India ink,[778] charcoal and lampblack (roughly spherical 10-20 nm particles) have been used for ornamental and official tattoos.[516] Colloidal carbon is usually assumed to be nontoxic.[773,4873] Large amounts of carbon particulate debris loose in the body, even around the spinal dura and nerves,[839] evidently are tolerable. Carbon black (CB), the most common amorphous carbon particles that have been subjected to extensive biological experimentation, are regarded as largely inert.[851] Carbon black is distinctly different from, and more benign than, carbon soot.[4867] Ultrafine carbon black particles are typically ~14 nm in diameter, while ordinary "fine" carbon black particles are typically ~260 nm in diameter.[769] Commercial carbon blacks may contain 88-99.5%

carbon, 0.3-11% oxygen, 0.1-1% hydrogen, up to 1% inorganic material, small amounts of other organics, and traces of sulfur, depending upon the method of manufacture. Both CB and ultrafine CB may contain numerous biologically relevant metals. One assay[769] of ultrafine CB found 19 ppm Fe, 11 ppm Zn, 3.5 ppm Cr, 1.9 ppm Pb, 0.8 ppm Cu, 0.02 ppm Be, and even 0.0039 ppm Tl, all of which may enhance the biological activity of these particles.

India ink, traditionally used for drawing, is a dispersion of carbon black in water. (One MSDS for India ink[6081] lists its only health hazard as irritant with TLV TWA of 2 mg/mm^3.) The suspension is often stabilized by various alkaline solutions, shellac dissolved in borax solution, soap, gelatin, glue, gum arabic, or dextrin. India ink is often used as a phagocytosis labeling agent or a cell differentiation tracer because CB is easily administered, is relatively nontoxic, and is easily observed in cells that have taken it up. India ink is useful diagnostically for detecting cryptococcal meningitis,[5918] easily demonstrating individual cryptococcus organisms by phase contrast microscopy. CB is also employed in tattoos, both cosmetic and medical. For example, India ink is used for endoscopic colonic tattooing[852-856,4861] and lymphatic mapping.[4862] It produces a long-lasting stain "with relatively low risk of adverse reaction and toxicity".[856] There are just a few rare cases reported of allergic reaction[855] to India ink, fever and abdominal pain,[856] colonic abscess and focal peritonitis,[853] abscess-like pseudotumor with chronic granulomatous inflammation,[856] inflammatory infiltrate with microhemorrhage and thrombosis,[852] inflamed vessels but without fibrinoid necrosis,[854] and early reactions including necrosis, edema, and neutrophilic infiltration in the submucosa and muscularis propria.[854] M. Sprintz notes it is possible that these adverse reactions were caused by something other than India ink, such as microperforations in the bowel during the procedures.

The chemical character of the CB particle surface mediates its biological reactivity.[857] The often partially-saturated attractive forces can allow these surfaces to readily adsorb large amounts of gases and solutes from solution.[858] Active surface groups on carbon blacks have been shown to adsorb and retain gaseous adsorbate molecules selectively.[859,860] Histone adsorption on the surface of carbon particles significantly stimulates their ingestion by rat peritoneal macrophages, hamster kidney fibroblasts, and mouse L-cells,[861] and the adsorption of polycyclic aromatic hydrocarbons (PAHs) and their nonpolar metabolites on the surface of carbon particles ingested by rat alveolar macrophages has been studied.[862]

The carbon immunoassay (CIA)[863] is a direct serological test relying on a specific reaction between the carbon particles of India ink and rabbit immunoglobulin G. (This assay is also known as the India-ink immuno-reaction (IIR) test.[864-866]) The carbon particles must be pretreated with staphylococcal protein A to induce a reaction to IgG antibodies in human serum in tests for toxoplasmosis. Carbon black can also have a significant adjuvant effect on the local immune-mediated inflammatory response and on the systemic specific IgE response to allergen (ovalbumin).[867] When CB is administered along with the allergen to mice, there is a significantly augmented response in the draining popliteal lymph node including increases in weight, cell numbers, cell proliferation, and local lymph node response duration.[867] Carbon black immunochromatographic testing is well known.[5882]

Immune and other cells clearly respond to the presence of carbon particles placed in the body. In one in vivo study,[868] chicken basophils, neutrophils, monocytes and platelets showed phagocytosis of dermally-implanted carbon particles although eosinophils ingested these particles only occasionally. In another chicken study,[883] platelets and monocytes took up carbon particles but neutrophils did not. In a human study,[869] scattered wear particles from carbon-coated subperiostal implants were surrounded by lymphocytes, macrophages, plasma cells, and tissue eosinophils. Active phagocytosis and Russell bodies were seen, with large masses of carbon surrounded by connective tissue.[869] In another study using cultured human monocytic cells,[4857] carbon black particles or diesel exhaust particles, by themselves, were unable to induce HLA-DR when applied to the surface of THP-1 antigen-presenting cells at concentrations of 0.1-1000 ng/cm^2 after 48 hours of incubation. However, carbon black (>1 ng/cm^2) plus diesel exhaust particles (>0.1 ng/cm^2) interacted with IFN-gamma (a known HLA-DR enhancer) to increase HLA-DR expression up to 2.5-fold, indicating a surface-chemistry-related "adjuvant" effect. The possibility that nanorobots could accidentally serve as adjuvants to induce cell damage[4857] or immune system activity[4860,4871] by other particles already present in the environment should be investigated further.

The uptake and long-term storage of carbon ink particles by the dermal and subcutaneous fibroblasts[778] is believed to represent a specific non-inflammatory defense mechanism that protects the living body, without immune reactions, against injuries and invasions by non-toxic foreign agencies. In young rats, subcutaneous injection of 0.02 ml of India ink almost completely eliminated small recirculating lymphocytes from the affected nodal structures, except in the center of the deep cortex units, similar to the effects of a whole-body 500 rad irradiation[870] (Section 6.3.7.1). Colloidal carbon particles injected into the cerebral cortex of the neonatal rat were readily ingested by young astrocytes.[773] Colloidal carbon administered intravenously in rats can retard chemotactic migration and phagocytic activity[871] or even produce complete blockade of the RES.[872] Macrophage blockade has been induced in mice by intravenous injection of ~1000 mg/kg of carbon particles.[873] Examination of the endothelial linings of capillaries, postcapillary venules and terminal arterioles also reveals a pronounced uptake of carbon particles by endothelial cells, different degrees of endothelial cell swelling, and often bulging into the microvessel lumens, possibly altering microvascular tone and arteriolar reactivity.[872]

Circulating monocytes ingest intravenously-injected colloidal carbon particles.[874,883] And uptake of intravenous India ink particles may transform monocytes into Kupffer cells.[779] In one experiment,[777] Kupffer cells as well as hepatic sinusoidal endothelial cells took up Indian ink particles by pinocytosis, and a few Ito cells and hepatocytes ingested a small number of particles. One month after the injection, large clumps of aggregated Kupffer cells containing numerous carbon-filled vacuoles were distributed in the Disse space (Figure 8.27) and other connective tissue spaces. The Kupffer cells in these clumps were in close contact and were partly fused with one another. After 3-6 months, large multinucleate foreign body giant cells with numerous large vacuoles containing densely-packed ink particles were seen throughout the liver tissue, probably formed by the fusion of Kupffer cells.[777] Kupffer cells in aging mice show reduced phagocytosis of colloidal carbon.[4863]

Macrophages are known to clear carbon particles from the blood.[775] Mouse omental macrophages phagocytize intraperitoneally injected carbon particles,[876] and colloidal carbon particles injected intravitreously into chicken eyes are actively ingested by hyalocytes (the resident macrophages) by the second day, without significant leukocyte recruitment.[771] After 30 days the carbon-laden macrophages disappeared from the vitreous body but accumulated on the pecten oculi and retina,[771] probably producing some small diminution of visual sensation. The number of free macrophages in mouse lungs increases in response to the intratracheal instillation of carbon particles.[766] There is early mononuclear phagocyte cell migration into alveoli and bronchioles from the blood compartment (e.g., from small pulmonary vessels[772]) and later migrations due to

egression of interstitial lung macrophages[877] which exhibit increased mitotic activity.[772] This is observed for up to 6 months post-instillation,[766] with macrophage accumulation localized to the areas of particulate deposition.[767] Ingestion of large amounts of carbon particles by alveolar macrophages also decreases the release of superoxide and hydrogen peroxide radicals[879] and reduces acid phosphatase and lysozyme enzyme intracellular concentrations[880] during bacterial phagocytosis. Elsewhere in the body, ingested insoluble carbon particles that accumulate in mouse intestinal Peyer's patches do not produce detectable alterations in macrophage morphology,[780] though carbon particles have induced production of macrophage colony-stimulating factor in mice.[878]

Platelets are also known to clear colloidal carbon particles from the blood.[775,881-883] For example, a single intravenous injection of colloidal carbon particles in Lewis rats at a dose of 320 mg/kg produced a prompt thrombocytopenia (reduced platelet count), with temporary sequestration of platelets in lung, liver and spleen.[875] Rat platelets were found to be involved in the initial removal of carbon from the blood.[875] Localization to the mesangium (the support structure of the renal glomerulus) is dose-dependent[875] and peaks at 32 hours post-injection.[774] India ink injected intravenously into mice also induces thrombocytopenia and markedly prolonged bleeding times (and prolonged thromboplastin and prothrombin times), reduces fibrinogen concentrations, and produces some cerebral thromboemboli, but does not cause substantial mast cell degranulation.[884] Chicken platelets also showed marked phagocytosis of carbon particles in both in vivo and in vitro systems.[883] Initially in both systems, platelets containing carbon particles tended to form clumps, but in the later stages clumping was less obvious in the in vivo system.[883] Another experiment described a simple and reproducible test for the phagocytic ability of human platelets.[885] Platelets obtained from heparinized venous blood were incubated with 0.11-micron colloidal carbon particles in autologous plasma at 37 °C. The number of platelets with or without carbon particles on smear preparations was determined at fixed intervals. Electron microscope observation confirmed that carbon particles were internalized in the vesicular or canalicular structures of about 67% of all platelets.[885]

The responses of various organs to carbon particles have also been investigated experimentally. The eye seems particularly sensitive. In one experiment,[886] 20-nm carbon particles were injected into the vitreous humor of rabbit eyes. Histological examination 8-10 weeks later showed partial posterior vitreous detachments, epiretinal cellular proliferation, and membranes in all eyes and retinal detachments in five eyes. Electron microscopy disclosed that the epiretinal membranes (resembling idiopathic preretinal gliosis or macular pucker) were formed mainly by Muller cell expansions, astrocytes, and macrophages. Muller cells penetrated the internal limiting membrane and removed carbon particles from the vitreous by endocytosis.[886] The experiments found that gaps are produced in the internal limiting membrane by glial cells and by macrophages that invade the vitreous in an attempt to remove foreign material.

In a subsequent experiment at the same laboratory,[887] 20-70 nm carbon microparticles injected into the vitreous humor of cynomolgus monkeys induced intravitreal cellular proliferation. At 1 week, there was conspicuous cyclitis showing exudative separation of the nonpigmented and pigmented ciliary epithelium, inflammatory cells, mononuclear phagocytes, and premacular vitreous detachment. Continued macrophagic response was accompanied by fibrovascular proliferation with ingrowth of vessels from the ciliary body into the vitreous at 3 weeks. By 4-5 weeks there was deposition of extracellular fibrous material and traction retinal detachment. At 10 weeks, all eyes had extensive retinal detachment with pre- and subretinal collagenous cellular membranes. Carbon-laden macrophages were aggregated over the optic disc and fovea, and prepapillary neovascularization and cystoid macular edema was seen. The exposure of the interior of the eye to carbon particles thus produced an inflammatory and phagocytic response, which induced intravitreal fibrovascular proliferation, vitreous contraction, and retinal detachment[887] — a possibly cautionary result for long-term ocular-indwelling medical nanorobots of similar size.

The response of lung tissue to carbon particles has been extensively studied. For example, chronic inhalation of carbon black particles in air can produce carcinoma in rat lungs. Chronic[760,4865] and subchronic[761] exposures impaired lung clearance and significantly increased mutation frequency in the hprt gene of rat alveolar epithelial cells at 7.1 mg/m^3 and above, but produced no detectable adverse lung effects at a 1.1 mg/m^3 level.[760] The official industrial threshold limit value for pure carbon black is 3.5 mg/m^3.[764] Inhalation of carbon black can produce pulmonary neoplasms in chronically exposed rats.[888] This is believed to be a result of a high lung burden of carbonaceous particles rather than from the genotoxicity of organic constituents.[888] Macrophages and neutrophils elicited by carbon black particles can exert a mutagenic effect on in vitro epithelial cells.[889] Carbon black has been linked to lung and bladder cancers at high occupational exposures[4864] (though not confirmed[4870]) and possibly also to genotoxicity in human alveolar epithelial cells[4869] and in rat lung tumors.[5881] Ultrafine carbon black particles activate apoptosis-related pathways in alveolar epithelial cells, whereas fine carbon black does not.[4858] At least one study claims that inhaling carbon black may transiently elevate the risk of myocardial infarctions in humans within a few hours after exposure.[4866]

Inflammatory effects of carbon black particles on the lungs are well studied.[890] For instance, rats intratracheally instilled with saline suspensions of 10 mg/kg or 100 mg/kg doses of carbon black produced neutrophilic inflammation in all rats at both doses.[889] Epithelial hyperplasia and elevated hprt gene mutation frequency in alveolar Type II cells were observed only at the higher dose.[889] Carbon particles instilled into the lungs of mice induced an inflammatory response with excess production of alveolar macrophages for 2 weeks, after which the macrophage count returned to normal with normal lung structure and no formation of multinucleated giant cells, granulomas, or fibrosis.[891] Deposition of carbon powder into injured mouse lungs near the time of injury results in increased translocation of the particles to the interstitium and elicits a large increase in inflammatory cells, but does not further stimulate an ongoing fibrotic process or induce additional fibroblast growth or collagen production.[851] In one study,[772] particle overload in mouse lungs produced by instilling 200 mg/kg of carbon particles caused some free carbon to cross the type I cells to reach the interstitium. These particles were later observed in peribronchial and perivascular interstitial cells.[772] In the alveoli, free macrophages were loaded with carbon but passage of these cells from airways to interstitium was never observed.[772] In another study,[892] <10-micron colloidal carbon particles instilled in the lungs of rabbits shortened the transit time of alveolar macrophage-recruited neutrophils through the bone marrow from 86 hours to 71 hours. The authors concluded that the phagocytosis of colloidal carbon by alveolar macrophages releases cytokine mediators that stimulate the bone marrow to release polymorphonuclear leukocytes.

Inflammatory lung effects appear to increase when smaller particles are inhaled.[4872] In one experiment,[769] ultrafine CB particles instilled intratracheally up to 0.5 mg/kg in 250-gm Wistar rats generated significant neutrophil alveolitis (alveolar inflammation) after 6 hours. The particles also produced a marked increase in lactate dehydrogenase (LDH) levels in bronchoalveolar lavage fluid and

caused the greatest decrease in glutathione (GSH) in lung tissue compared to control.[769] Much larger fine CB particles similarly instilled generated no alveolitis and caused a much smaller increase in LDH and a much smaller decrease in GSH. Ordinary carbon black inhaled at 5 mg/m^3 produces no significant physiological effects in rats.[4859] Fine CB shows a dose-related increasing inflammatory response. In contrast, ultrafine CB at the highest dose induces less of a neutrophil influx than at the lower dose, which the authors surmise is because particle mass dominates the response rather than surface area at higher doses. Ultrafine CB threshold dose for neutrophil influx 6 hours after instillation is 0.2 mg/kg.[769] Renwick et al[4868] found that ultrafine particles impair alveolar macrophage phagocytosis to a greater extent than fine particles compared on a mass basis.

However, at another laboratory 5 mg/kg of ultrafine and fine carbon particles were instilled intratracheally in rats and produced "little if any effect on lung permeability, epithelial marker enzymes, or inflammation, despite being given at a dose which readily translocated the epithelium and has been reported by others to cause inflammation".[857] The authors concluded that particle surface chemistry may be more important than particle size per se, in explaining the biological reactivity of the particle,[857] though a later study[5883] at this laboratory found that oxidative damage by inhaled CB particles was more strongly ameliorated by a surrogate epithelial lining fluid for coarse particles than for fine particles. In the 1990s, the relevant details of carbon surface chemistry were being investigated largely in the context of air pollution. For example, in one study[893] the inhalation of 10 mg/m^3 of carbon black by mice induced no inflammatory response and had no effect on alveolar macrophage phagocytosis. But if combined with exposure to ozone at 1.5 ppm, inflammatory response was greatly enhanced and macrophage phagocytosis was significantly suppressed in comparison with exposure to ozone alone. The authors hypothesized that the carbon acts as a carrier mechanism via adsorption of ozone at the particle surface, or that O_3 alters the physicochemistry of the particulate from a nontoxic to a toxic form.[893] In another study,[894] a 4-hour exposure to 10 mg/m^3 of carbon black aerosol at high or low humidity, assessed 3 days later, had no effect on mouse alveolar macrophage phagocytosis. But chemisorption of 10 ppm SO_2 at high humidity on the carbon particles catalyzed oxidation to SO_4^{--}, a lung toxin which significantly suppressed alveolar macrophage phagocytosis.[894] There is preliminary evidence that inhaled carbon black (possibly in combination with adsorbed sulfuric acid) might promote esophageal cancer in "a handful of occupational exposures",[4817] though a competing study[2598] found no change in cell viability in lymphocytes taken from guinea pig tracheobronchial lymph nodes of animals exposed to 1500 μg/m^3 diesel exhaust (carbon) particles for up to 8 weeks.

Finally, carbon-coated microbeads (Durasphere) have been tried as injectable bulking agents for treatment of urinary incontinence.[4856] But as with similar Teflon treatments (Section 15.3.4.4(2)), the particles show significant migration into local and distant lymph nodes as well as into the urethral mucosa.[4856]

15.3.3.6 Corrosion Degradation Effects

Haubold et al[955] have pointed out that in the "practical" galvanic series,[234] carbon falls with the noble metals. The sequence from least to most "noble" (cathodic) is silver, titanium, graphite, gold, and platinum. When coupled in vivo with less noble or "base" (anodic) metals, carbon can accelerate corrosion by galvanic action, especially when the ratio of the surface area of carbon to that of the metal is large. Mixed potential corrosion theory and potentiostatic polarization data from Thompson et al[1084] suggest that LTI carbon in contact with stainless steel in isotonic saline can accelerate the in vitro corrosion rate through the pitting mechanism, a conclusion shared by Rostoker et al.[1085] Stainless steel screws in contact with a large LTI carbon percutaneous device in simulated body fluids in vitro produced a small corrosion current (1.5 μamp at 120 millivolts) flowing from carbon to steel, although subsequent tests failed to confirm any actual corrosion effects in vivo.[1086] Graphite and other carbon-containing composite materials are electrochemically compatible with various titanium, Cr/Co, and nickel alloys in 3.5% saline solution.[1087]

Even diamond may not be entirely immune from these effects, though the results will seldom be clinically relevant. At high temperature or pressure, carbon from diamond in direct contact with carbide-forming metals such as W, Ta, Ti, and Zr can migrate and form a metal carbide phase.[1088] Metal oxides of Cu, Fe, Co, and Ni in contact with diamond are reduced to the metal (a redox reaction with the carbon escaping as oxide) upon heating in vacuo[539] (Section 9.3.5.3.6).

15.3.4 Biocompatibility of Fluorocarbon Polymer

Fluoropassivated carbon polymers and coatings are among the most hydrophobic surfaces known, and are widely employed in "non-stick" applications. They are also extremely chemically inert. In the nanomedical context, polymeric fluorocarbons have already been suggested as in vivo message carriers (Section 7.2.1.1) and for nanocomputer memory tape (Section 10.2.1). Fluoropassivated diamond has been mentioned in the earlier discussions of in vivo nano-morcellation tools (Section 9.3.5.1) and surface data storage (Section 10.2.1), and could in theory be useful at the exterior surfaces of medical nanorobots or as a coating for internal nanofluidics channels. The biocompatibility of low-n fluorocarbons was briefly reviewed in Section 7.2.1.1 (e.g., some potential for liver damage[6204] but generally low-toxicity;[6217] clearance rates decrease as n increases,[6205] though triglyceride accumulation induced by perfluorinated fatty acids appears concentration-dependent regardless of chain length[6206]). We now extend this analysis to longer-chain fluorocarbons.

Polytetrafluoroethylene (PTFE), a form of Teflon,[1310] is perhaps the most common medical polymeric fluorocarbon.[1311] Commercial Teflon is a packed vinyl polymer, lacking a rigid 2D graphitic or 3D diamondoid crystalline structure. Many different kinds of Teflon are or have been in widespread use, including particulate pastes,[1312,1313] surface films,[1314,1315] wire coatings,[1316,1317] fiber sutures,[1157-1159] yarns,[1169] microporous membranes[1166-1172] (e.g., Biopore[1193]), high-porosity grafts,[1318] multifilament mesh[1194-1196] or textile Teflons,[1319] felts,[1157] sponges,[1158] foils,[1164,1165] sheets,[1201-1206] expanded Teflon or e-PTFE (e.g., Gore-Tex[1190-1194]), denucleated e-PTFE or dePTFE,[1680] and dense masses, tablets, or disks.[1179-1190] Completely fluorinated surfaces exhibit very low intermolecular forces.[858] The coefficient of friction of Teflon in air is 0.05-0.1, about the same as diamond.[1320] Teflon bulk density is ~2130 kg/m^3.[1322]

Teflon in bulk is relatively bioinert. In this Section we review what is known about protein adsorption on Teflon surfaces (Section 15.3.4.1), cell and tissue responses to bulk Teflon (Section 15.3.4.2), the biocompatibility of Teflon-coated prostheses (Section 15.3.4.3), the biocompatibility of fluorocarbon and Teflon particles (Section 15.3.4.4), and the chemical inertness of Teflon (Section 15.3.4.5). But the biocompatibility of atomically smooth fluorocarbon polymer or fluoropassivated diamond surfaces (possibly of greatest relevance in nanomedical applications) has yet to be

seriously investigated experimentally, so the results described here can only be regarded as suggestive.

E. Pinkhassik notes that "one can imagine an interesting material produced by the addition of fluorine to the double bonds of fullerenes. The material will be quite different from Teflon and fluorinated diamond. This monomolecular 2-D material may be useful in the construction of nanodevices. So far, the methods for the complete fluorination of C_{60} have not been developed but [as of late 2002] there are at least two groups working on it (Jamie L. Adcock[5866,5867] at University of Tennessee, Knoxville, and Benjamin T. King[5868] at University of Nevada, Reno)."

15.3.4.1 Protein Adsorption on Teflon Surfaces

Teflon is very hydrophobic[1033] but has protein-binding capacity.[1193] Despite Teflon's reputation as a non-stick material, serum proteins bind almost instantly to its surface, principally via hydrophobic interactions.[901] Hydrophobic fluorocarbon films also show high protein retention.[1113-1114] Higher protein deposition has been observed on fluoroethylenpropylene than on tetrafluoroethylene surfaces,[1321] and on Teflon surfaces modified by exposure to nitrogen or oxygen plasmas than on unmodified Teflon.[1224] Protein adsorption is slightly higher to Teflon than to siliconized glass despite its slightly lower surface tension.[1322] Fungal hyphae can firmly attach to Teflon surface, mediated by SC3p hydrophobin protein.[1323] (Teflon surface hydrophobicity changes upon adsorption of fungal protein, probably as a bilayer.[1324]) The human plasma proteins fibrinogen, albumin and fibronectin influence bacterial adherence to Teflon.[1325]

Adsorption of cell adhesive proteins with known thrombogenic activity such as fibrinogen, fibronectin, and vitronectin on Teflon surface has been studied.[1207-1209] Platelet adhesive proteins such as von Willebrand factor are also adsorbed, with less than 1% of the surface covered by fibrin.[1209] Teflon exposed to human blood preferentially adsorbs fibrinogen.[1209] In one canine experiment, luminal fibrinogen adherence to Teflon vascular graft surface was 320 mg/m^2 (570,000 molecules/$micron^2$) after 4 weeks and 124 mg/m^2 (220,000 molecules/$micron^2$) after 12 weeks[1326] in vivo. This implies multiple layers of deposition. Glow-discharge-treated Teflon surfaces have lower surface free energy and retain a larger fraction of adsorbed fibrinogen (e.g., lower elutability) than ordinary untreated Teflon surfaces.[1327,1328]

Glow-discharge-treated Teflon surfaces also exhibit tenacious adsorption (e.g., tight binding, low elutability) of albumin.[1328] This is believed to contribute to the thromboresistant character of these surfaces including resistance to thrombus deposition, embolization, and thrombotic occlusion.[1330] The strong binding of albumin to such surfaces "may be exploited clinically to enhance the retention of albumin preadsorbed to blood-contacting surfaces to render them thromboresistant".[1328] However, nondenatured albumin adsorbed on ordinary Teflon maintains weak protein-polymer and protein-protein bonds, whereas fibrinogen adsorbates are fostered by strong protein-protein interactions.[1331]

Protein deposits have been observed microscopically on Teflon surfaces.[1332] For instance, TEM images of protein adsorption on Teflon[1331] show albumin deposits that are irregular in shape, unconnected and with low surface coverage, with deposits following surface structural details to a scale of 400 nm. In contrast, fibrinogen deposits are reticulated, connected, and have high surface coverage not reflecting the details of surface structure.

The three-dimensional structure of Teflon-bound proteins is significantly perturbed by the adsorption interaction.[901] For example, fibrinogen undergoes biologically significant conformational changes upon adsorption. This may contribute to the hemocompatibility of the polymer following implantation in the body.[1333] Fibrinogen unfolds and spreads on Teflon to minimize interfacial free energy in water and to maximize the protein-surface interaction.[1327] Adsorbed fibrinogen assumes a state which prevents its recognition and binding by platelet receptors. This improves thromboresistance because fibrinogen must be loosely held by an artificial surface to facilitate maximum interaction with platelet receptors.[1327]

Major structural changes have been observed in other Teflon-adsorbed proteins. For instance, changes in the secondary structure of β-casein upon adsorption at the Teflon-water interface (as a function of pH) have been reported.[1334] The proteolytic enzyme α-chymotrypsin, once adsorbed from aqueous solution onto hydrophobic Teflon surface, assumes a remarkably stable helical structure.[1335] Conversely, adsorption of the lipolytic enzyme cutinase reduces the protein's helical structure.[1335] Adsorption-induced denaturation of immunoglobulin G (IgG) doesn't lead to complete unfolding into an extended polypeptide chain, but leaves a significant part of the IgG molecule in a globular or corpuscular form and enhances the formation of alpha-helices and random coils while reducing the beta-sheet content.[1336]

In many cases, adhesion of enzymes to hydrophobic surfaces results in large conformational changes with significant loss of enzymatic activity.[1337] For example, adsorption of xanthine oxidase onto Teflon distorts protein structure to the extent that all biologic activity is eliminated.[901] As another example, the proteolytic enzyme savinase (the inhibited form of subtilisin) alters its conformation (e.g., increased alpha-helix content) when it adsorbs on Teflon at low surface coverage, although at full monolayer coverage the protein retains its original structure.[1338] Savinase adsorption on the surface of hydrophobic Teflon particles deactivates the enzyme with a half-life of 0.7 hours.[1339] Interestingly, modification of enzymes by adding a large number of fluorocarbon residues forms a hydrophobic envelope around the protein, which can help to prevent enzyme deactivation upon adsorption.[1337]

Lipids are rapidly adsorbed onto Teflon surfaces, influenced by their strong affinity for the highly hydrophobic polymer.[1340]

15.3.4.2 Cell and Tissue Response to Bulk Teflon

In general, bulk Teflon has little adhesion to living cells[1033] or tissues,[5031] and is not cytotoxic.[1141,1190] Indeed, Teflon is often used as an inert negative control[1172-1178] in cytotoxicity studies. Many different types of cells and tissues have been evaluated for their response to bulk Teflon:

1. *Monocytes and Macrophages*. Human monocyte-derived macrophages cultured on non-adherent Teflon liners in Petri dishes,[1210-1213] hydrophobic Teflon bags,[1198-1200,5030] beakers[1341] and membranes,[1162] and other Teflon culture vessels[1160-1163] retain their immunocompetence[1213] and are not stimulated or activated. Thus they can be sustained in long-term culture[1212] for up to 200 days.[1162] Maturing macrophages are readily detached from the Teflon surfaces[1164,1166] and show no obvious structural or functional defects.[1162-1166] Culturing in the presence of Teflon does not suppress succinic dehydrogenase activity of THP-1 human monocytes, nor does it elicit the expression of TNF-α or IL-1β.[1178] In one study,[1163] Teflon-cultured monocytes demonstrated a significantly enhanced CSF (colony stimulating factor) cytokine release over culturing on polystyrene plates. But nonadherent peripheral blood cells cultured in Teflon chambers express relatively low levels of IL-8, a potent neutrophil chemoattractant and activating cytokine.[1342]

2. *Leukocytes and Inflammation*. Inflammatory tissue reactions to Teflon have been observed in mice, rats, rabbits and other animal models since at least the 1970s.[1343] Early studies found that Teflon felts and fibers implanted in canine pleural cavities elicited mild to moderate inflammatory reactions, but hematocele (blood cyst) occurred only upon implantation in the aorta with direct blood contact and exposure to arterial pressures.[1157] Teflon tubes implanted percutaneously can cause an inflammatory reaction.[1191] But in another experiment, sterile Teflon tablets implanted subcutaneously on the backs of rats elicited only a few inflammatory (leukocyte) cells in the tissues bordering the Teflon for up to 3 weeks post-implantation.[1185] Teflon-coated catheters have significantly reduced superoxide radical production by human polymorphonuclear leukocytes, suggesting that Teflon may inhibit the bactericidal function (respiratory burst) of these leukocytes.[1184] However, in the same experiment the uptake of opsonized *Staphylococcus aureus* (e.g., phagocytic function) was unaffected by the Teflon.[1184] Teflon implanted in the quadriceps muscle of guinea pigs and assessed histologically after 2 days to 26 weeks showed no prominent tissue inflammation or foreign body giant cell response.[1344] Leukocytes are generally not activated by Teflon in vitro. For example, human leukocytes incubated with knitted Teflon or e-PTFE exhibited no peak metabolic activity (implying the material is noninflammatory).[1195] In another experiment,[1173] culturing neutrophils in Teflon bags did not trigger cell activity, whereas cells incubated in uncoated glass or plastic tubes adhered and released O_2^-. However, neutrophils incubated in the presence of lipopolysaccharide (LPS) could adhere to Teflon and release O_2^-,[1173] and Teflon surfaces elicited a transient increase of cellular calcium levels, indicating a G protein-coupled activation of the granulocytes used as a biological test for inflammatory mediators.[1189]

3. *Fibroblasts*. Microporous e-PTFE Teflon implanted beneath the transversalis fascia in the groins of rabbits was completely invaded by fibroblasts at 8 weeks, with flat orientation of graft to the fibrous tissue forming a neofascia with local or peritoneal inflammatory reaction.[1167] Teflon membranes incubated in collagen promote attachment of fibroblasts.[1172] Porous or knitted Teflon material coated with collagen, fibronectin, gelatin or laminin promotes human fibroblast migration over and adherence to Teflon.[1196] Granulomatous reaction and tissue formation has been observed around cannulated Teflon cylinders implanted subdermally in rats, producing exudation with cell infiltration, granuloma growth, and formation of prostaglandins.[1181] Sterile Teflon tablets implanted subcutaneously on the backs of rats elicits a connective tissue capsula after 3 weeks.[1185,1186] Fibrous tissue encapsulates subcutaneously implanted Teflon disks in rats.[1187]

4. *Lymphocytes*. Bovine lymphocytes exposed to bulk Teflon retain their ability to activate, hence bulk Teflon appears to be lymphocompatible.[1345] Teflon implanted in temporal (skull) bone elicits fibrous tissue formation and a few giant cells with some lymphocyte infiltration.[1346]

5. *Platelets and Thrombogenesis*. Platelet deposition on Teflon surfaces placed in sanguo is greatest immediately post-implantation, then declines over time.[1202] In short-term exposures, platelet adhesion was measured experimentally as 0.0037 platelets/micron^2 on dePTFE, ~0.014/micron^2 on e-PTFE, and 0.0168/micron^2 on woven Dacron, after a 5-minute exposure to fresh human blood flowing at a wall shear rate (Section 9.4.1.1) of 50 sec^{-1}.[1680] Tested for longer exposures, luminal platelet adherence to Teflon graft surface in a canine model was 0.564 platelets/micron^2 at 4 weeks and 0.124 platelets/micron^2 at 12 weeks.[1326] Teflon vascular grafts incorporated into femoral arterial-arterial shunts in baboons for 1 hour produced a platelet deposition of ~2 platelets/micron^2.[1204] Teflon may enhance platelet reactivity,[1159] though some data appear contradictory. One experiment[1195] found that human platelets exposed to Teflon experience a rapid increase in metabolic activity, followed by a steady state for more than 1 hour, which suggests that bulk Teflon is thrombogenic. However, another experiment[1209] determined that platelet adhesion to Teflon is shear rate independent, with the large percentage of platelets not spread out on the surface, indicating that the material is a poor platelet activator. Studies of platelets on Teflon often employ anticoagulants[1326] because some forms of Teflon are so thrombogenic, more so than Dacron.[1209] Rotating disks[1180] and atrial septal defect patches[1347,1348,5020] made of Teflon are very mechanically hemolytic. Intense thrombogenicity was observed with Teflon-coated guidewires in both clinical[5010] and in vitro settings, with formed thrombi ranging from 50-100 microns in size.[1317] Gore-Tex used in vascular grafts is acutely thrombogenic, accumulating 8 platelets/micron^2 in the first hour of exposure to human blood.[1192] The same study found that a series of plasma-modified polymers based on tetrafluoroethylene, hexafluoroethane and hexafluoroethane/H2, when deposited on silicone rubber, consumed platelets at rates ranging from 1.1-5.6 platelets/micron^2-day, which was considered relatively nonthrombogenic.[1192] And a second study[1205] found that a graft of stretchable Teflon implanted in pig iliac arteries produced a 68% thrombus-free surface, compared to only 37% for standard Teflon fabric grafts. Surface roughness may play an important role. In one experiment[1315] very thin fluorocarbon films were plasma-deposited on rough but hemocompatible poly(hydroxybutyrate), and on smoother but more thrombogenic polysulphone, to study the relative influence of surface roughness and surface energy on polymer thrombogenicity. In vitro protein adsorption and blood clotting tests proved that surface roughness influences thrombogenicity more than other surface properties.[1315] Interestingly, centimeter-size nanoporous Teflon chambers implanted intraperitoneally have been tested in guinea pigs and rhesus monkeys as in vivo clotting factor dispensers, as a potential treatment for hemophilia.[1407]

6. *Bone Cells and Tissues*. Osseous tissue cell reactions to Teflon implants have been studied for decades.[1214-1216] For example, Teflon tubes implanted percutaneously in rats near demineralized bone matrix produced chondrogenesis and osteogenesis in the subcutaneous tissues.[1191] Osteogenesis was inhibited near the foreign material but there was good circumferential bone formation.[1191] Hollow Teflon capsules implanted in rat jaw bone were infiltrated by new bone to 31% of the cross-sectional area after 60 days and to 45% after 120 days.[5012] So bone tissue appears more sensitive to the presence of Teflon. One experiment with Teflon tubes implanted in the mandible of guinea pigs found that the Teflon elicited a soft tissue capsule which separated regenerated bone from the implant.[1349] An independent study using the same animal model found a persistent moderate inflammation reaction and a thick fibrous encapsulation after 4-12 weeks, except in areas where poorly condensed material was dispersed into the bony tissue where chronic inflammation and active phagocytosis was also observed along the surface of the material.[1350] Dental applications of Teflon have been investigated sporadically.[1217-1220] In one experiment,[1220]

exposed pulps of Rhesus monkey teeth received Teflon caps for 3 days to 8 weeks. Resolution of the soft tissue inflammatory response and healing were slow, with only 20% of teeth treated for 5-8 weeks showing hard tissue formation at the exposure site.[1220]

7. *Endothelial Cells*. Cultured human endothelial cells show poor attachment to hydrophobic polymers such as Teflon.[1224,1329] In one experiment, human microvessel endothelial cell attachment compared to control was 47% for albumin-coated Dacron but only 3% for Teflon graft material.[1351] Precoating Dacron or Teflon with fibronectin allows endothelialization to occur, up to 500 cells/mm^2, compared to ~70 cells/mm^2 for uncoated surface, after culturing for 8 days.[1329] Alternatively, when Teflon is surface modified by exposure to nitrogen or oxygen plasmas, creating a 1 nm thick modified layer, the surface can then sustain a monolayer of cultured endothelial cells.[1224] (But Teflon precoated with albumin, high-density lipoprotein, or IgG inhibits endothelial adhesion.[1329]) Teflon felt and Teflon-coated fibers tested in vitro with endothelial cells on cultured canine saphenous vein explants have shown no signs of toxic reactions.[1157] Culturing in the presence of Teflon does not suppress succinic dehydrogenase activity of human microvascular endothelial cells, nor does it elicit the expression of ICAM-1.[1178]

8. *Epithelial Cells*. Porous or knitted Teflon material coated with collagen, fibronectin, gelatin or laminin promotes human conjunctival epithelial cell migration over and adherence to Teflon.[1196] In vitro human junctional epithelial cells do not attach to Teflon.[1193] In this experiment,[1193] cells adjacent to the Teflon substrata were nonproliferative and did exhibit signs of degeneration or cell differentiation. However, an earlier study in mice had shown that subcutaneously implanted Teflon cylinders with etched surfaces produced closed tissue contact, with signs of toxic tissue reactions completely absent.[1182] There is one decades-old report[1179] of subcutaneous fibrosarcomas induced in 30-94% of BALB/c, C3Hf/Dp, and C57BL/He female mice by implantation of a Teflon disc, with mean latency of 61-82 weeks, but the reliability of this study is unknown and the results appear not to have been replicated.

9. *Neural Cells*. Dissociated mouse cerebellar cells containing both glia and neurons in tissue culture were exposed to spongy and fibrous Teflon, which had little or no effect on the growth of these cells.[1158] Some adhesion of both glia and neurons to the Teflon surface was seen, but the attachment was not extensive.[1158] There is at least one case of aseptic meningitis that persisted for 5 months and did not resolve until after surgical removal of Teflon that had been used to pad the trigeminal nerve to provide microvascular decompression to relieve trigeminal neuralgia.[1352] There is also one reported case of recurrent trigeminal neuralgia caused by a Teflon prosthesis that had been inserted between the trigeminal nerve and the superior cerebellar artery, and which then became hard and compressed the trigeminal nerve 17 months after the initial surgery.[1353] The ability of amorphous Teflon copolymer to inhibit or bio-pattern cell adhesion has also been tested with various neural cell lines.[1354]

10. *Sperm and Embryo Cells*. Teflon is relatively inert with respect to its biocompatibility toward sperm motility and penetrability of zona-free hamster eggs, and toward the ability of two-cell mouse embryos to divide.[1355] Teflon coated catheters appear nonspermiotoxic to bull sperm, reducing sperm motility by only ~6% after 90 minutes exposure. Teflon embryonation capillaries are well tolerated by embryos.[1356]

11. *Hematopoietic Cells*. Human hematopoietic cells proliferate near-normally when cultured on Teflon perfluoroalkoxy or Teflon fluorinated ethylene propylene.[1357]

12. *Bacterial Cells*. Microbial tooth plaque accumulation and adhesion are reduced on Teflon-coated metal surfaces.[1358] Some bacteria such as *S. epidermidis* attach readily to Teflon surfaces,[1225-1227] forming biofilms.[1226,1359] Here again there are conflicting claims in the literature, suggesting further research is needed. For example, one study reported that adhesion of the staphylococci to fluorinated polyethylene-propylene films was not related to the relative surface charge or the hydrophobicity of the bacteria,[1360] while another study reported that adherence to Teflon catheters was significantly influenced by the degree of hydrophobicity of the microbial strains.[1361] Preincubation in serum reduces bacteria adhesion on Teflon, mainly due to the inhibitory effects of adsorbed albumin.[1360,1361]

13. *Other Cells*. Hepatocytes grow normally on Teflon membrane culture dishes.[5025]

15.3.4.3 Biocompatibility of Teflon-Coated Prostheses

The first implantation of bulk Teflon into the dog peritoneal cavity was reported in 1949 by Leveen and Barbario.[1681] Teflon has been used as a solid implant in cardiovascular surgery (e.g., cardiac valves, vascular patches and catheters), orthopedics (e.g., hip prostheses), facial surgery (e.g., maxillary and orbital implants), and neurosurgery (e.g., dura mater implants, derivation valves).[1311]

While Teflon is non-antigenic,[1196-1198] complement activation has been demonstrated by Teflon tubes in contact with whole venous blood for 10 minutes,[1189] and Teflon suture and graft materials cause significant activation of C5a complement.[1159]

Teflon coatings have often been applied to prostheses to achieve anti-adhesive effects,[1314] but with a mixed record of success. For example, after a long period of widespread use,[1362,1363] Proplast-Teflon temporomandibular joint (TMJ) interpositional implants manufactured by Vitek had to be removed from the market in 1995 by the FDA. This was due to complications including severe bony destruction of both condyle and fossa as a result of extensive granulomatous and exuberant foreign body giant cell reactions,[1364] cerebrospinal fluid leak,[1365] fibrosis, calcification, inflammation and pain,[1366] soft tissue destruction[1160] and the exacerbation of existing connective tissue or autoimmune disease problems.[1362] Failed Proplast-Teflon TMJ implants[1367] had to be replaced, and removal led to increased rates of immune-mediated and somatization-related conditions, allergies, or symptoms of environmental sensitivity.[1188]

Other problems occur infrequently with mechanical Teflon prostheses. There is at least one case of an eroded prosthetic Teflon cardiac disc valve in the tricuspid position that became embolic, producing foreign material that was later found in the vessels, vessel walls, and parenchyma of the lung, associated with a foreign body type of inflammatory reaction.[1277,1368] A case of Teflon embolization to the lungs from Teflon pledgets deployed during cardiac surgery, with pathological changes found in the pulmonary arteries, has also been reported.[1369]

Teflon aortic grafts have been implanted in human patients undergoing abdominal aortic aneurysmectomy.[1203] Other Teflon arterial prostheses have been studied in humans,[1221-1225] and grafts in other arteries have been studied in baboon[1201,1204] and canine[1318] models. In one study,[1370] Teflon prostheses placed arterially in human patients for periods from 2 months to 18 years were initially permeated by thrombus containing platelet antigens. This became

organized and converted to granulation, and then to fibrous, tissue. The newly formed tissue contained foreign body giant cells in contact with the prosthesis and showed evidence of permeation by plasma proteins. The oldest grafts also showed stenosis, calcification, or aneurysm formation.[1370] A Teflon coated aortic stent implanted in dogs for 1-4 weeks reacted only moderately with the vessel wall, producing a neointimal layer 115 microns thick.[1372] By comparison, gold-coated stents produced the fewest macroscopic and histopathologic changes in the aorta with an 83.9-micron-thick neointima, while a copper-coated stent produced severe erosion of the vessel wall, marked thrombus formation, and aortic rupture.[1372] But while large-diameter (>5mm diameter) vascular grafts can remain excellent for >10 years after implantation, smaller-diameter Teflon vascular grafts may occlude rapidly upon implantation.[1371]

Early Teflon catheters implanted to provide drainage in the bile duct over periods from 1 week to 8 months were at best partially effective. There was insufficient drainage and bile duct infection in most patients, spontaneous dislocation of the endoprosthesis in many patients, and death in one patient due to an intrahepatic aneurysm adjacent to the puncture tract.[1373] More recently, in vitro studies of biliary stents have shown less clogging and sludge formation in Teflon biliary stents, but clinical studies have given conflicting results.[1228-1231,5018] Part of the continuing difficulty may be due to the irregular surface which features multiple shallow pits and ridges with multiple particles projecting into the lumen, which are visible at the submicron scale under SEM examination.[1374] Venous Teflon catheters used for parenteral nutrition produced the most extensive thromboses among the five major types of catheter materials tested.[1375] Intravenous Teflon catheters have a slightly increased risk[5024] of catheter-induced phlebitis compared to Vialon (PTFE) catheters, even though both materials are fluorocarbons.

Teflon transplants following scleroplasty (plastic surgery of the sclera of the eye) have shown good experimental biocompatibility.[1170] In one early study, e-PTFE was episclerally implanted for evaluation as an adjunctive material for retinal detachment surgery. The implant demonstrated a minimal inflammatory response and ingrowth of connective tissue, creating a thick, fibrovascular intrascleral implant.[1376] A later study using sterilized thin Teflon sheets implanted in surgically prepared pockets in the sclera of rabbit eyes demonstrated excellent compatibility. The implanted sheets elicited histiocytes, fibroblasts, collagen and blood vessels infiltrating the internodal spaces of the highly porous material after 14 days. The number of cells and amount of extracellular matrix material deposited in the implants increased with time.[1206] In a 1999 experiment,[1377] oval-shaped e-PTFE episcleral implants focally placed in rabbit eyes for 3-11 months elicited a newly formed capsule that constantly encased the implants. The inner surface of the capsule was often covered with numerous giant cells, attesting to a foreign-body granuloma developed against the irregular outline and the hydrophobic character of the implants.[1377] No intrusion or extrusion of episcleral implants (which were well tolerated experimentally) was observed. Porosity and surface irregularity of the implant allowed its colonization by a fibrovascular and inflammatory tissue mainly in its peripheral layers. Sclera under the implant was thinned and invaginated.[1377] e-PTFE is well tolerated for scleral buckling surgery of rhegmatogenous retinal detachment, with no complications such as migration, infection, erosion, extrusion, or intrusion, and excellent tolerance and biocompatibility over a 14-26 month follow-up period.[5013]

Teflon-coated intraocular lenses implanted in vivo in rabbit eyes for 1-2 months showed significantly fewer cell deposits and no iris-lens synechias compared to non-Teflon controls which showed extensive synechias along with lens epithelium proliferation and spindle-shaped cell deposits.[1314] e-PTFE alloplasts have shown high biocompatibility and can be ingrown by fibrovascular tissue in vascular, abdominal, and reconstructive surgery. But corneal implants, though well tolerated from a biocompatibility standpoint, show no evidence of fibrovascular ingrowth.[1378] An e-PTFE drainage implant with 20- to 50-micron pores for glaucoma filtering surgery was tested in rabbit eyes for 3 months. There was no postoperative hypotony, migration, extrusion, intraocular inflammation, or infection, and there was greatly extended filtering patency compared with conventional trabeculectomy and laser sclerectomy.[1171] A PTFE patch graft implanted into anophthalmic patients for 6-13 months was well tolerated without extrusion, granuloma formation, or irritation.[1197]

Proplast II is a porous alloplastic composite of Teflon polymer and alumina alleged to have been used successfully as a subperiosteal implant to treat anophthalmic enophthalmos, giving good correction of preoperative upper eyelid sulcus deformity while integrating well with the surrounding tissues and minimizing the risk of subsequent implant migration and extrusion.[1379] A Teflon tube has been successfully used as a lacrimal drainage stent in the lower canaliculus, and as a bypass tube in connection with canaliculus laceration repair.[1380] For many years, good results in otosclerosis surgery (for the purpose of closing eardrum perforations and rebuilding the ossicular chain, thus rehabilitating conductive hearing loss) have been achieved using a prosthesis made of Teflon-coated platinum wire with gold pistons.[1316]

A microporous Teflon tracheal prosthesis[1381] has been tested in rabbits and was successfully incorporated (e.g., luminal side covered by connective tissue and epithelium) within 2-4 weeks without inflammation or granulation tissue at the anastomoses.[1168] Two minor complications included infection of the prosthesis before incorporation was complete (which can be overcome by antibiotics) and obstruction of the lumen at the center of the prosthesis by granulation tissue or a deformed Teflon wall (which can be overcome by using a stiffer prosthesis).[1168]

Fluoropolymer-coated polyester fibers have been tested as prosthetic grafts in the surgical management of abdominal hernias,[1169,1194] in cases where the defect is too large or the surrounding tissue is not available for repair. Teflon netting has been employed as a replacement material for subcutaneous tissue and a substitute for superficial fascia destroyed by tumor infiltration involving neurofibroma of the face.[5016] Teflon has been used as a nasal septal splint[1382] and as a penile graft implant as a treatment for Peyronie's disease and erectile dysfunction,[5778-5781] and Teflon as Gore-Tex has been used as periodontal material.[1193]

15.3.4.4 Biocompatibility of Teflon Particles

Small-chain fluorocarbon molecules are generally biocompatible in low doses. However:

a. macrophages which have ingested perfluoro compounds may show some loss of phagocytic function and possible release of cytokines and other immune mediators;[1383]

b. oxypherol, a commercially available perfluorochemical used in animal tests, is slightly adsorbed on the surface of red blood cells, causing a decrease in erythrocyte deformability;[1384]

c. tetrafluoroethylene (a monomer used in Teflon manufacture) is hepatocarcinogenic in inhalation studies in mice after 2-year exposures at 312-1250 ppm concentrations;[1385]

d. Fluosol (an oxygenatible fluorochemical) elicits anaphylactoid-type reactions in a small percentage of patients at blood concentrations as low as ~0.1 gm/liter;[1386] and

e. biological enzymes modified by adding a large number of fluorocarbon residues do not undergo large conformational changes upon adsorption on a Teflon surface and thus are not deactivated.[1337]

Pure fluorocarbons and fluorocarbon moieties have very strong intramolecular bonds and very weak intermolecular interactions,[1387] hence should display low particle aggregation.* The stability and permeability of fluorinated liposomes has been widely studied.[1306-1309] For example, aqueous-suspended 30-70 nm fluorovesicles have a maximum tolerated IV dose up to 0.5 gm/kg body weight in mice (~5 gm/liter blood volume).[1308] Hemolytic activity sharply decreases with increasing degree of fluorination.[1308]

There are no confirmed reports of Teflon particle inhalation toxicity. Polymer fume fever[1683,2120,2121] due to inhalation of Teflon pyrolysis products is well known, though pyrolysis products are very different chemically from Teflon and are inevitably toxic due to their high reactivity. (This is true for other polymers as well, and does not directly relate to the biological performance of the polymer material.) For example, in one case[1388] two men were occupationally exposed to Teflon powder and experienced episodes at work of fever, leukocytosis and general malaise, all of short duration, which ceased after there was no further exposure to Teflon. It was concluded that the cause was inhalation of Teflon combustion products originating from Teflon-contaminated cigarettes. There are also reports of bird toxicity from heated Teflon fumes.[1683] Ultrafine (<100 nm) particle fumes produced by heating Teflon to 486 °C in air are extremely toxic to rats in concentrations of ~50 $\mu g/m^3$ when inhaled for only 15 minutes,[4846] possibly due to the presence of radicals on the surface. Ultrafine Teflon particles rapidly translocate across the epithelium after their deposition in the lungs.[4846] But when these particles are generated by heating in an argon atmosphere they are no longer toxic, implicating possible radicals on the particle surface for the toxicity. Interestingly, the researchers[4846] noted that "the pulmonary toxicity of the ultrafine Teflon fumes could be prevented by adapting the animals with short 5-minute exposures on 3 days prior to a 15-minute exposure." Particles larger than 100 nm no longer caused toxicity in exposed animals.[4846]

Teflon particle injections have been used for decades to treat a variety of human medical conditions, as summarized below. The most common injectant is a commercial preparation known as polytef paste. Polytef paste consists of pyrolyzed Teflon particles measuring 4-100 microns in diameter and irregular in shape, suspended in a glycerin carrier.[1256,1389] The principal intended therapeutic effect of the implanted particles is to passively increase local tissue volume. Experimental and clinical doses typically range from 0.1-1 cm^3 of paste,[1390] representing 0.1-10 billion Teflon particles per dose.

But when injected in particulate form, Teflon can sometimes provoke severe inflammatory reactions[900,901] and can elevate serum levels of allergen-specific IgE and IgG2a.[5026] In one experiment with Teflon particles,[1389] mice received subcutaneous dorsal injections, rabbits received subareolar injections, and dogs received subareolar and periurethral injections. Subsequent histological examination of the biopsy sites revealed a persistent chronic inflammatory reaction with progressive growth of the involved tissue volume, evoking inflammatory pseudo-tumors.[1389] In addition to giant cells and macrophages, lymphocytes became apparent at 3 months and constituted up to 40% of the cellular infiltrate by 1 year. Plasma cells were also noted in the rabbits after 1 year.[1389] In another experiment,[1391] 48 days after submucosal injections of Teflon paste into the peritoneum of mice, many particles were found (1) in peritoneal macrophages, (2) in microphages and macrophages of regional lymph nodes and the spleen, and (3) in Kupffer cells of the liver.[1391] Phagocytes containing Teflon particles can induce local inflammation and fibrosis.[1391]

Implanted Teflon particle migration from the site of injection to lungs and brain has been reported in many animal studies.[1392] For example, small amounts of Teflon paste particles injected intravascularly into peripheral veins and the right carotid artery of dogs were found in cerebral vessels 6 months after arterial but not venous injections.[1392] Brain tissue sections showed particles in vessels with focal foreign-body reaction but no infarction, no nerve fiber abnormality, no astrocytosis, and no demyelination around vessels containing the particles and the parenchyma — in summary, no brain parenchymal tissue damage.[1392] Nevertheless, concerns with particle migration[1280] led the FDA in 1984 to prohibit the medical use of Teflon particles in the U.S.[1311]

Medical conditions which have been treated (with varying degrees of success) by Teflon particle injections, or experimentally evaluated in animal models for possible human treatment, include:

1. *Vocal Cord Paralysis* (first used, 1962). Since the 1920s, reinnervation attempts have been unsuccessful in restoring motion to paralyzed vocal cords.[1240] In 1962, Arnold[1682] used injectable Teflon particles to reintroduce Brunings' technique for rehabilitating the paralyzed vocal cord.[1237] Since then, transcutaneous Teflon injection of paralyzed and bowed vocal cords has been used to treat unilateral paralytic dysphonia.[900,1232-1251,1260] There are several good historical and literature reviews.[1243-1246] The major defect of unilateral vocal cord paralysis, which manifests as a soft and breathy voice, can be eliminated by moving the edge of the paralyzed vocal cord to the midline via Teflon injection.[1240] This allows the mobile vocal cord to adduct and vibrate firmly against the edge of the paralyzed vocal cord during phonation, eliminating the air leak between the vocal cords. The treatment is commonly performed by indirect laryngoscopy under local anesthesia so that the effect on the voice can be monitored during the injection. Teflon is easily removed from the vocal cord via direct laryngoscopy.[1240] Teflon particles appear to be noncarcinogenic.[1237,1249] The foreign body reaction to the laryngeal Teflon implant shows giant cells, few lymphocytes, and no polymorphonuclear leukocytes. This reaction may be described as a bland, chronic type consistent with the age of the implant, and lacking any areas of florid, acute reaction.[1249] Partial extrusion of polytef through the cricothyroid space is sometimes observed, but usually without signs of unfavorable tissue reaction or intolerance.[1249]

   Failure or complications in this procedure are sometimes reported.[1246-1248] These complications may include: acute or chronic inflammatory reaction;[900,1251,1262] cough or choking;[1262] swallowing difficulties;[1262] laryngeal stenosis[900] or airway obstruction;[1250,1260-1262] acute foreign-body giant cell reaction;[1252-1255] extravasation and infiltration into the soft tissues of the neck;[1260] particle migration into the lymphatics[900,1390] or surrounding muscle tissues;[1253] persistent hoarseness or voice changes;[1260] and even dysphonia.[1252,1262] A rare complication

** Fluorocarbons have much weaker intermolecular interactions than hydrocarbons. Their intermolecular interactions are among the weakest known for organic molecules. This is manifested most prominently in the low boiling points of fluorocarbons, since a comparison of boiling points for compounds of similar molecular weight gives a good idea of the magnitude of intermolecular interactions. For example, the fluorocarbon perfluorocyclobutane (MW = 200) has a boiling point of -6 °C, whereas the hydrocarbon tetradecane (MW = 198) has a boiling point of 253 °C; even the non-fluorinated hydrocarbon cyclobutane (MW = 56) has a boiling point of 13 °C.*

is "teflonoma"[1255-1260,5021] or large granuloma formation.[1248-1253] Teflonomas have been initially been mistaken for thyroid tumors[1249,1258-1260] or carotid body tumors.[1256] Today, collagen particles,[1237] autologous lipids,[5014] and other materials[5032] show more promise as possibly safer particle-implantation tissue-bulking alternatives.

2. *Urinary Incontinence* (first used, 1973). Periurethral Teflon injection is commonly used to control urinary incontinence,[1267-1280] stress incontinence,[1283-1286] and post-prostatectomy incontinence.[1263-1265] Tissue reactions in males are generally limited to modest infiltration of lymphocytes and monocytes, and a slight increase in collagen fibers. Particles are generally well tolerated[1393] with minimal migration to lungs or brain in pig and dog models.[1394] Complications have included: clumping of paste;[1393] pain;[1263] fever and malaise upon removal;[1282] inflammatory reaction;[1268] possible infection or intolerance;[1268] periurethral abscess and urethral diverticulum;[1265,1286] elevated erythrocyte sedimentation rate;[1282] fibrosis;[1268] foreign-body giant cell granulomatous reaction[1266,1267,1280-1282] and polyps;[1398] pulmonary granuloma[1286-1288] with urethral wall prolapse;[1286] teflonoma[1264-1266] with urethral wall prolapse;[1265] migration of particles[1280,1397,1398] particularly into lymphatic,[1280] perineal,[1263] kidney,[1280] spleen,[1280] brain,[1280] and pulmonary[1277,1280] tissues, and to the skin;[1282] and even complete urinary obstruction.[1266-1268] These potential complications have led some to recommend that periurethral Teflon injections should only be used in special cases,[1284] although autologous lipoinjection has an even poorer success rate.[5022]

3. *Cosmetic Surgery* (first used, 1976). Subcutaneous injection of facial wrinkles with Teflon paste in the 1970s produced granulomas.[1395] In another case,[1396] granular Teflon paste was injected into the upper eyelid to remodel the upper palpebral furrow which had been retracted by scars. Large foreign-body granulomas developed a few weeks later, necessitating excision and leading the surgeons to advise against using Teflon injections in well-vascularized loose tissue.[1396]

4. *Vesicoureteric Reflux* (first used, 1981). Vesicoureteric reflux or VUR is the reflux of urine up the ureter during micturition. Endoscopic submucosal Teflon injection (STING) to correct VUR was performed for the first time by Matouschek[1289] in 1981. The procedure has since been widely employed in clinical practices by Puri and O'Donnell[1399] and others[1305,1312] for treatment of ureteric, vesicorenal or vesicoureteral reflux.[1289-1305,5011] The procedure is also used to correct VUR prior to renal transplantation procedures[1304] and to treat ureteroceles.[1291] STING gives a high cure rate in children[1297-1303,5029,5033] and adults[1294,1303] with generally good results,[1292,1298] although a second injection is often required.[1301-1305] There is no major morbidity or risk of nephroureterectomy,[1304] and there are no signs or symptoms of embolization of the implant material.[1296] Possible carcinogenic risks have been noted[1312] but no carcinogenic degeneration has yet been observed[1385] and Teflon powder is not considered to be carcinogenic.[1311]

   Complications may include: postoperative Teflon leakage from the injection site;[1296,1400] encapsulation of the implant by a thin layer of fibrous tissue;[1399] foreign body granulomatous reaction locally involving histiocytes and giant cells within the implant[1399,1401] and also involving locoregional lymph nodes;[1401] ureteral stenosis in 1% of cases;[1312] and one possible case of ischemic brain injury (stroke).[1402] The risk of particle migration has been noted[1304,1312] although most studies have detected no migration[1296,1399] to liver,[1312] lungs,[1312] or brain.[1312] In one animal study,[1401] rare particles of Teflon were observed in the lungs but not in the brains of rabbits that had received Teflon injections in the bladder submucosa. In another animal study,[1403] numerous particles were recovered from lungs and brain within 2 weeks of Teflon particle injection in the manner used to treat VUR. Particles in the brain measured up to 15 microns, indicating that the pulmonary bed is an inefficient filter of particles gaining access to the venous circulation.[1403] No adverse neurological effects have been reported clinically, but the authors warned that some particles could lodge in the brain where they could block the cerebral microcirculation.[1403] In a human clinical study, most of the Teflon particles injected for VUR in one child of 83 treated were observed by CT scan to have disappeared from the original site of injection. It was speculated that the material had been extruded into the bladder.[1400] A few practitioners have now abandoned polytef injection for treating VUR.[1295] Collagen particles have given disappointing results, but microparticulate silicone[1312] and bioresorbable microspheres[5453] appear more promising.

5. *Velopharyngeal Incompetence* (first used, 1985). Teflon injection into the submucosa of a child's posterior pharyngeal wall was used to treat severe open nasality due to velopharyngeal incompetence. A biopsy after 8 years revealed a marked foreign body reaction with a persistent inflammation and fibrosis.[1404] Lipoinjection may be a preferable alternative here.[5019]

6. *Partial Fecal Incontinence* (first used, 1993). Perianal injection of polytef particle paste into the rectal neck submucosa in patients with partial fecal incontinence resulted in an increase in rectal neck pressure produced by the cushion effect of the Teflon particles. All patients showed at least partial improvement, and two-thirds experienced long-term cure.[1405]

7. *Low Esophageal Sphincter Pressure* (first used, 1996). Intraabdominal injection of Teflon paste at the gastroesophageal junction produced a well defined Teflon mass at the site of the injection. The implant was encapsulated by a thin layer of fibrous tissue and a benign foreign body granulomatous reaction with round cells surrounded the implant. The procedure increased lower esophageal sphincter pressure from 29.7 mmHg preoperative to 37.6 mmHg postoperative in rabbits.[1313]

15.3.4.5 Chemical Inertness of Teflon

Teflon is inert to chemical attack, being unaffected by ozone, elemental fluorine, boiling nitric acid or aqua regia, concentrated sulfuric acid, or strong oxidizing agents such as potassium permanganate.[1406] Reducing agents such as hydrogen or carbon do not affect it even at temperatures as high as 1000 °C.[1406] Fluorocarbons are attacked only by hot metals such as molten sodium.[858] Some of the chemical stability of fluorine derivatives must be attributed to the impossibility of expansion of the octet of fluorine and the inability of water to coordinate to fluorine or carbon as the first step in hydrolysis.[858] Also, C-F bonds are among the strongest covalent bonds known. Fluorine atoms are larger than hydrogen atoms, so the F atoms effectively shield the carbon atoms from attack much better than the H atoms in hydrocarbons. Since the C-F bond is very polar, the carbon can be considered to be effectively oxidized (whereas the C-H bond is only slightly polar, so the carbon is not nearly as reduced), so there is no tendency for oxidation by oxygen.[858] Teflon can be heated in air without burning[1406] up to

450-500 °C.[1310] When pyrolyzed, fluorocarbons tend to split at C-C rather than C-F bonds.[858] This is because carbon-carbon bonds are much weaker than carbon-fluorine bonds. In fluorocarbons, C-C bond energies are approximately 80 kcal/mole, while C-F bond energies are 115 kcal/mole. Since it takes less energy to break C-C bonds than C-F bonds, fluorocarbons will split at the C-C bonds.

Teflon is a chemically inert,[1197,1310,1378] bioinactive,[1183] nonabsorbable[1196] implant material. It is relatively stable in the tissues and is not readily dissolved or digested by the host.[1033] Teflon particles are indigestible by macrophages and Kupffer cells,[1391] and bulk Teflon is not cytotoxic.[1190] As noted elsewhere in this Section there can be some biocompatibility problems with traditional medical fluorocarbon-based surfaces, but atomically smooth surfaces of this type have yet to be rigorously investigated.

15.3.5 Biocompatibility of Sapphire, Ruby, and Alumina

Pure corundum (aluminum oxide or alumina) is colorless and can have a strength and hardness (Table 9.3) and a chemical inertness (Section 15.3.5.6) that is only slightly inferior to diamond. Sapphire and ruby, the best-known crystalline forms, are primarily single-crystal α-Al_2O_3. The crystal can be manufactured in a full spectrum of colors (Section 5.3.7). The material characteristics of sapphire are reviewed elsewhere (Section 5.3.7, Section 9.3.5.3.6, Table 9.3, etc.). Scanning force microscopy has been used to image the atomic structure of the (0001) surface of α-alumina crystal, and to observe the formation of hydroxide clusters after exposure to water.[4796] The atomic structure of the hydrated α-alumina surface has also been investigated by X-ray diffraction.[1751] The high-density single-crystal sapphire form of alumina may be produced when Al_2O_3 is compressed under isostatic pressure and fired at 1500 °C to 1700 °C.[956] Alumina nanotubes have also been synthesized.[4804]

To summarize the utility of sapphire in medical nanorobotics: First, sapphire is almost as strong and hard as diamond (Table 9.3), and only slightly more dense. Second, sapphire is already fully oxidized, so in particulate form (e.g., micron-size nanorobots) it cannot burn in air like diamond, and its crystalline structure remains stable to higher temperatures than diamond. Third, sapphire has more favorable bulk thermophysical characteristics. The thermal conductivity of sapphire is 100-1000 times less than for diamond, reducing the increase in the thermal conductivity of tissues that are loaded with sapphire nanostructures, as compared to tissues containing pure-diamond nanostructures (Section 15.3.8). Sapphire also has 60% greater heat capacity per unit volume than diamond. Fourth, sapphire offers designers an alternative hydrophilic surface chemistry as compared to hydrophobic diamond. Sapphire is amphoteric, absorbing H^+ ions in very acidic environments (acquiring a positive charge) and absorbing OH^- ions in alkaline environments (acquiring a negative charge), while remaining isoelectric (electrically neutral) at intermediate pH values near human physiologic at ~7.4 (Section 15.5.6.1). Fifth, sapphire can be manufactured in a full spectrum of colors (Section 5.3.7) by replacing 0.01%-0.1% of the aluminum atoms with atoms of iron, titanium, or chromium, while producing only modest changes in the physical and chemical properties of the material.

Apparently no studies have been done on the biocompatibility of ruby, but high-density monocrystalline sapphire[1034] and alumina (e.g., either porous or polycrystalline[970]) materials have been widely investigated and are already in extensive clinical use. (Amorphous or γ-alumina[959] and other transitional or "activated" forms[958] are not discussed here.) For instance, sapphire is often used as a dental implant (Section 15.3.5.2), though it is so hard that it must be resected using a diamond bur.[971] Alumina[845,972-974] and sapphire[1031-1036,1050] are generally regarded as nontoxic bioinert ceramic materials. While the biocompatibility of sapphire appears to be in some ways slightly poorer than diamond, nevertheless in applications requiring hydrophilic, nonoxidizable, or colored surfaces, sapphire may be the better choice of nanorobotic building material.[34] Sapphire is already being used in nanofluidics[4786] and other near-term nanomedical applications, and is being considered for use in the manufacture of prosthetic heart valves.[4788]

This Section briefly reviews protein adsorption on alumina and sapphire (Section 15.3.5.1), the tissue response to sapphire dental implants (Section 15.3.5.2) and other alumina and sapphire implant surfaces and prostheses (Section 15.3.5.3), the cellular response to alumina and sapphire surfaces (Section 15.3.5.4), the biocompatibility of alumina and sapphire particles (Section 15.3.5.5), and finally the chemical stability of alumina and sapphire in vivo (Section 15.3.5.6). The reader is cautioned that some of the experimental and clinical results reported here for polycrystalline or other forms of alumina ceramic may differ from results to be obtained for the atomically-precise monocrystalline sapphire likely to be employed in medical nanorobots.

15.3.5.1 Protein Adsorption on Alumina and Sapphire

Alumina ceramic is a hydrophilic material with high wettability.[973] The rates of adsorption and desorption to the alumina surface of proteins[975,1059,4791,4798] including albumin, glycoprotein, plasminogen, fibrinogen, fibronectin, IgA, IgG, and IgM, and of other substances such as sulfapyridine[976] (a sulfa drug component), various pesticides[4802] and surfactants,[4807] and carbon monoxide[4808] have been investigated, though a comprehensive survey is beyond the scope of this text. For example, in one experiment the adsorption of blood proteins on α-alumina ceramic disks after 2 hours at 37 °C and pH 7.35 after removal of eluate was measured as 0.0147 mg/m^2 (130 molecules/micron^2) for albumin but only 0.00198 mg/m^2 (4 molecules/micron^2) for fibrinogen.[977] Another experiment found that attachment and spreading of human bone-derived cells cultured on Al_2O_3 ceramic surface during the first 90 minutes was reduced by 73-83% in vitronectin-free serum, with much less reduction in fibronectin-free serum, suggesting that initial attachment and spreading of cells to an alumina surface is a function of vitronectin adsorption.[978]

As with aqueous solubility,[980] protein adsorption to alumina is pH dependent. Thus at pH 7.6, for example, acetylated ovalbumin does not show any affinity for alumina surface while unmodified protein does.[981] Electrostatic interactions, surface unfolding of proteins, and surface hydrophobicity of protein also control the adsorption of ovalbumin onto alumina.[981] An extensive series of experiments by Sarkar and Chattoraj[982-987] have examined the competitive adsorption and desorption, relative affinities, and the molecular size, shape, orientation and folding of proteins (esp. bovine serum albumin, β-lactoglobulin, gelatin, hemoglobin, lysozyme and myosin) at the alumina-water interface as a function of pH, ionic strength of various salts, temperature, and protein concentration. For example, at physiological human blood serum albumin concentrations (35-52 x 10^{-3} gm/cm^3; Appendix B) and 27 °C, albumin (BSA) adsorption onto ~20-nm alumina powder surface is 36,400 molecules/micron^2 at pH 6.4, 14,300 molecules/micron^2 at pH 5.0, and zero at pH 3.6.[985] At the two higher pH values, adsorption reaches a plateau above an environmental albumin concentration of 0.6-1 x 10^{-3} gm/cm^3. (For ~50-nm graphite particles under similar conditions, albumin adsorption is 13,300 molecules/micron^2 at pH 6.4, 22,100 molecules/micron^2 at pH 5.0, and 41,800 molecules/micron^2 at pH 3.6, with adsorption plateaus at all pH values, for albumin concentrations between 0.3-1.5 gm/cm^3.[985])

Since anchorage and binding of protein to the alumina surface are enthalpy-controlled processes, whereas surface denaturation (including protein rearrangement and folding) is an entropy controlled process,[986] the initial adsorption processes can be characterized by the standard free energy of transfer as measured at the state of monolayer saturation. For one mole of protein or protein mixture, under various physiochemical conditions, the standard free energy of transfer is observed to be ~38.5 KJ/mole[985,987] or ~64 zJ/molecule. Let us provisionally take this figure as representative of the molecular binding energies required at a nanorobot sorboregulatory surface (Section 15.2.2.4) capable of providing desired specific proteophobic or proteophilic action upon exposure to physiological blood serum. Assuming noncovalent (van der Waals) adsorption forces only, then from Table 3.6 a sorboregulatory surface should incorporate physical binding features on the order of ~6 nm^2 in area or ~1.5 nm^3 in volume. A number density of ~10^4-10^5 receptors/$micron^2$ would imply an areal surface coverage ranging from 6-60%. Sorboregulatory surfaces must bind tightly enough to forestall desorption of the preferred protein as environmental conditions change. For instance, it is known that when β-lactoglobulin is added to the environment, previously adsorbed bovine serum albumin can be quantitatively desorbed from alumina surface back into solution.[983]

Other useful simple surface modifications have been demonstrated. For instance, Yoshida et al[899] have fabricated an ultrasmooth single-crystal α-Al_2O_3 sapphire plate which was shown via AFM scanning to have terraces with atomic steps only 0.2 nm in height, comparable to the exterior surface roughness anticipated in medical nanorobotic devices. This material, as obtained by high-temperature annealing, had relatively hydrophobic surfaces (e.g., water-drop contact angle θ ~ 80°) and thus could not be used for the AFM observation of plasmid DNA. When the material was treated with alkaline Na_3PO_4 aqueous solution, the surface became uniformly coated with a 0.3-nm-thick Na_2HPO_4 compound layer having a more hydrophilic character (e.g., water-drop contact angle θ ~ 20°), allowing DNA molecules to adhere and be scanned by AFM.[899] Other polarized organic molecules such as the mucopolysaccharides[1037] may attach to the polarized alumina surface (in the wet milieu)[1023] by van der Waals forces. Specific enzymes have also been covalently immobilized onto polyethyleneimine-impregnated gamma-alumina surfaces.[4772]

Interestingly, single-crystal sapphire that is exposed to 30 kilogray gamma-ray irradiation (as is common in gamma ray sterilization) produces oxygen vacancies in the sapphire structure accompanied by a deformation of the crystalline lattice resulting in a modification of electrical properties.[4773] At room temperature, irradiated α-Al_2O_3, unlike non-irradiated α-Al_2O_3, can trap electrons, from which it can be concluded that gamma-ray sterilization modifies the cohesive energy of α-Al_2O_3. This could lead to mechanical changes in surface charge, friction, wear, fracture strength, and the like.[4773]

15.3.5.2 Sapphire Dental Implants

Sapphire exhibits an elastic modulus 20 times greater than that of cortical bone,[956] though it is prone to fracture[1021,1029] if sufficient shear forces are imposed. Tooth implants are short, compact, and require mainly compressive strength. This is why many thousands of single-crystal alumina (sapphire) dental implants[989-996] have been performed over the last two decades in extensive animal[997-1006] and human[1010-1021] clinical trials. Commercially-produced alumina dental implant materials such as Bioceram,[990,995,1018,1019] BionitR[1025] and Frialit[1021,1050] are available for all tooth areas. Such materials also may serve as in-bone anchors for bridges and dentures.[956,4761] In modern dental practice, titanium bone anchors are preferred because pure sapphire is too brittle in the masticatory environment and tends to fracture after ~6 months of normal use [Thomas G. Wilson, personal communication, 2001], and because of poorer long-term results[4787] — most of these devices are made from titanium[5695,5696,5700,5705] and feature altered surface structures or coatings. However, zirconia frameworks[4758] or composites[4784] provide twice the mechanical strength of Ceram alumina,[4758] "allowing the restorations to bear the high mastication forces in the molar region." Tinschert et al[4813] suggest that current CAD-CAM dental fabrication procedures may induce surface and subsurface flaws that adversely affect the structural reliability of an otherwise more reliable[4818] material. Interestingly, the growth rates of cracks in single-crystal sapphire are significantly higher in C Ringer's solution at 37 °C (a simulated physiological environment) than in humid air at 24 °C, although no true cyclic fatigue effect has yet been found.[4788]

During the 1980s and 1990s it was found that sapphire exhibits good hard-tissue and soft-tissue biocompatibility when used in the mouth.[998,1021,1024-1031,1033] Peri-implant mucosa are nearly free from inflammatory cell infiltrations[1006] and when successful are usually free from connective tissue capsules between the implant and the adjacent alveolar bone.[1021] Generally there are no serious inflammatory reactions in the surrounding soft tissues — only a minimal inflammatory infiltrate is seen when the implant/abutment interface is located below the gum tissue.[1018,1021] One investigation of neutrophil number and activity around sapphire dental implants in 19 partially or completely edentulous patients found lower neutrophil activity around sapphire implants in completely toothless patients, but higher neutrophil activity on both teeth and implants in patients with remaining teeth.[1020]

Ultrastructural evidence reveals that an attachment complex forms between gingival epithelium and alumina that is analogous to that seen around natural teeth,[1003-1009] with a high rate of bone contact on the sapphire surface,[1003,1005] or osseointegration.[1021] In one case of an aluminum oxide ceramic implant removed because of fracture of the abutment after a 30-month loading period, it was observed microscopically that the implant was covered by highly mineralized mature compact lamellar bone, with no connective tissue or inflammatory cells present at the interface.[1029] Osteocytes were found very close to the bone-implant interface, indicating the good biocompatibility of the implant.[1029] In another study,[1030] soft tissues surrounding single crystal sapphire implants were studied by conventional light- and transmission electron microscopy and by immunohistochemical markers for cytokeratin, protein S-100, factor VIII and KP1. Histological sections of biopsies obtained from clinically healthy peri-implant mucosa were separated into a keratinized outer implant epithelium and an inner, non-keratinized epithelium, both immunoreactive towards cytokeratin. The inner implant epithelium terminated in a junctional epithelium, apically not a few cell layers thick. The cells adjacent to the implant showed a condensed cytoplasm that resembled hemidesmosomes[1004,1007,1030] — i.e., good biocompatibility.

No significant difference in subgingival microflora is observed between dental plaque that accumulates on natural teeth or on single-crystal sapphire dental implants in the mandibular and maxillary edentulous regions in monkeys[1002] and humans.[5691] Microbiota in healthy and diseased implant and natural tooth sites are very similar.[1027] Peri-implant tissues behave very similarly to periodontal tissues.[1027] Investigations of possible prophylactic treatments of sapphire-coated dental implants have been undertaken by SEM.[1042] One minor difference that has been observed between natural and implant dentition is that the tactile sensibility threshold

can be slightly higher for sapphire implants than for natural teeth, among sensory receptors located in the connective tissues around the implants.[1028]

15.3.5.3 Tissue Response to Bulk Alumina and Sapphire

Aside from dental implants, sapphire and alumina ceramics are most commonly employed in a variety of bone implants.[1050] Alumina ceramic surface has shown excellent in vivo tissue compatibility when implanted in the crania of rabbits for 2 months.[1043] In the human jaw, a single-crystal sapphire bone screw was applied for rigid internal fixation of sagittal split osteotomies in 86 cases from 1982-1986 and showed excellent biocompatibility.[1035] There was excellent bone adaptation to the threaded portion and no noticeable bone loss around the screws, which could mechanically support the split mandibular rami until bone union occurred.[1035] (Complications due to the screw were not encountered in follow-up periods of 0.5-3.5 years.) Experiments with alumina ceramic implants designed to reconstruct the bony bridge of the nose and the nasal septum of rabbits found that nasal septum implants were covered with connective tissue and coated with respiratory mucosa, and that implants in bony areas always showed a layer of connective tissue between the implant's surface and the rebuilt bone.[1046] All implants healed without inflammatory reactions and were solidly fixed to the surrounding tissue after 7.5 months.[1046]

Monocrystalline sapphire pins have been used in dozens of patients as an internal fixation device for hand and elbow problems.[1034] In follow-up studies, good bone healing was observed in all cases except for one delayed union in a fracture of the diaphysis of the proximal phalanx. Radiographs showed no pin migration or osteolytic reaction around the pins.[1034] There is some clinical experience using alumina ceramic pins for rib fractures.[1047] Sintered alumina implants inserted into the iliac crests (hip bones) and mandibles of rabbits were well tolerated, although the alumina excited a slightly greater tissue response than did vitreous carbon.[782]

Modular total hip prostheses have been successfully employed since the mid-1970s,[4806] and often consist of an alumina femoral head (ball) which articulates with an alumina acetabulum (cup).[956,1048,1049,4794] These show much improved wear characteristics (e.g., wear rates reported from an anomalously-low ~25 nm/year[1105] up to a more probable ~3 microns/year,[4762] with up to 38.8 microns/year for early systems implanted in the 1970s[4809]). Such systems produce lower frictional heating[4805] and fewer wear particles[4799] than alternatives such as metal-on-polyethylene[1050,1051,4797,4803] (e.g., ~100 microns/year[1105]), metal on alumina ceramic (e.g., 26.9 microns/year[4809]), or alumina ceramic-on-polyethylene[4803] (e.g., 34 microns/year[4795] to 80-200 microns/year[4810]) systems. By the year 2000, some 2.5 million ceramic femoral heads (mostly 28-mm-diameter BIOLOX heads with a European taper[1049]) had been implanted, mainly in Europe but also in North America and Japan.[1049] Results are generally good,[4790] although the orthopedic community has reported (1) a few in vivo mechanical failures of monophase alumina ceramic,[4756,4815] (2) a few cases of moderate[4775] or significant[4771] wear, and (3) mechanical pathological changes in the articular cartilage and menisci from paired alumina knee-joint implants inserted into canine femoral condyles.[4760] Innovations are constantly arising.[4776-4782] By 2002 a new generation of alumina-zirconia nanocomposites were being tested in total hip replacement applications because of their improved crack-growth resistance[4756,4783] and because zirconia ceramics are known to be highly biocompatible.[4757]

As for leg bones, single-crystal sapphire and several other materials implanted into the tibia of rats were subsequently encapsulated by newly formed compact bone,[1032] and bone tissue grew deeply into alumina pores.[4769] In another series of experiments,[970] three alumina implants — single-crystal alumina (SA), dense polycrystal alumina (DPA), and porous polycrystal alumina (PPA) — were inserted transcortically, extending into the medullary canal of rat tibiae. There was no difference in the degree of maturation of newly formed bone around the three kinds of alumina. SA (sapphire) and DPA were encapsulated with a continuous bone layer, but some bone tissue was attached focally around PPA. Multinucleated giant cells appeared on the surface of DPA and PPA, but not on SA. Quantitative evaluation of bone contact rate, bone contact thickness, and bone contact area ranked SA the highest and PPA the lowest, suggesting that sapphire is superior to the other two as an implant material.[970] In a human clinical study,[1052] the metatarsal (foot) bone was elongated by intercalary implantation of a single-crystal alumina ceramic in 7 patients with brachymetatarsy. The implants were encased with new bone 24 months after surgery and resulted in 5.2 mm to 9.2 mm elongation of the metatarsal bone. There was no resorption or pseudoarthrosis of the bones, and no loosening or breakage of the implants. Sapphire bone screws and anchors have been tested in animals and used clinically since at least the late 1970s.[1036]

Sapphire implants show good biocompatibility in soft tissues.[4768] Such implants can elicit some foreign body reaction (Section 15.4.3.5), but there is often minimal fibrosis in response to bulk alumina implants.[973,1053] For example, Akagawa et al[1032] implanted single-crystal sapphire and other materials such as titanium and Co-Cr-Mo alloy into the subcutaneous tissue of rats. The resulting tissue reaction, from early necrotic change and acute inflammation to final encapsulation by fibrous connective tissue, was least pronounced around the sapphire implants. Arvidson et al[1031] found slight or no tissue reaction when sapphire rods were inserted subcutaneously into rats for 4, 8, and 12 weeks. Reuling et al[1054] implanted dental alumina ceramics intramuscularly and subcutaneously in rabbits and guinea pigs. Cylindrical rough surfaces produced the strongest foreign body reactions. Spindle-shaped smooth surfaces elicited bland tissue reactions, including a significant increase in subcapsular adipose tissue and significantly less thickness of the connective tissue capsule.[1054] Small alumina chips (1.6 mm x 6.3 mm) implanted in rat paravertebral muscles produced a 77.5-micron-thick surrounding connective tissue membrane after 2 weeks, subsequently shrinking to 46 microns after 4 weeks, 36 microns after 8 weeks, and 24.4 microns after 26 weeks, with a shifting cell population including a nearly closed layer of macrophages towards the implant.[1053] Up to 1 year, a shifting layer of fatty tissue remained between membrane and muscle, functionally excluding the implant.[1053]

A recent series of experiments[1055-1057] at the University of Tokushima School of Medicine and University Hospital, in Japan, investigated the time course of tissue reactions to crystalline alumina implants in the form of Bioceram disks used for synthetic auditory ossicle. In the first of these experiments,[1055] the ceramic was implanted subcutaneously in the interscapular region of rats, then removed after 1, 3, 7 and 14 days. Decalcified 6-micron thick sections were stained with hematoxylin and eosin, and cell types around the implants were counted microscopically. An acute inflammatory reaction dominated by macrophages and neutrophils occurred after 1 day, almost disappearing after about 7 days. Fibrosis began at 3 days but foreign body giant cells were seen in only one specimen at 3 days. Chemical irritation to subcutaneous tissue was slight. However, the physical irritation of Bioceram lasted continuously and induced fibrosis around the bioimplant. The second

study,[1056] which extended the implant durations to 300 days, found that the inflammatory cell reaction decreased rapidly within 14 days, similar to the reaction in control groups. From 30 days to 300 days after implantation, there was continuous reduction of macrophages and lymphocytes to very low levels while the fibrous connective tissue capsule around the implants matured. The third study[1057] extended implantation time to 6-20 months and confirmed that small numbers of macrophages (~2.8% of max) and lymphocytes (~2.7% of max) were observed at 6 months, gradually decreasing to zero at 16, 18 and 20 months. Neither neutrophils nor foreign body giant cells were seen in any specimens. The thickness of fibrous capsules surrounding the implants was closely related to the shape of the implant, but there was no significant change from 6-20 months post-implantation and stereoscopic microscopy revealed no changes in Bioceram surfaces during this period. These results indicate that a sapphire-like ceramic is a satisfactory biocompatible material for reconstructive surgery from the viewpoint of inflammatory cellular and long-term tissue responses.

Alumina ceramic has also been used to provide short- and mid-term biocompatibility in blood-contacting LVAD surfaces.[613] For instance, high-purity alumina was used in the double pivot bearings of the Gyro C1E3 centrifugal blood pump developed as a completely sealless pump for long-term usage.[1058] The ceramic was determined to be a good biocompatible blood-contacting material after a standard in vitro and in vivo analysis including systemic toxicity, sensitization, cytotoxicity, mutagenicity, direct contact hemolysis, and thrombogenicity.[1058-1060] In another application, catheters using alumina-coated Teflon or alumina-coated pyrolytic carbon implanted intraperitoneally in dogs were retrieved after 12 weeks and only thin capsules were observed, of varying thickness and blood supply, surrounding the end of the catheters.[895]

15.3.5.4 Cell Response to Bulk Alumina and Sapphire

A number of experiments have been performed to determine the response of fibroblasts to alumina and sapphire surfaces. For example, alumina ceramic surface has shown excellent in vitro biocompatibility in a tissue culture of rabbit fibroblasts[1043] and cultured embryonic mouse fibroblasts.[1050] Colony-forming Chinese hamster V79 fibroblast cells proliferated equally well on alumina ceramic and control surfaces.[1044] Fibroblast-like mesenchymal cell populations cultured on solid alumina ceramic surfaces induced no cytotoxic or antiproliferative effects on monolayer populations in vitro, leading the researchers[972] to conclude that "the aluminum oxide ceramic presents itself as an absolutely bioinert material." A scanning electron microscopic study[1045] was conducted on the adhesion, spreading and formation of confluent cell monolayers from fibroblasts and epithelioid cells on Al_2O_3 ceramics. The study found that the cells adhered, spread, migrated and proliferated on the surfaces tested, leading to the conclusion that this implant material is compatible with cells.[1045] In general, such cells adhere well to single-crystal or polycrystalline alumina.[1023] Experiments by Mawn et al[4774] found that human orbital fibroblasts grown on alumina bioceramic implant were free of debris and had the largest cell count, whereas cells grown on hydroxyapatite or porous polyethylene implants had cellular debris associated with them.

The response of bone cells to alumina ceramic has also been examined. For instance, the nature of the contact sites (including focal contact formation and cytoskeletal organization) formed during the adhesion of neonatal rat calvarial (cranial) osteoblasts attaching to and spreading on alumina orthopedic implant materials was investigated by fluorescence microscopy.[1061] Focal contacts are regions where the plasma membrane approaches the substrate to within 10-15 nm and where bundles of cytoskeletal microfilaments terminate. Fluorescent-labeling of F-actin-containing microfilaments demonstrated a typical sequence of events as rounded, suspended osteoblasts spread onto the alumina substrates, initially showing the formation of streak-like vinculin-mediated focal patches.[1061] In another study, the morphological responses of individual osteoblasts as they attached and spread on alumina surfaces in vitro were examined with scanning electron microscopy.[1062] The cells were round after 30 minutes, then spread radially during the next 1.5 hours until they were almost flat with a nuclear bulge on both rough and polished alumina.[1062] More recently, Josset et al[1104] confirmed that normal biochemical and biological functions of cultured human osteoblasts are preserved in the presence of 6-mm-diameter 1.2-mm-thick alumina disks. Their results also suggested the absence of a mutagenic or carcinogenic effect on cells during the 30-day testing period, given that DNA image cytometry and interphase silver-NOR quantification showed no changes in cell ploidy, growth rates, or DNA replication compared to controls.[1104] Another recent experiment[4759] found no differences in cell viability between human osteoblasts cultured on polished surfaces of alumina or hydroxyapatite after 48 hours. However, osteoblast adhesion[4763] and osteoclast-like cell function[4764] are increased on nanophase alumina (grain sizes <100 nm) compared to conventional alumina. The responses of human osteoblasts cultured on an alumina surface and subjected to cyclic stretching has also been examined,[4767] and included unchanged alkaline phosphatase activity and increased synthesis of collagen and total protein.

Others have investigated the response of various oral cells to sapphire dental implant surfaces. In one study,[1031] the influence of single-crystal sapphire on the behavior of human epithelial cells and fibroblasts derived from biopsies of the oral mucosa was studied. Compared to control cultures, no effects on cell morphology and growth characteristics were observed. Another study[1063] sought to elucidate the ultrastructure of peri-implant junctional epithelium (IJE) on single-crystal sapphire dental implants connected to adjacent teeth by a metal superstructure, by examining the peri-implant gingivae of ten monkeys using a transmission electron microscope at 3, 6 and 12 months after implant insertion. At the time of examination, the ultrastructural features of the IJE were almost identical to those of the natural junctional epithelium attached to natural teeth. These features included developed Golgi complexes, rough-surfaced endoplasmic reticulum, numerous free ribosomes and mitochondria. The innermost cells of IJE were attached to the implant surface by means of 50-100-nm thick basal lamina-like structures and hemidesmosomes, but lacked a dental cuticle as seen on teeth. This epithelial attachment of the IJE was often indistinct or absent at the apical portion of the IJE which terminated at the level of alveolar crest. In yet another study,[1064] amorphous alumina was found to be slightly bioactive but more cytocompatible than titanium for human alveolar (tooth socket) bone osteoblasts and gingival fibroblasts. Cytocompatibility was assessed at the level of both the basic (attachment, proliferation, cell protein content) and the specific features (intracellular alkaline phosphatase activity, cytoskeleton) of the cells that were in direct contact with the coating.[1064]

Surface chemistry modifies cell response. For instance, a comparison of the response of costochondral (rib cartilage) chondrocytes at two stages of endochondral development demonstrated that the effects of various materials were surface- and cell-maturation-dependent. Cells cultured on titanium exhibited increased alkaline-phosphatase-specific activity, whereas those cultured on Al_2O_3 showed decreased enzyme activity.[1065] Another in vitro study[1066] investigated the effect of surface chemistry modification

of bioceramics on human bone-derived cells grown on biomaterial surfaces for 2 weeks. Cells were cultured on either pure alumina (Al_2O_3), alumina doped with magnesium ions ([Mg]-Al_2O_3), hydroxyapatite (HAP) or tissue culture polystyrene (TCPS). The researchers measured expression of alkaline phosphatase (ALP), thrombospondin (Tsp), osteopontin (OP), osteocalcin (OC), osteonectin (ON/SPARC), type I collagen (Col I), and bone sialoprotein (BSP). Protein levels for ALP, OP, OC, and BSP were significantly greater at day 5 in cells cultured on [Mg]-Al_2O_3 than in cells grown on pure Al_2O_3. By day 14, the levels of ALP, Tsp, Col I, OP, ON/SPARC, and BSP rose significantly above those occurring in cells grown on pure Al_2O_3, HAP, and TCPS. This suggests both that cells from the same patient respond to differences in surface chemical groups, and that substratum chemistry which facilitates cellular adhesion will enhance cellular differentiation[1066] — though there is evidence that Al_2O_3 cannot act as a co-carcinogenic carrier for polycyclic aromatic hydrocarbons (PAHs).[862]

As with other materials, the interaction of cells with alumina implant materials is usually protein-mediated. For example, the adherence of *Streptococcus mutans* OMZ-176 bacteria was the lowest on uncoated polycrystalline alumina and on single-crystal alumina (sapphire) precoated with human serum or saliva, of six common implant materials tested.[979] Surface free energy of uncoated material was strongly (negatively) correlated with *S. mutans* bacterial adherence.[979] However, the correlation disappeared when coated materials were tested.[979] This suggests that other binding mechanisms (e.g., protein-surface interactions) are commonly of greater importance to microbial adhesion to implant surfaces in vivo, although hydrophobic interactions may sometimes play an important role.[1108-1110] Another study[1142] found that differences in surface energy achieved by changing implant material composition of a ternary mixture of Al_2O_3, SiO_2, and TiO_2 could not be correlated to varying cell responses, although overall biocompatibility (in terms of cell proliferation and metabolic activity) was good.

What about blood cells? Alumina ceramic male pivots used in a totally implantable centrifugal artificial heart were evaluated for vitro platelet adhesion and activation, events which may play key roles in thrombogenesis on foreign surfaces.[1060] Platelet adhesion on alumina, assessed using monoclonal antibody (CD61) directed against glycoprotein IIIa, was found to be about the same as for pure titanium, silicon carbide, and ultrahigh molecular weight polyethylene, somewhat higher than for Ti-6A1-4V alloy, but much lower than for polycarbonate. Platelet activation on alumina was evaluated[1060] by measuring P-selectin (GMP-140) released from irreversibly activated platelets. GMP-140 levels for all tested materials were not significantly different from the control value of 45.9 nanogram/cm^3, and platelet activation by alumina was not observed under the static conditions in this work.[1060] Another study found only 0.5 platelets/mm^2 adhered to alumina surfaces that had been exposed to human whole blood, although significant fibrin was also adhered.[977]

Alumina-coated surfaces have also been found to significantly reduce adhesion of *Porphyromonas gingivalis* ATCC33277,[4814] an oral anaerobic bacterium important in periodontal disease and oral malodor.

15.3.5.5 Alumina and Sapphire Particles

The biocompatibility of alumina and sapphire particles has been investigated because it is important to understand the biological reaction to inhaled particles and to wear particles that might be produced by frictional forces in long-term prosthetic implants. Such studies generally involve micron-scale particles, roughly the size range of future medical nanorobots.

First, is alumina powder lethal? Massive administration of several bioactive <44-micron ceramic powders were lethal to Balb/c mice in 5 gm/kg doses when injected intraperitoneally, producing a swollen kidney having an ischemic color, with edema of interstitial tissue in the kidney cortex, severe degenerative changes in the tubular epithelial cells, and hyaline deposits in the renal collecting tubules, along with edema and inflammation in pulmonary tissues.[1067] Nonbioactive alumina powder similarly injected as a control (equivalent to 90 trillion 1-micron^3 nanorobots injected into the peritoneal cavity of a 70-kg human) was not lethal and elicited no significant changes in blood chemistry, though there was some loss of body weight.[1067] All powders had almost no systemic effects when injected intramuscularly or subcutaneously.[1067] IP-injected particle pathogenesis was believed to derive from phagocytosis by lymphocytes and macrophages, leading to release of lymphokines and free radicals that could damage kidney, lungs, and liver, with small amounts of bioactive ceramic powder being removed rapidly from the peritoneal cavity. Ceramics in fine powder form are generally believed to have higher bioactivity and to be associated with higher mortality. In this experiment,[1067] as ceramic particle size was increased the fatal effects in mice decreased. Consistent with their extremely low water solubility in the near-neutral pH range (Section 15.3.5.6), aluminas are minimally absorbed from the essentially aqueous intestinal contents, and for the same reason are blocked from absorption through the skin.[958]

Early studies[1050] of 0.5- to 5-micron alumina particles implanted subcutaneously and intraarticularly (knee joint) for up to 5 months in mice revealed no persistent inflammatory or progressive fibrotic reactions around the powder deposits. After an initial acute (3-7 day) granulocytic inflammatory phase, the material was gradually contained within macrophages and deposited locally without significant fibrous tissue reaction. Some particles were transported via lymphatic vessels into regional lymph nodes.[1050] Particles were found in the interstitium of the lung (Figure 8.15); in the reticuloendothelial cells of the liver, spleen, and bone marrow; and in one case in the meshwork of a renal glomerulum; but rarely in the bloodstream. Such crystal deposits caused no local cell necrosis, fibrosis, or granulomatous reaction in any of these organs.[1050]

Rat tissue responses to alumina powder administered at low doses were investigated by Di Silvestre et al,[1068] who found that powdered alumina implantation in the subcutis, the muscle and the peritoneum of the rat produced the same intense acute inflammatory reaction in all implantation sites after 2 weeks. However, after 8 weeks the inflammatory reaction had regressed and there was a thin layer of connective tissue around the implanted material, completely isolating it from the surrounding tissues.[1068] Examination of human biopsies from well-fixed human total hip prostheses showed that alumina particle deposits increase with time with only a low-grade macrophagic reaction. An inflammatory reaction appeared when joint loosening occurred, but this reaction was less striking than with loose metal-polyethylene prostheses.[1069] The amount of necrosis and fibrosis was lower for alumina implant wear debris than that associated with metal or polyethylene implants.[973] Intraperitoneal and intramuscular implantation of powdered alumina particles in rats showed an initial granulocytic reaction with some uptake by the reticuloendothelial system.[1053] Intra-articular injection of alumina wear particles into rat knees revealed a correlation between the numbers of particles and the macrophage response in the tissues. At 1 week the macrophage response to Co-Cr particles similarly injected was significantly greater than for the Al_2O_3 particles, possibly due to the necrosis of macrophages induced by Co-Cr particles.[1070] No antigenicity of alumina ceramic was found

in another study that attempted induction of footpad swelling in ceramic-immunized mice.[1048] Histopathological studies of alumina powder applied to dog tooth wounds have been reported.[1071]

Most cytocompatibility studies of alumina particles have examined the foreign-body reactions of macrophages.[1106] For example, it is known that rat alveolar macrophages readily ingest aluminum oxide particles.[862,1053] Toxicity tests of alumina powder in vitro using rabbit alveolar macrophages and in vivo using direct intratracheal injection into rat lungs found that the powder had low toxicity for macrophages and minimal recruitment of airway cells and neutrophils in the rat lungs,[845] although soluble aluminum salts employed as vaccine adjuvants may have been implicated in macrophagic myofasciitis.[1752]

Sapphire is generally biocompatible with macrophages. Pizzoferato et al[1077] found that saline-suspended 1- to 12.5-micron alumina particles were only slightly phagocytosed in vivo by mouse peritoneal macrophage cells lavaged 1 week post-injection. Harms and Mausle[1053] tested the biocompatibility of alumina ceramic in macrophage cultures and found no acute cytotoxicity. Christel[973] noted that an examination of human biopsies from failed total hip prostheses revealed a foreign-body reaction containing predominantly macrophages, loaded with alumina particles, that had no morphologic alteration and had not lost their chemotactic ability[973] — though one more recent study found that macrophages grown from monocytes in the presence of alumina were somewhat negatively affected.[1072] In another study by Rader et al,[1073] human monocytic THP1 cells were differentiated over a period of five days in the presence of vitamin D3 and GM-CSF in macrophage-like cells in the presence of various particles and concentrations. The secretion of tumor necrosis factor (TNF) — considered to be the initiator protein of particle disease leading to aseptic loosening of endoprostheses — was measured and was found to be elevated 4 times control for alumina ceramic particles, compared to 23 times the control level for polyethylene particles and 25 times control for cobalt particles. Nakashima et al[1103] reported that 1-, 100-, and 1000-micron alumina particles could induce the release of bone resorbing mediators (IL-6, TNF-α, IL1-α) by macrophages in a dose-dependent manner, but hydroxyapatite particles of equal size stimulated a greater release than the alumina. Nkamgueu et al[2596] found that alumina microparticles ingested by human blood monocytes that had been forced to differentiate into macrophages over a 7-day period decreased the macrophages' intracellular K/Na ratio (a measure of cell vitality), decreased their phagocytic ability by 27%, and reduced their oxidative metabolism by a factor of 5.

Catelas et al[1074] measured the effects of size (0.6- to 4.5-micron), concentration (5-1250 particles/macrophage), and composition (e.g., alumina) of ceramic particles on phagocytosis and cell mortality in the J774 mouse macrophage cell line. Kinetic studies (from 5 min to 24 hours) revealed that phagocytosis of the particles begins very early after cell exposure, increasing with time and particle concentration and reaching a plateau after ~15 hours. Phagocytosis increases with concentration for particles up to 2 microns. For larger particles up to 4.5 microns, phagocytosis reaches a plateau independent of particle size and concentration, suggesting a saturation effect most likely dependent on the total volume ingested.[1074] There was no significant difference in phagocytosis between Al_2O_3 and ZrO_2 at 0.6 microns, though alumina seemed to be more easily phagocytosed than high density polyethylene (HDP) at the same size (4.5 microns) and concentrations. Cytotoxicity studies revealed that macrophage mortality increases with particle size and concentration for sizes greater than 2 microns (to >30% cell mortality). Smaller particles (0.6 microns) cause cell mortality only at higher concentrations, and the mortality is still very low (~10%).[1074] There is no significant difference in cell mortality and inflammatory mediator TNF-α release between Al_2O_3 and ZrO_2. TNF-α release increases with particle concentrations and is significantly higher with HDP than with alumina.[1074] Related studies by Catelas et al[1075,4789] using the same cell model investigated the induction of apoptotic cell death (Section 10.4.1.1) in macrophages by alumina ceramic and other powders of different sizes and concentrations. Of some concern, Catelas found that the apoptotic effect of ceramic particles on nuclear morphology was size- and concentration-dependent, but that alumina ceramic particles induce apoptosis more effectively than polyethylene particles at concentrations of 125-250 particles/macrophage for ~2 hours.[4789] A more recent study by Nkamgueu et al[2400] found slightly decreased cell vitality and a 27% decrease in phagocytic ability in human macrophages that phagocytosed alumina particles.

The responses of a few other cell types to alumina ceramic powders have also been investigated. For example, cultured human fibroblasts exposed to 1-500 $\mu g/cm^3$ alumina powder showed no cytotoxic effects with cell viability at different exposure times measured by colony formation efficiency, neutral red uptake and colorimetric tetrazolium reduction.[1076] No cytotoxic or antiproliferative effects were induced in fibroblast-like mesenchymal cell monolayer populations cultured in vitro on powdery alumina ceramic.[972] Alumina powders generally induce no cytotoxicity in cell cultures[598] of human gingival fibroblasts or osteoblastlike cells.[1107] Nishio et al[4765] found that the δ-crystal phase of alumina powder promoted greater differentiation in osteoblasts than the α-crystal phase when present in a complex composite ceramic. Rodrigo et al[4766] found some change in osteoblast function from 10-micron α-alumina particles in human bone cell cultures, and that while both polyethylene and α-alumina increase the expression and secretion of IL-6 in human osteoblastic cells, the stimulation is weaker from α-alumina at the same particle dose.[4792] Oonishi et al[974] observed no inflammation or cell infiltration for 10- and 100-micron alumina particles implanted in holes drilled in the femoral condyles of rabbits. Dion et al[643] found that the hemolysis eventually initiated in vitro by alumina powder is almost zero.

As for inhalation toxicity, human experience with alumina powders strongly suggests that they are not associated with major specific pulmonary hazards under typical 20th century conditions of occupational inhalation exposure,[958,4816,4817] though rodent experiments suggest that clearance of alumina particles from the lung is slow.[4812] OSHA occupational exposure limits for alumina dust are 10 mg/m^3 (total fraction) and 5 mg/m^3 (respirable fraction), respectively, according to the official Material Safety Data Sheets.[958] (10 mg/m^3 of sapphire particles equates to ~3 billion/m^3 airborne cubic nanorobots, each 1 micron in diameter.) Alumina refinery workers exposed to >100 mg/m^3-year of gamma aluminas for >20 years had a 3- to 4-fold excess of individuals with an abnormal forced expiratory volume at 1 second, with abnormal being defined as <80% of the predicted figure, though smoking had a far more deleterious effect on ventilatory capacity.[962] α-alumina 100-700 nm particles have only minimal[963] or no[965] fibrogenic reactivity, and only at doses instilled intratracheally that are massive compared to the amount which could reasonably be inhaled in any one breath. Such massive doses of γ-alumina in the 20-40 nm size range did produce a fatal fibrosis of the lungs in rats.[964] Corundum dust has no significant effect on the in vitro enzyme activity of alveolar macrophages in the rat.[2496] Intratracheal instillation of 2 mg of alumina silicate refractory fiber in male Wistar rats produces no evidence of pulmonary fibrosis, unlike other fiber materials.[4800]

15.3.5.6 Chemical Stability of Alumina and Sapphire

It is generally accepted that alumina ceramics such as BionitR[1025] and single-crystal sapphire[1031,1035] have excellent biological inertness and chemical stability. Atomically ultrasmooth sapphire surfaces are stable in air and water for months.[899] Exposed to water, the polished single-crystal α-alumina (0001) surface elicits a hydration reaction, with a water vapor pressure of ~1 torr sufficient to fully hydroxylate the surface.[1751] Alumina is corrosion-resistant because it exists in the highest oxidation state that aluminum metal can possess. Thus this material has the potential for microstructural control of the interface (with tissue) without formation of toxic corrosion products.[956]

However, it is also known that α-alumina is very slightly soluble in highly acidic or alkaline aqueous environments (Section 9.3.5.3.6). This solubility has been measured experimentally using in vivo intratracheal and biopersistence studies of high-alumina rock wool fibers.[4811] While inert particles such as carbon can reside uneventfully in phagolysosomes for long periods of time, sapphire particles could release ions into the relatively acidic intra-organelle environment. Since aluminum ions are generally considered toxic,[1079-1083,5388] and since aluminum-containing bone cements have on rare occasion caused death from neurotoxicity,[4770] it is of interest to determine whether or not these ions can leach into the body from alumina implants or sapphire nanorobots. Early studies in the 1970s found no movement of known contaminants into the surrounding tissue from sintered alumina implants inserted into the iliac crests (hip bones) and mandibles of rabbits.[782] During the 1980s and 1990s, small increases in blood aluminum concentrations were demonstrated in smelter workers.[960] However, this potential exposure level is several orders of magnitude less than for bodily uptake of more soluble aluminum compounds used as food additives,[961] as antacid medication,[960] or from food packaging materials and cooking utensils.[966] In 1990, Lewandowska-Szumiel and Komender[988] investigated aluminum release from an alumina bioceramic during standardized biocompatibility testing in an animal experiment. Alumina implants introduced into rat femurs and guinea-pig mandibles and then removed 6-8 months later were found to be well tolerated, and no changes in the surfaces of the removed implants were observed under SEM examination. The researchers decided to compare the aluminum content of the femurs of experimental and control rats using atomic absorption spectroscopy, and discovered that the level of aluminum was higher in the bones of the experimental animals.

In 1991, Arvidson et al[1031] investigated the corrosion resistance of single-crystal sapphire implants with respect to the release of aluminum ions, and found no ions in the test solutions. The next year, Christel[973] reported that alumina exhibited greater bioinertness than all other implant materials currently available for joint replacement, and that no lymphocyte or plasma-cell infiltration into joint implants is observed "because of the absence of soluble component release."

Then in 1992, Wang et al at the Shanghai Institute of Traumatology and Orthopedics[1041] bored a hole, 6 mm in diameter and 2 mm deep, on each iliac crest of 30 rabbits, then implanted 2 pieces of alumina into the hole on one side, leaving the opposite side as a control. Calcium, phosphorus and aluminum contents of iliac bone on both sides were determined by Inductively Coupled Plasma-Atomic Emission Spectrometry at 10, 20, 40, 60 and 90 days after operation. The aluminum content of the implanted side was higher than that of the control and the difference was statistically significant in the 10-, 40- and 60-day groups, demonstrating that the implant released aluminum into the bone. Calcium and phosphorus also were significantly lower on the implanted side than on the control side in the 10- and 20-day groups. Wang concluded that aluminum released from the implant in the early stage might be interfering with the local calcium and phosphorus metabolism and delaying the mineralization of the bone.[1041]

Another study in 1994 by Toni et al at the Orthopaedic Clinic, University of Bologna, Italy[1022] examined the behavior of human bone tissue adjacent to the alumina coating in eight cementless hip prosthetic stems that appeared radiologically stable and were explanted because of pain. Histologic evaluation demonstrated the presence of a consistent layer of decalcified bone tissue in continuity with and parallel to the prosthetic interface, a demineralization phenomenon which the authors attributed to a high local concentration of aluminum ions with metabolic bone disease.[1022] This is histologically comparable to the osteomalacic osteodystrophy described in dialysis patients.[5363-5366]

Can medical nanorobots with primarily sapphire exteriors avoid solvation in the aqueous biological environment? A therapeutic population of 10^{12} nanorobots present in one human blood volume implies ~5400 micron^3 per nanorobot (~0.1% nanocrit for 1.75-micron wide cubic devices). Taking equilibrium solubility of alumina as 10^{-7} - 10^{-5} M at normal blood pH (Section 9.3.5.3.6), we should expect an equilibrium aluminum ion concentration of 100-10,000 ions/micron^3. However, the human bloodstream concentration of aluminum ranges from 1-88 x 10^{-8} gm/cm^3 (Appendix B), or roughly 200-20,000 ions/micron^3, fairly close to the 0.1% Nct equilibrium solvation concentration. There is also evidence that atomically-precise ultrasmooth sapphire surfaces[899] are somewhat hydrophobic (Section 15.3.5.1), which might help to reduce the solvation problem. A comprehensive investigation would inquire first whether there is a clinically significant amount of sapphire leaching, and if so, what are the precise limits of toxicity and the minimum thresholds for biological effects? Further research is needed to resolve these issues.

15.3.6 Biocompatibility of Other Nanomedical Materials

A great variety of additional materials and nanoparticulates[6084] might be employed in the fabrication of medical nanodevices and nanorobots for which biocompatibility must be assessed. Only a few of these many possibilities can be mentioned here, including DNA (Section 15.3.6.1), nitinol (Section 15.3.6.2), metals and semiconductors (Section 15.3.6.3), and dendrimers (Section 15.3.6.4). Neural cell biocompatibility is briefly addressed in Section 15.3.6.5, and Section 15.3.6.6 examines the possible biofouling of medical nanorobots by natural biomaterials found in the human body. A short discussion of the biocompatibility of free diamondoid nanoparts from nanorobots, or free organic nanoparts set loose from biorobots (e.g., cell parts such as free organelles, released into the human bloodstream), may be found in Section 15.4.4. Interestingly, in 2001 Rice University established a new Center for Biological and Environmental Nanotechnology[5229] to investigate the effects of novel nanomaterials on the environment[6258] and on biological systems;[5227] other efforts of this sort[6259] are strongly encouraged.

15.3.6.1 Biocompatibility of DNA

Seeman[2247,5666-5668] has pioneered the exploration of DNA as a nanoscale construction material* (Section 2.3.1), and a few others have employed DNA in related contexts,[6180-6182] raising the question of the biocompatibility of structural nucleotides that might be

** It has been proposed that the mechanical properties of DNA may have contributed to the ability of early cellular life (protocells) to withstand turgor pressure.[5979]*

used to build early-generation nanomedical devices. Other popular variants on DNA such as peptide nucleic acid molecules[5664] might also find utility in nanomedicine and genetic therapies,[5665] and metal-containing DNA[6019] or metallo-DNA could be used as nanocomputer wiring and thus might be found inside the body upon accidental fragmentation (Section 15.4.4, Chapter 17) of nanorobots using this type of circuitry.

DNA in its natural helical state (dry bulk DNA density ~ 1.65 gm/cm^3)[6249] is usually nonimmunogenic in normal animals.[1760] Ordinary DNA placed in human serum is degraded rapidly by natural nuclease enzymes (plasma nucleases); post-apoptotic nuclear DNA is depolymerized and opsonized by serum factors.[2248] IgG in human blood serum[2250] and in human milk[2251] can hydrolyze both DNA and RNA. Nucleases in human blood serum can degrade double-stranded DNA, RNA and synthetic polyribonucleotides,[2252] antisense oligonucleotides,[2253] and various oligodeoxynucleotides.[2254] Single-stranded (ss) oligonucleotides are more susceptible to hydrolysis than double-stranded (ds) oligonucleotides.[2254] High molecular weight ssDNA is rapidly cleaved to 20-30 kD fragments by endonucleases, with mononucleotide breakdown products appearing in circulation with no lag time.[2368] The short half-life of DNA can be exploited for use with certain therapeutics that require moment-to-moment control, especially aptamers that have been developed to alter blood coagulation[5801-5807] or other biologic processes.[5808-5810] Chemical modifications[2255-2257] can improve the resistance of oligonucleotides — especially antisense oligonucleotides[4698-4719] — to nuclease attack. These methods might prove useful in serum-proofing early DNA-based medical nanodevices.[5097] However, some of these changes cause the synthetic material to become toxic in vivo, so every form of chemically modified nucleic acid will have to be extensively evaluated in animal and human toxicity testing.

The physiological response to free DNA may be relevant to bloodborne DNA-based nanodevices. The normal concentration of free DNA in human serum is very low,[2369] typically 5-40 ng/ml.[2370] Free fetal DNA is found in maternal plasma[2371] at 0.2 ng/ml (range 0.03-0.6 ng/ml) in early pregnancy, 0.6 ng/ml in midterm pregnant women, 2 ng/ml (range 0.6-6 ng/ml) in late pregnancy, 3 ng/ml in preeclamptic women,[2370,2372] and then falling to near undetectable levels 2 hours postpartum.[2373] Circulating DNA is found in patients with (1) autoimmune thyroid disorders;[2374] (2) pulmonary embolism;[2375] (3) systemic arterial inflammation or vasculitis (20-50 ng/ml plasma dsDNA);[2376] and (4) neoplasms of various types such as benign gastrointestinal lesions (118 ng/ml)[2377] or malignant disease (412 ng/ml).[2377] It is also found in patients during hemodialysis (up to 5000 ng/ml plasma DNA),[2378] presumably due to release from leukocytes, and DNA plasma concentrations as high as 16,000 ng/ml (~ 50 billion $micron^3$, whole bloodstream) have been recorded (Appendix B). The mean half-life for circulating fetal DNA in maternal plasma is 16 min (range 4-30 min).[2373] Clearance of free dsDNA has a half-life of 18 min in nonhuman primates, or 11 min for immune-complexed (IC) dsDNA.[2379] Up to 85% of IC-dsDNA (typically IgG[2380]) binds to erythrocyte surfaces within 2 min of injection.[2379] The liver is the primary uptake site.[2369,2379] Organ uptake is more rapid for ssDNA than for dsDNA.[2368,2381] DNA larger than 15 bp does not measurably persist in the mouse bloodstream longer than 20 min for ssDNA, or 40 min for dsDNA.[2381] At high doses the clearance rate reaches a maximum, allowing larger amounts of ssDNA to remain in circulation.[2368]

Anti-DNA antibodies are found in normal human subjects[2258] and in the sera of patients with some autoimmune diseases such as systemic lupus erythematosis (SLE),[2259] catastrophic or even asymptomatic/remission antiphospholipid syndrome (APS),[5392] or thyroid disorders.[2374] SLE patients produce anti-DNA that targets conserved sites on both ssDNA and dsDNA from essentially all species,[2260] with anti-dsDNA antibodies possibly recognizing unique structures around the G+C regions or G+C clusters of DNA[2261] and binding preferentially to poly(dA-dC) and poly(dG-dT).[2267] In normal subjects without SLE, the serum only contains anti-DNA antibodies that selectively bind to DNA from certain bacteria,[2260] but native DNA mutated by UV light and hydrogen peroxide has been rendered immunogenic in experimental animals.[2262] Bacterial DNA is a potent mitogen and immunogen. Immunization of normal animals with bacterial DNA elicits antibodies that bind mammalian as well as bacterial ssDNA, and also induces cytokine production in the mouse[2260] and can produce other immunostimulatory effects depending on methylation.[5811-5813]

Solid-phase binding of DNA segments (as might occur in DNA-based medical nanomachines) dramatically reduces DNA antigenicity because constraints on topological and conformational rearrangements of DNA in the solid phase hinder antibody[2263] and nuclease (a potentially confounding issue) interactions. The length of these DNA segments appears unimportant, at least in undiseased humans.[2264] Antibodies can recognize B-DNA,[2269] A-DNA/RNA hybrids,[2269] and even the left-handed Z-DNA[2265-2269] found in some of Seeman's earlier experimental structures. (In 2002, the most promising structures appeared to be DNA-based PX-JX2 devices[5666] that used no Z-DNA [Nadrian C. Seeman, personal communication, 2002]; antibody recognition of these new structures had not yet been reported.) The usual risk of insertional mutagenesis from nucleic acid medicines[2270] should be greatly reduced in DNA-based nanodevices as long as these nanomachines remain intact. Biological activity (translational, enzymatic, etc.) of artificial DNA sequences comprising DNA-based devices or their fragments cannot be ruled out and should be investigated in every case; such activity is most likely to occur in devices having components specifically designed for biochemical interaction, or having sequences derived from natural templates (e.g., viral, bacterial, mammalian). (Infective naked viral DNA should not be considered "biocompatible.") DNA-coated charcoal granules and carbon fibers have shown good biocompatibility,[2271] and some synthetic oligonucleotides actually inhibit coagulation and reduced hemolytic complement activity in vitro,[2272,2273] an effect which appears to be nucleotide sequence-independent[2273] as mentioned above.

As with many cell types, keratinocytes[5576] can take up oligodeoxynucleotides and plasmid DNA, probably by receptor-mediated endocytosis, inducing the production of interleukin (IL)-1alpha, IL-1beta, integrin-beta(1), alpha-tubulin, and follistatin. Free deoxynucleoside in concentrations of 2-5 mM is well tolerated by living cells experimentally.[5577] As for free DNA released intracellularly, leukocytes contain nucleases that break down ingested DNA,[2249] and intracellular nucleic acids are starting to be studied for their possible diagnostic value.[5578] Intracellular nucleases are known for DNA[5579] and RNA[5580-5583] degradation, and especially for mRNA[5584-5589] degradation, wherein the degradation process is initiated by deadenylation[5601] and is tightly regulated.[5589-5592] Both single- and double-stranded circular plasmid DNA is degraded in ~1 hour by cytosolic nucleases.[4295,4305,4306] It should also be noted that apoptotic cells (Section 10.4.1.1) degrade their DNA before it is released, preventing inflammatory responses.

Double-stranded RNA (e.g., ~500 nucleotides in length[5972]) can induce the degradation of homologous mRNAs in organisms as diverse as protozoa, animals, plants and fungi, and especially mammals,[5972] resulting in post-transcriptional gene silencing (termed RNA interference or RNAi)[5973,6016] that takes place only in the cytoplasm.[5974] The dsRNAi is itself degraded in the cell.[5975] Apparently RNA interference reflects an elaborate cellular apparatus that eliminates abundant but defective mRNAs and defends against molecular parasites such as transposons and viruses.[5976] The recently discovered process of DNA-RNA interference[5977] suggests that cells are very sensitive to double-stranded DNA or RNA — which is apparently misinterpreted as a viral infection, causing cells to enter viral defense mode and/or turn off those genes that are producing dsDNA/RNA. Even mRNA-cDNA hybrid constructs can produce relatively long-term interference of specific gene expression.[5978] Nanorobots using nonhomologous DNA/RNA sequences in the cytosol-accessible portion of their structures should not elicit these cellular responses.

15.3.6.2 Biocompatibility of Shape Memory Materials

Another interesting material of possible nanomedical relevance is Nitinol (an equiatomic alloy of nickel and titanium) and other shape memory effect (SME) alloys[1408,1409] and polymers[5671] that are capable of temperature-driven reversible phase transformations. Some may allow thermal cycling between 30-50 °C[1419] at frequencies up to ~100 Hz[1419] and applied loads of ~3-6 x 10^8 N/m^2.[1408,1419] TiNi alloys can be deformed below a martensite finish temperature but recover their initial shape when heated above a temperature corresponding to the austenite temperature.[1409] Grain phases are often a few microns in size.[1409] Grain sizes smaller than 100-200 nm inhibit SME in experiments on bulk materials,[1410] and bulk-deposited TiNi films thinner than 100 nm apparently cannot readily transform to martensite.[1411,1412] However, ~40 nm reaction layers have been studied,[1413,1414] and TiNi transitions are known to occur between a cubic austenite phase with lattice size c = 0.3015 nm[1415] and a monoclinic martensite phase with lattice sizes c = 0.4622 nm[1415] or c = 0.4646 nm.[1416] So it is not inconceivable that nanomanufactured Nitinol crystal having molecular-size grain structures placed with atomic precision could demonstrate SME near the nanometer scale. TiNi has already found uses in microrobotics.[1417-1419] Thin-film actuated TiNi microvalves have been successfully operated for up to 2 million cycles[1420] at 1% strain[1421] although long-term SME stability remains a concern.[1408]

Nitinol has good biocompatibility[1422] and is as nontoxic as titanium.[1423] This good biocompatibility is believed to be due to the tendency of TiNi to develop a compact thin film of titanium dioxide upon exposure to air,[1422,1424] which largely[1425,1426,6165] prevents the cytotoxic Ni component from leaching out. One in vitro experiment[1424] tested TiNi particles ≤ 5 microns in diameter on BHK-21 cells cultured in 10% infant calf serum. Naked metal particles induced obvious morphological transformation clones whereas TiO_2-coated particles produced results not significantly different from negative controls. (Less than 1% internal oxygen impurity poisons the SME, however.[1427]) TiNi is found in many medical applications including orthodontic tasks,[1428] bone clamps,[1429] bronchial prostheses,[1430] and even eyeglass frames.[1431] The material has been investigated for intravascular therapy as a microgripper[1419] and as a means for controlled snakelike motion of small active catheters[1432] with expandable TiNi components that can be fed through the catheters to break up blood clots and prevent embolisms.[1431] Interestingly, one recently-discovered polymorph of titanium dioxide is the hardest known oxide,[4744] and the biocompatibility of TiO_2 particles has been investigated.[4745-4747]

Porous Nitinol shows no adverse effects and shows good bone attachment and tissue ingrowth when implanted in rabbit tibias and back muscle for 3-12 weeks. TiNi demonstrates good healing of bone tissue and bone remodeling with osteoclastic and osteoblastic activity in the bone cortex.[1433] Porous TiNi implanted in rabbit cranial bone made bone contact with cranial hard tissue. This contacted bone has the same properties as surrounding cranial bone, suggesting that Nitinol is suitable for craniofacial applications.[1434] TiNi has good in vitro biocompatibility with human osteoblasts and fibroblasts.[1426] The material induces no toxic effects, no decrease in cell proliferation, and no inhibition of growth of cells in contact with the metal surface. Nitinol does not induce inhibition of mitosis in cultured human fibroblasts.[1423] Fibroblasts seeded on porous TiNi sheets grow into the holes, showing good cytocompatible behavior.[1433] TiNi implanted perineurally or in muscle is nontoxic and nonirritating in rat soft tissues over 2-26 weeks,[1435] with low immune cell response and a modest inflammatory response similar to stainless steel and Ti-6Al-4V alloy.[1435] No necroses, granulomas, or signs of dystrophic soft tissue calcification were found. Only a few foreign-body giant cells were present with an encapsulating membrane about the same thickness as for stainless steel after 26 weeks.[1435] In vivo studies of Nitinol implanted for 3-17 months in beagles also showed no adverse tissue reactions from the implants.[1425]

15.3.6.3 Biocompatibility of Metals, Semiconductors, and Quantum Dots

Noble metals[2282-2286] such as gold, platinum,[5685-5687] and palladium are very biocompatible, silver[2360-2363] (including nanocrystalline silver[6207-6210]) is moderately biocompatible, and titanium is widely used in implants and surgical staples (Section 15.2.1.3). The biocompatibility of metals and metal leachates is particularly well-studied.[2022,6030-6033] Titanium shows excellent biocompatibility[280-282,1423,5695-5710,6053] and is apparently well tolerated after implantation for at least up to 13 years,[5823] as is, more specifically, titanium dioxide or titania[5700,6153-6164] — although a U.S. Army study found slightly higher toxicity with TiO_2 ultrafine smoke particles than with larger particles,[6183] and TiO_2 nanoparticles used in sunscreens apparently catalyze the photooxidation of organics with hydroxyl radical formation[6184-6186] with at least one group[6184] reporting (and still a matter of ongoing dispute[6186,6187]) sunlight-illuminated titania nanopowder catalyzing DNA damage both in vitro and in some human cells. Single-crystal silicon is not as biocompatible[569] (the body will grow a protein sheath around it to isolate it[2287,2288]), and phagocytosable hydrophilic silica crystal particles are highly membranolytic,[2330] cytotoxic,[652] and produce crystal-induced inflammation.[2323] But porous single-crystal silicon provides better mechanical anchorage for cells and thus is more biocompatible than nonporous silicon.[1769] Porous silicon can support the ingrowth of the natural mineral hydroxyapatite, the chief structural component of human bone, without producing an isolation sheath.[2288] Silicon nitride also appears to have good biocompatibility.[2518] Fluoride-ion surface-implanted titanium has antibacterial properties but does not inhibit the proliferation of fibroblast L929 cells.[4801]

Luminescent semiconductor quantum dots[5740] and other nanoparticles have been covalently coupled to biorecognition molecules and used in ultrasensitive biological detection[5246-5253,5639,5741-5745] or drug delivery.[5746] These nanometer-sized

conjugates are said to be water-soluble and biocompatible,[5253] and it is true that a few micron^3/cell of engineered nanoparticles are tolerated by living cells when employed as intracellular fluorescent reporters.[4238] However, these nanoparticles often contain arsenic- or cadmium-based compounds.[5248-5250] These are potentially highly toxic metals[5254] if solubilized or eluted from the nanoparticles into the cytosol or extracellular fluids. Other approaches, such as PEBBLE (Probes Encapsulated By Biologically Localized Embedding) sensors,[4258] are nanoscale spherical devices consisting of sensor molecules trapped in a chemically inert protective matrix which allows dyes to be used for intracellular sensing that would normally be cytotoxic; Halas group's "nanoshells" are also being investigated as sensors and for drug delivery.[5746,6066-6068] Thorough toxicological,[5747] environmental,[5748,5749] and biocompatibility[5638,5742,5750] studies of these materials have not yet been undertaken but would be well advised.

Ruoslahti and coworkers[5739] have developed hybrid organic/inorganic molecules consisting of nanocrystalline semiconductor particles (<10 nm ZnS-capped CdSe quantum dots) coated with peptide segments ("homing peptides" much smaller than antibodies) that target specific vascular addresses[5751-5756] inside the bloodstream and living tissues, for example, lymphatic vessels in tumors.[5739] The nanoparticles reportedly produce no blood clotting,[5757] and the addition of polyethylene glycol to the coating prevents nonselective accumulation in reticuloendothelial tissues.[5739] Notes Ruoslahti: "These results encourage the construction of more complex nanostructures with capabilities such as disease sensing and drug delivery." And fluorescent semiconductor nanocrystals individually encapsulated in phospholipid block-copolymer micelles were nontoxic (at <5 x10^9 nanocrystals per cell) when injected into *Xenopus* embryos by Dubertret et al.[6027]

Timp's group at the University of Illinois[6235] is experimenting with 7-micron silicon-based microchips inserted into living cells to verify cell viability, as a precursor to testing GHz-frequency rf microtransponders using nanotube antennas inside cells.

15.3.6.4 Biocompatibility of Dendrimers

Dendrimers[5098-5105,6015] are tree-shaped synthetic macromolecules with a regular highly-branched structure emanating outward from a core. Dendrimers are formed almost nanometer by nanometer, with the number of synthetic layers or "generations" dictating the exact size of the particles. Each molecule is typically a few nanometers wide but some have been constructed up to 30 nanometers wide, incorporating more than 100,000 atoms. The peripheral layer of the dendrimer molecule can be made to form a dense layer of molecular groups that serve as hooks for attaching other useful molecules, such as DNA, in the outermost branches.[5106] Dendrimers offer many exciting near-term opportunities in nanomedicine for the design of novel drug-carriers,[5107,5108] gene delivery systems,[5109-5127] imaging or contrast agents,[5128-5138] cell labeling agents,[5139] biosensors,[5140-5145] artificial catalytic sites,[5146-5149] catalytic antibodies,[5150] and DNA/protein microarrays.[5151-5154] Dendrimers also hold great promise in tissue targeting applications and controlled drug release,[5155] affording relatively easy passage across biological barriers by transcytosis[5156-5159] due to their controllable nanoscopic architecture and flexibility for tailored functionalization.[2397,5160-5162]

In 1998, James R. Baker Jr. co-founded the Center for Biologic Nanotechnology at the University of Michigan to bring together doctors, medical researchers, chemists and engineers to pursue the use of dendrimers as a safer and more effective medical therapy agent.[5163] For Baker, these nanostructures are attractive because they can sneak DNA and other materials into cells while avoiding triggering an immune response, unlike the viral vectors commonly employed today for transfection. The dendrimer molecule is decorated with specific snippets of DNA, then injected into biological tissue. Upon encountering a living cell, dendrimers of a certain size trigger endocytosis, in which a vesicle encloses the dendrimer and admits the particle into the cell's interior. Once inside, the DNA is released and migrates to the nucleus where it becomes part of the cell's genome. The technique was first tested on a variety of mammalian cell types,[5164] and in 2001 Baker began animal trials of dendrimer gene therapy. Baker and Donald Tomalia, another co-founder of the Center for Biologic Nanotechnology, report using glycodendrimer "nanodecoys" to trap and deactivate some influenza virus subtype strains.[5165] Here the glycodendrimers present a surface that mimics the sialic acid groups normally found in the mammalian cell membrane. This causes virus particles to adhere to the outer branches of the decoys instead of the natural cells.

The biocompatibility of dendrimers is determined by the nature and conformational mobility of their exterior. One of the earliest studies[2395] of dendrimer biocompatibility looked at Starburst dendrimers. These are spherical macromolecules composed of repeating polyamidoamino (PAMAM[5166]) units that can be produced in successive generations, each with a defined size, molecular weight, and number of terminal amino groups. Roberts et al[2395] investigated Generation 3 (G3; MW = 5,147; 24 terminal amines), Generation 5 (G5; MW = 21,563; 96 amines), and Generation 7 (G7; MW = 87,227; 384 amines) PAMAMs in V79 cells or in Swiss-Webster mice for a number of biological properties, including in-vitro toxicity, in-vivo toxicity, immunogenicity, and biodistribution. Potential biological complications were observed only with G7, and there was no evidence of immunogenicity. Dendrimer G3 showed the highest accumulation in kidney tissue, whereas G5 and G7 preferentially localized in the pancreas. G7 showed extremely high urinary excretion.

A more comprehensive study of dendrimer biocompatibility by Malik et al[2397] looked at polyamidoamine (PAMAM, Starburst), poly(propyleneimine) with either diaminobutane or diaminoethane as core, and poly(ethylene oxide) (PEO) grafted carbosilane (CSi-PEO) dendrimers to study systematically the effect of dendrimer generation and surface functionality on biological properties in vitro. Dendrimers with -NH_2 termini displayed concentration- and (in PAMAM) generation-dependent hemolysis. Changes in red cell morphology were observed after 1 hour even at low concentrations (10 μg/ml). At concentrations below 1 mg/ml CSi-PEO dendrimers and dendrimers with carboxylate (COONa) terminal groups were neither hemolytic nor cytotoxic towards a panel of cell lines in vitro, but cationic dendrimers were cytotoxic with IC50 values of 50-300 μg/ml depending on dendrimer type, cell type, and generation.[2397] Polyether dendrimers with carboxylate and malonate surfaces were not hemolytic at 1 hour, but were lytic after 24 h, unlike anionic PAMAM dendrimers.[2397] Cationic ^{125}I-labelled PAMAM G3 and G4 dendrimers administered intravenously to Wistar rats at ~10 μg/ml were cleared rapidly from the circulation, with <2% recovered dose in blood at 1 hour. Anionic PAMAM dendrimers (G2.5, G3.5 and G5.5) showed longer circulation times, with 20-40% recovered dose in blood at 1 hour and generation-dependent clearance rates (lower generations circulated longer).[2397] PAMAM dendrimers injected intraperitoneally appeared in the bloodstream within 1 hour and their subsequent biodistribution mirrored that seen following intravenous injection.[2397] Malik et al[2397] concluded that inherent toxicity probably ruled out using higher generation cationic dendrimers for parenteral

administration, especially if they needed to be used at a high dose, and that dendrimer structure would have to be carefully tailored to avoid rapid hepatic uptake if targeting elsewhere (e.g., tumor targeting) was a primary objective.[2397] Other related studies have examined dendrimer interactions with human arterial endothelial cells,[5167] muscle cells,[5168] proteins,[5169] and nuclear pores;[5170] complement activation by DNA-dendrimer complexes;[5171] microvascular extravasation profiles of dendrimers;[5172] whole-body biodistribution of dendrimer-based agents;[5173] modification of cell adhesion to surfaces;[5174] the synthesis of dendrimer-fullerene films;[5175] and the morphology of DNA-dendrimer complexes as a function of ionic strength.[5176] Thus, toxicity relates mostly to charge and surface functionality.

In applications, dendrimeric macromolecules have been investigated as delivery vehicles for antisense[2396,5177-5180] or therapeutic[5181-5184] oligonucleotides, antiangiogenic agents,[5185] antiapoptosis agents,[5186] selectin antagonists,[5187] plasmid-based gene delivery vectors,[5188] photodynamic therapy[5189] and radioimmunotherapy[5190-5193] agents, adjuvants,[5194] vaccines,[5195] bacterial toxin inhibitors,[5196] various anti-cancer drugs[2398,5107,5160,5197-5202] including 5-fluorouracil,[5203] and even as potentially useful objects for DNA-based bottom-up nanoassembly.[5097] Dendrimeric peptides selective for microbial surfaces have been developed which have broad antimicrobial activity while achieving low hemolytic activity to human erythrocytes,[5204] and other antimicrobial,[2399,5205] antiviral,[5206-5210] and antiprion[5211] dendrimeric agents have been investigated. E. Pinkhassik suggests that solid particles coated with the same residues as the dendrimers might exhibit identical solubility and biocompatibility.

15.3.6.5 Biocompatibility with Neural Cells

Central nervous system (CNS) neurons, unlike those of the peripheral nervous system, do not spontaneously regenerate following injury, and it has been shown that in the developing CNS a combination of cell-adhesive and cell-repulsive cues guide growing axons to their targets.[1528,4961] Neural cells respond to patterned surfaces[4962,4963] (Section 15.2.2.3). For example, glass surfaces functionalized with spatially-precise patterns of cell-adhesive (peptide) regions and cell-repulsive (PEG) regions can control the direction of neuron cell adhesion and neurite outgrowth across the surface.[1528] Schwann cells have been cultured on and preferentially attach to micropatterned laminin-coated stripes separated by BSA, with cell orientation driven by the laminin-BSA interface.[4964] Lines of polylysine-conjugated laminin as narrow as 2.6 microns induce linear axonal guidance outgrowth and adherence of hippocampal neurons.[4965] Polyphosphoester polymers have high biocompatibility as nerve guide conduits.[4966] Self-assembling peptide scaffolds can serve as biologically compatible substrates for neurite outgrowth and synapse formation.[4967] Varying the mechanical,[4968] electrical[4969,4970] and chemical[4971] characteristics of the contact surface also influences the neurite outgrowth rate in neuronal contact guidance, and can even allow control of neuron shape.[5735]

Adhesion and patterning of cortical neurons has been investigated[4972] on isolated islands of neuron-adhesive polyethylenimine (PEI) surrounded by a neuron-repellent fluorocarbon layer. The patterns consisted of PEI-coated wells (diameter 150 microns, depth 0.5 micron) etched in a fluorocarbon coating atop polyimide-coated glass. The separation distance between the PEI-coated wells was varied between 10-90 microns, resulting in highly compliant patterns of adhering cortical neurons after one day in vitro and interconnecting neurite fascicles between PEI-coated wells present on patterns with a separation distance of 10 microns after 8 days in vitro.[4972]

Immunoisolation of dopamine-secreting PC12 cells by microencapsulation in semi-permeable 75:25 2-hydroxyethyl methacrylate/methyl methacrylate (HEMA/MMA) copolymer membranes has been evaluated as a promising strategy for dopamine replacement for Parkinson's disease.[4973] There was good biocompatibility between the HEMA/MMA copolymer and the host brain, as evidenced by the absence of gross tissue damage at the neuronal tissue/capsule interface and only a moderate inflammatory response by reactive astrocytes confined to the immediate vicinity of the injection tract,[4973] despite other work suggesting that pure MMA can be neurotoxic to human cortical neurons.[4974] In another experiment,[4975] neuronal and glial cells (Schwann cells and astrocytes) were immobilized within N-(2-hydroxypropyl) methacrylamide (HPMA) polymer hydrogels to produce cell-based polymer hybrid devices, with some cells exhibiting spreading or process outgrowth and secretion of laminin which offers a possible model for tissue replacement in the central nervous system using these cell-based polymer constructs. Similar constructs involving polycarbonate tubes filled with lens capsule-derived extracellular matrix coated with cultured neonatal Schwann cells are being studied for their ability to promote the regrowth of retinal ganglion cell (RGC) and other axons across surgically induced tissue defects in the CNS.[4976] Genetically engineered cells have been combined with biocompatible polymers to elicit axon regrowth across tissue defects in injured rat CNS,[4977] and the direct transplantation of neural tissue into the mammalian brain has been studied for a century.[4978]

Although early electrodes implanted in brain or peripheral nerve often left corrosion- or abrasion-related deposits,[4979] good long-term biocompatibility of various electrode materials has been demonstrated (1) at nerves;[4980,4981] (2) in cochlear implants at scala tympani electrode arrays[4982,4983] and potential CNS auditory prostheses;[4989] (3) in retinal chip implants,[4984] semiconductor-based microphotodiode arrays designed to be placed under the neural retina in the subretinal space,[4985-4987] and visual cortex microelectrode arrays;[4991] (4) in other neural implants intended for mobilization of paraplegics, phrenic pacing, or cardiac assist;[4970] and (5) for a variety of microwires[4988] and electrode materials including silicon,[4989-4991] platinum,[4989,4992] iridium,[4989,4993] polyesterimide-insulated gold wires,[4994] peptide-coated glassy carbon pins,[4995] carbon nanotubes,[4820] and polymer-based electrodes.[4996] Silicon nitride[4992,5041] and silicon dioxide[5041] are dielectrics used as an electrode passivation layer. Certain metals cannot be used in the brain without provoking necrosis and phagocytosis. For instance, copper induces active phagocytosis and silver yields inactive phagocytes after implantation for 37 days in rat brain.[4997] On the other hand, stainless steel and Nichrome (with varnish insulators such as Epoxylite or polyimide) can be implanted without producing any detectable damage beyond that of the initial trauma and brief phagocytosis limited to the edge of the electrode track.[4997] Larger electrodes create more tissue reaction at least up to 37 days.[4997] Other aspects of electrocompatibility are discussed in Section 15.5.6.1.

Many materials show good biocompatibility when implanted in the brain or CNS, including various gels,[4998,4999] biopolymers[5000-5003] and polymer capsules,[5004] hollow dialysis fibers,[5005] and other biomaterials.[5006,5007] The overall neurobiocompatibility of diamond (Section 15.3.1.4) and diamond-like carbon,[629] carbon nanotubes (Section 15.3.2.1) and functionalized fullerenes (e.g., Section 15.3.2.3(4)), carbon fiber,[4962] Nitinol (Section 15.3.6.2), and metal coatings such as tantalum, tungsten, platinum, gold, iridium, palladium, and brass (further altered to promote or inhibit cell growth and spreading by an additional overcoat of biological

materials including ECM proteins, laminin, fibronectin, and collagen IV)[629] have also been examined. In one experiment,[5008] titanium microscrews and monofilament stainless steel wire were implanted into the parietal region of rabbits and produced no behavioral changes or neurological deficits suggestive of either systemic or localized toxicity from the implant materials. However, at 2 weeks the titanium had caused the largest inflammatory response in surrounding brain parenchyma based on analysis of markers for microglial proliferation, gliosis, and leukocyte infiltration. After 26 weeks the greatest leukocyte response was found with stainless steel implants, as compared to silicone elastomer which produced the least inflammation. Silicone elastomer has well-established brain biocompatibility and is commonly used as a neurosurgical implant material.[5008]

The neurobiocompatibility of bulk Teflon (Section 15.3.4.2(9)), Teflon implants (Section 15.3.4.3) and Teflon particles (Section 15.3.4.4) has already been briefly discussed. In general, Teflon is relatively inert with poor cell attachment when used as an implant in the central nervous system.[1158] For example, Proplast (a fluorocarbon polymer) shows no reaction with dura and brain,[5009] although this material was withdrawn from the market for other reasons (Section 15.3.4.3). As another example, a 12-micron thick Teflon film prevents adhesions between an implanted electrode array and the dura, in cat brains.[5031]

Special risks of particles in the brain should also be investigated further. For example, diffuse iron particles were found in the cortex of a patient who showed increasing frequency of seizures 12 years after a blunt head injury, which the researchers believed might have contributed to progressing traumatic epilepsy;[5922] though strictly neurochemical alterations might be responsible for epileptogenesis or seizures.[5923] If seizures can be induced by particles of certain types in the cortex, this could have relevance for medical nanorobots navigating or residing in these spaces.

Motile nanorobots performing missions in brain tissue can be injected directly into nonvascular regions of brain tissue, thus entirely avoiding the blood-brain barrier (BBB) which serves as a formidable obstacle for traditional drug molecules, particularly peptides. According to one excellent brief summary,[6085] the BBB is found in all vertebrate brains and is formed around the endothelial cells of the brain capillaries (~640 km of vessels of total surface area ~9.3 m^2). The endothelial cells comprising the tubular capillaries in brain are cemented together by intercellular tight junctions which eliminate a paracellular pathway of solute movement through the BBB, and the virtual absence of pinocytosis across brain capillary endothelium[6086] eliminates transcellular bulk flow of circulating solute through the BBB. "Under these conditions, solute may gain access to brain interstitium via only one of two pathways: lipid mediation or catalyzed transport. Lipid-mediated transport is restricted to small molecules (with a molecular weight less than a threshold of approximately 700 Da) and is generally, but not always, proportional to the lipid solubility of the molecule. Catalyzed transport includes carrier-mediated or receptor-mediated processes. The BBB is actually composed of two membranes in series: the lumenal and the ablumenal membranes of the brain capillary endothelial cell, which are separated by approximately 300 nm of endothelial cytoplasm."[6085]

While there are direct routes for nanorobots into brain tissue that avoid the BBB (e.g., injection into the neuropil,[6089,6090] injection into cerebrospinal fluid,[6091] histonatation (Section 9.4.4), etc.), some mission scenarios might require bloodborne medical nanorobots to cross the blood-brain barrier. It has long been known that passive particles of colloidal size can receive special coatings that engage various naturally occurring endocytic and transcytic transport mechanisms[6092] while causing no large-scale openings in the tight junctions of the brain endothelium.[6093] For example, polysorbate 80- or 85-coated biodegradable polybutylcyanoacrylate (PBCA) nanoparticles trigger phagocytic uptake by brain blood vessel endothelial cells[6094] which allows particle-bound small molecules that normally do not cross the BBB to be transported across it. Overcoating with polysorbates apparently leads to the adsorption of apolipoproteins from blood plasma onto the nanoparticle surface,[6095,6096] whereupon the coated particles mimic low density lipoprotein (LDL) particles and can interact with the LDL receptor, leading to their uptake by the endothelial cells.[6097] Small cargo molecules that have been transported in this manner experimentally through the endothelium and thence into the neuropil include the Leu-enkephalin (analgesic) hexapeptide dalargin,[6098-6100] the Met-enkephalin kyotorphin,[6101] the antitumor antibiotic doxorubicin,[6102] the NMDA receptor antagonist MRZ 2/576,[6103] loperamide[6104] and tubocurarine.[6105] The lipophilic antitumor drug camptothecin,[6106] the drug 3',5'-dioctanoyl-5-fluoro-2'-deoxyuridine (DO-FUdR),[6107] tobramycin[6108] and idarubicin[6109] have been transported into the brain using ~200-nm solid lipid nanoparticles, and similarly the antitrypanosomal drug diminazenediaceturate has crossed the BBB using 364-442 nm lipid-drug conjugates.[6110] Some BBB penetration has even been shown by long-circulating pegylated nanoparticles.[6111]

However, nanorobots will most likely need to enter the neuropil themselves — not merely broadcast small-molecule effluents into it through the BBB from an extraendothelial location, or release cargo molecules from an intraendothelial waystation. In a cell culture model of the BBB using a co-culture of bovine brain capillary endothelial cells and rat astrocytes, lipid-coated ionically-charged nanoparticles 60-nm in diameter have been induced to cross the BBB by transcytosis without any degradation.[6112] More significantly, the BBB can be temporarily and reversibly opened to allow small-particle passage by osmotic disruption[6087-6089] via intracarotid infusion of hypertonic saccharide solution,[6113] e.g., mannitol or arabinose, which results in transient shrinkage of cerebrovascular endothelial cells with subsequent increased permeability of the tight junctions.[6114,6115] This allows the passage of magnetite-dextran nanoparticles[6116-6118] (e.g., MION nanoparticle unimodal hydrodynamic diameter ~40 nm[6122]), replication-defective adenovirus[6118-6120] (70-90 nm diameter[6123]) particles, and herpes simplex virus (HSV)[6118,6120,6121] (150-200 nm diameter[6123]) particles through the BBB endothelium and into the neuropil. The BBB can also be reversibly opened for some small molecules using the vasoactive peptide bradykinin analog Cereport (RMP-7, receptor mediated permeabilizer-7),[6124] though apparently bradykinin itself is not as effective.[6125]

The BBB is also disrupted during diseases such as experimental allergic encephalomyelitis,[6126,6127] HIV encephalitis,[6128] and multiple sclerosis in which >1000-nm-size T cells and macrophages invade neural tissue through BBB tight junctions, and during experimental bacterial meningitis which produces focal pial venular leaks of in situ perfused 0.01% colloidal carbon black.[6129] Nanorobots could similarly locally manipulate the signaling pathways involved in BBB tight junction regulation,[6130] possibly commanding junctional gaps to open or close at need — e.g., ICAM-1-mediated signaling in brain endothelial cells is known to be a crucial regulatory step in the process of lymphocyte recruitment and migration through the BBB.[6131]

Fenart et al[6112] notes that the customary drawback to methods that involve an increase in BBB permeability is that there is poor specificity, with circulating blood compounds such as albumin

gaining indiscriminant and pathological access to the brain. However, in the case of medical nanorobots these methods could be applied on a highly localized basis, followed by rapid convoy formation entry (Section 15.5.2.3). A similar solution involves the protein transduction domains (PTDs) — naturally-occurring protein sequences that allow rapid crossing of cell membranes of all mammalian cell types without compromising membrane structure or function.[6132] PTDs have been demonstrated as suitable for in vivo delivery of "peptides, small proteins, full-length enzymes, DNA oligomers, peptide-nucleic acid oligomers, liposomes, and magnetic nanoparticles" across the blood brain barrier,[6132] and these "keys to the city" could in principle also be applied locally.

Additionally, the BBB is not a structurally perfect barrier. Gaps and imperfections of various sizes are naturally present. Nanorobots seeking entry to the neuropil from the bloodstream can search out and exploit these randomly-placed natural junctional gaps. BBB ultrastructure has been lightly studied[6133] and 0.5-micron perijunctional gaps have been observed,[6134] but the author can find in the literature no precise estimate of the number density or distribution of micron-size gaps throughout the entire BBB network of the human brain. In one rat experiment[6135] it was found that in control animals 0.4%-0.6% of circulating albumin appeared in the subendothelial space and in the basement membrane of control animals prior to osmotic disruption (rising to 56% 30 minutes after osmotic disruption), so many gaps of some size clearly exist; another study[6136] reports 0.5%-2.4% BBB penetration by various peptide molecules prior to BBB disruption. Certain brain regions (e.g., selected circumventricular organs including the pineal gland, neurohypophysis, and choroid plexus) are known to have particularly leaky BBB capillaries.[6136] The area postrema deserves mention as another possible site of circumventricular entry, as it is also the chemoreceptor trigger zone and is often the site that triggers nausea and vomiting in response to detection of toxic substances in the bloodstream. Hypertension can produce measurably leaky venules[6137] and other leaks in the BBB.[6138] And while glycated albumin-gold colloid complexes injected into the common carotid artery do not significantly permeate the BBB, nevertheless "a few" gold particles are observed in the perivascular neuropil after 15 minutes.[6139]

If a population of N_{bot} nanorobots of (assumed cubical) volume V_{bot} transit in convoy (Section 15.5.2.3) at velocity v_{bot} through randomly-placed $>V_{bot}^{2/3}$-area holes in the BBB (i.e., large enough to admit one nanorobot at a time) of collective hole area A_{total} with the objective of infusing the entire nanorobot population into the neuropil in $t_{infusion}$ seconds, then $v_{bot} = N_{bot} V_{bot} / A_{total} t_{infusion}$. Taking $N_{bot} = 10^9$ nanorobots, $V_{bot} = 1\ \mu m^3$, and $t_{infusion} = 100$ sec, then even assuming a very conservative transit speed of $v_{bot} = 100\ \mu m/sec$, the total area of all ~micron-size holes need only be $A_{total} = 10^{-7}\ m^2$ or just ~0.000001% of the total BBB surface area. If the actual total area of micron-size holes A_{total} is less than $10^5\ \mu m^2$, the transit velocity v_{bot} or the infusion time $t_{infusion}$ may be increased as required.

Even in the complete absence of large BBB junctional gaps as posited above, properly mission-designed active motile nanorobots could employ a combination of cytopenetration (Section 9.4.5), in cyto locomotion (Section 9.4.6) and histonatation (Section 9.4.4) through the BBB to achieve ready access to the neuropil.

Other aspects of nanorobotic neurobiocompatibility discussed elsewhere in this Volume include the hypothalamic induction of hypo- or hyperthermia analogously to Shapiro Syndrome (Section 15.2.7), the fate of microparticles placed in the brain (Section 15.4.3.3.1), neuronal chemorepellents (Section 15.4.3.6.1), neuronal exocytosis (Section 15.4.3.6.6), mechanical strain (Section 15.5.4.1) and membrane wounding (Sections 15.5.7.2.1 and 15.5.7.2.2) in neural cells, nanorobot-induced neural cytoskeleton disorganization (Section 15.5.7.3.1), motor neuron diseases (Section 15.5.7.3.2), intracellular shock wave damage to neurons (Section 15.5.7.4), the possibility of mechanically-induced neuron apoptosis (Section 15.5.7.6), and storage diseases in neurons (Section 15.6.3.2).

15.3.6.6 Biofouling of Medical Nanorobots

Another biocompatibility issue in nanorobotic medicine is biofouling[4749-4755] — the possible incapacitation of nanorobotic systems which may become jammed with biological macromolecules, structures, microorganisms, or debris. The biocompatibility of medical nanorobots made of diamond has already been reviewed (Section 15.3.1), but such nanorobots likely will not present smooth unbroken surfaces to the in vivo environment. Rather, nanorobot surfaces will frequently be interrupted by various transtegumental structures such as sorting rotor binding sites (Section 3.4.2), chemical sensors (Section 4.2), pressure sensors (Section 4.5), energy transducers (Section 6.3), communications transducers (Section 7.2), manipulatory appendages (Section 9.3), and so forth. The biocompatibility of each of these structures (or their fragments; Section 15.4.4) must be separately assessed, and assessed in various plausible combinations. A comprehensive evaluation is beyond the scope of this introductory text.

The biocompatibility of exposed chemical binding sites found on binding pads, sensors, or sorting rotors used for molecular transport, and ligand presentation surface moieties (Section 15.2.2.4) may be the easiest to analyze. Small-molecule receptors probably will avoid antibody recognition due to steric constraints. Macrophages and other phagocytic cells should not be able to recognize rapidly spinning synthetic sorting rotor binding sites, which are deeply embedded in an otherwise passive diamondoid structure. Nor should these cells be able to recognize display ligands (Section 5.3.6), which are presented and then retracted a short time later. Artificial monoclonal antibodies are easily raised against natural biological receptor sites,[1715] but natural antibodies to such receptors normally have been removed by clonal deletion and thus should not be available to participate in an interaction with medical nanorobot receptors whose structure is homologous to the natural receptors. Natural antagonists to receptors for highly regulated cytokines[2156-2160] and similar biomolecules may exist in the body, and might therefore also be available to interact with artificial nanorobot binding sites. However, such interactions may be minimized (1) by careful design of sorting rotor competitive binding site specificities, (2) by employing recessed active structures and self-cleaning grilles, and (3) by executing preprogrammed prophylactic nanorobot behaviors such as periodic counterrotational backflushing of all binding sites. Designers also must avoid creating binding sites which might inadvertently trigger cytotoxic reactions. For instance, silicic acid and silica particles are hemolytic, inducing permeability changes in biological membrane systems.[652] The biocompatibility of enzymes immobilized on surfaces in experimental therapies has also been studied.[6030]

Possible biofouling or clogging of nanosieve pores (Section 3.3.1), nanoscale pipes (Section 9.2.5), spinning molecular sorting rotors (Section 15.5.7.1), protruding telescoping manipulators (Section 15.5.7.7), nonadhesive (Section 15.2.2.1) and adhesioregulatory (Section 15.2.2.4) nanorobot surfaces, and implant surfaces with bacterial overgrowths or biofilms (Section 15.2.1.4) have already been discussed, at least briefly, elsewhere in this book series.

Biofouling by microorganisms is of particular interest because early nanodevices may be involved in bulk production processes for pharmaceutical agents such as antibiotics and drugs, for food products such as cheese, and for many other industrial materials, long before the introduction of suspensions of sophisticated nanorobots into the human body is permitted. It has long been known[5790] that bacteria adhere to Teflon in continuous culture of the sort commonly employed in biotechnology production methods,[5791] and may form biofilms on Teflon[1225-1227,1358-1361] (Section 15.3.4.2(12)). Bacteria may also grow well on graphite surfaces (Section 15.3.3.3), though rigorous studies of biofilms on diamond have not been published in the literature.

Finally, nanoscale pores, pipes, rotors, manipulators, and active surfaces are subject to possible damage by free radicals or other highly reactive moieties that may be present in the natural biological environment in which nanorobots must operate for extended periods of time. While graphene sheets are largely impervious to carbon radicals (Section 5.3.2.4), intact diamond surfaces are susceptible to chemical attack by atomic oxygen (Section 9.3.5.3.6 (I)) and non-intact diamond (Section 9.3.5.3.6 (I)) and sapphire (Section 9.3.5.3.6 (I)) surfaces are even more susceptible. J. Soreff (Section 9.3.5.3.6 (IV)) has suggested that microbes could be designed that are capable of applying excited oxidants such as singlet oxygen to breach a diamond surface. No in vivo studies have yet been reported, though H-passivated diamond cannot resist free radical attack by photodissociated products of fluoroalkyl iodides[6236] and at least one other instance of diamond/free-radical activity is known.[6237] As a useful benchmark, Drexler[10] notes that "proteins in living systems provide a model for molecular machines in a relatively complex, chemically aggressive environment. Metabolic enzymes can have lifetimes of several days,[6238] despite the relative fragility of protein structures." The lifetime of a single unprotected diamondoid sorting rotor of greater chemical stability may be even longer, perhaps on the order of ~10^6 sec.

Several methods may be used to extend this operational lifetime. For example, medical nanorobot designs commonly include tenfold redundancy in sorting rotors,[2762,3573] manipulator arms,[2762] and other mechanisms[4609] exposed to natural biological fluids. Since rotors can be safely banked until needed, the simple expedient of sequentially engaging spares when active units are damaged may extend mission lifetime by up to a factor of ten, given tenfold redundancy of the affected mechanisms; thousandfold or higher redundancies may be practical for the most critical fluid-exposed medical nanorobot components. Another alternative, suggested by Drexler[10] in a different context, involves the use of sacrificial getters positioned anterior in the fluid flow to susceptible components: "Damage resulting from trace quantities of highly reactive contaminants can be minimized by flowing feedstock solutions past surfaces bearing bound moieties resembling those used on critical rotor surfaces, but selected for higher reactivity. Sacrificial moieties of this sort can combine with and neutralize many reactive species, including free radicals." Such getters could be positioned along the walls of access channels leading to enclosed sorting rotors, with getter moieties mounted on detachable tool tips in the manner of presentation semaphores (Section 5.3.6) and either recycled, refurbished or replaced from internal inventory as needed. A related biocompatibility concern is whether diamondoid surfaces, once attacked or covalently bonded by active moieties, become more visible to the immune, complement, inflammatory, or thrombogenic systems of the human body. These subjects deserve further research.

15.3.7 Biocompatibility of Nanorobot Effluents and Leachates

The biocompatibility of both purposeful and accidental effluents that might be released by medical nanorobots must also be examined. By and large, such effluents should have relatively low molecular weight (although chemical byproducts of energy generation or proteins broken down by nanomotors might be larger). For example, glucose engine (Section 6.3.4.4) effluents such as CO_2 and H_2O present few problems, and most low-molecular-weight chemicals (including many 20th century drugs and antibiotics) must be coupled with other substances such as proteins or conjugates before they can be recognized by the immune system.[2274] Such chemicals are called haptens.[1760] (Of course, entirely aside from their immunoreactivity, these low-molecular-weight chemicals could be directly toxic, especially if not efficiently cleared by the liver, and it has been proposed that small molecules originating from microbes might underlie nonspecific pyoinflammatory diseases.[5820])

There is a distinction often made between antigens and immunogens that may be useful to emphasize here.[1760] An antigen is an agent that can bind specifically to components of the immune response, whereas an immunogen is an agent that can induce an immune response. Thus all immunogens are antigens, but not all antigens are immunogens. In general, compounds with molecular weight less than 1000-2000 daltons (e.g., penicillin, progesterone, aspirin, carbon dioxide, or kerosene[2275]) are not immunogenic.[1760,2332] Compounds with molecular weight between 2000-6000 daltons may or may not be immunogenic, but compounds over 6000 daltons generally are immunogenic.[1760]

A compound also needs a certain minimum chemical complexity to be immunogenic. For instance, amino acid homopolymers (e.g., a 30,000 dalton pure lysine polymer) are rarely good immunogens, and a 50,000 dalton homopolymer of poly-γ-D-glutamic acid (the capsular material of *Bacillus anthracis*[2336]) is not immunogenic at all. Large copolymers of several different amino acids tend to be highly immunogenic,[1760] albeit due to T cell processing and not size per se (a substance cannot be an antigen if there is no T cell epitope). Lipids and nucleic acids are poor immunogens[1760,2332] (though antibodies have been raised to them), but become immunogenic when conjugated to protein carriers.[1760,2332] Many carbohydrates and virtually all proteins are immunogenic.[1760,2332] Most polysaccharides, fibrilar proteins (e.g., silk fibroin), and single-stranded nucleic acid polymers have sequence-specific antigenic determinants or "epitopes." On the other hand, native double-stranded nucleic acids and most globular proteins have conformation-dependent epitopes[2332] — antibodies can recognize primary, secondary, tertiary or even quarternary protein structures.[1760] A molecule that is "foreign" will also be immunogenic. For example, the release into the bloodstream of animal-derived synthetic proteins that have not been properly humanized[2276-2278,5593] might induce a strong immune response. Most protein toxins are strongly immunogenic,[1760] while small chemical toxins are not.

Besides size and complexity, one final requirement for immunogenicity of possible nanorobot effluent molecules is degradability. In order for most antigens to stimulate T-cell-mediated immune responses, interactions must occur between antigen-presenting cells (APC) and helper T cells.[1760] (Most effective B cell responses are dependent on T cell help, but B cells per se do not need degradation to recognize and respond to antigens.) APCs must enzymatically degrade a protein antigen into fragments

that can be bound to MHC proteins and then be presented at the APC surface to T cell receptors, activating the response. Thus proteins composed entirely of D-amino acids, which are resistant to enzymatic degradation, have low immunogenicity,[2337,2338] whereas peptides composed of L-isomers can be broken down and have normal immunogenicity — though counterexamples exist.[2339] (Bacteria employ D-isomer amino acids in their coats[2340] for this very reason.) Carbohydrates are not processed or presented and thus are unable to activate T cells, although they can sometimes directly activate B cells.[1760] Biological sugars are typically monoisomeric, so polysaccharide molecules comprised of isomerically unusual sugar monomers that are unrecognizable to natural enzymatic degradation processes[2341] (e.g., L-glucose or D-tagatose[2342]) might be relatively nonimmunogenic and cytotolerant,[2343] though as yet there appear to be no experimental tests of this possibility. As noted earlier, pure diamond is expected to be nonimmunogenic, but fullerene and sapphire surfaces might be immunogenic in some circumstances (Section 15.2.3.3) and other structures such as exposed sorting rotor binding pockets or detached protein-based presentation semaphores might also be immunogenic — more research is needed to reach definitive answers. (Even if nanoparticulate forms of these substances are nonimmunogenic, there is a small possibility that they could act as inert irritants capable of activating nonspecific inflammatory responses (Section 15.2.4); the biocompatibility of larger nanorobot fragments is briefly discussed in Section 15.4.4.)

Nanorobot effluents might also collect as gas bubbles or solute crystals adhering to the nanodevice exterior, which material could then be recognized by the immune or inflammatory systems. This difficulty should largely be preventable by good design. In one experiment by Ward et al,[2590] eliminating trapped air microbubbles from materials having low surface tension significantly reduced complement activation by these materials, in rabbits. A related issue is that most surfaces exposed to ambient air acquire an adsorbed layer of hydrocarbons and other small molecules that is at least a few angstroms thick, and larger particles may also be present in the form of adherent dust or other debris.[2279] The inflammatory potential of these adherent materials should also be investigated.

In physiological environments, leaching of undesired moieties from intact nanorobots or chemically pure nanorobotic materials is unlikely with the possible exception of aluminum ions from sapphire (Section 15.3.5.6). There are no reports of such leaching even from comparatively impure contemporary diamond-like carbon (DLC) or CVD diamond surfaces (Section 15.3.1.3), although some elution of biomolecules (e.g., heparin) from organic coatings on diamond, graphene (e.g., fullerene), or fluorocarbon surfaces might be expected in some circumstances.[5782,5783] Antibody-targeted chelated-radioisotope therapeutic agents can be chemically unstable under physiological conditions and can allow some radioisotope atoms to leach out into unintended tissues, but radioatoms trapped endohedrally inside fullerenes such as C_{60} (Section 15.3.2.2) cannot leach out and thus are inherently safer. No leaching has been observed even from dye-impregnated ceramic coatings on glassy-carbon electrodes,[5784] though silicon additives often found in pyrolytic carbon (Section 15.3.3.2) might possibly increase susceptibility to leaching of some components of those additives and ion leaching from graphite has been reported in specialized industrial applications.[5785] Traditional fluorocarbon applications in medicine often relate not to implantation but to inertness and purity — e.g., Teflon tubing[5786] delivers biosolutions without altering them significantly by leaching organics or by chemically reacting with the solutions, Teflon surfaces support cell cultures without emitting toxic leachates,[1190,1357,5782] Teflon coatings prevent toxic leaching from underlying materials,[5787] and Teflon is often used as a negative control in cytotoxicity studies of leachates.[5788] Teflon composites containing non-fluorocarbon components can produce (often nontoxic[5789]) leachates.

15.3.8 Nanorobotic Thermocompatibility

The issue of nanorobotic thermocompatibility arises in at least two contexts: First, the active production of waste heat (or localized cooling) by individual nanorobots, nanoorgans, or other nanorobotic systems implanted within the human body; and, second, the physiological effects of nanomedical implants that may result from the passive thermophysical characteristics of those implants, or from the materials with which they are constructed.

Previous discussions of thermally active systems include nanorobot waste heat conduction (Section 4.6.6), the local and global in vivo thermogenic limits of nanorobotic systems (Section 6.5.2), thermographic navigation (Section 8.4.1), and the thermal safety of in vivo electrical (Section 6.4.3.1) and mechanical (Section 6.4.3.4) systems. For instance, excessive nanorobotic waste heat generation (e.g., creating localized temperatures >42 °C) can stimulate thermosensitive channels in keratinocytes and in a specialized group of heat-sensing sensory neurons terminating in the skin.[5669]

Previous discussions of passive conductivity include the thermophysical characteristics (Table 8.12 and Appendix A) and the thermal conductivity (Section 10.5.4) of biological and other materials. Individual nanorobots also can alter the thermophysical properties of biological tissues or fluids, although typical therapeutic terabot doses[2762,3573] should not produce clinically significant effects. Maxwell's theoretical model[5629] predicts that the effective thermal conductivity K_{eff} of liquids containing suspended micron-size (and larger) spherical particles increases with the volume fraction f_{nano} of the suspended particles as: $K_{eff}/K_{liq} = 1 + \{3\ f_{nano} / ([(K_{nano} + 2K_{liq})/(K_{nano} - K_{liq})] — f_{nano})\}$, where K_{liq} is the thermal conductivity of the pure liquid, K_{nano} is the thermal conductivity of pure particles (e.g., nanorobots), assuming the particles do not interact thermally (e.g., $f_{nano} << 1$).[5630] The interaction between spheres even at large volume fraction, as calculated by Rayleigh, produces only a small correction, which is why Maxwell's simpler derivation is usually employed.[5630] For "perfectly conducting" (i.e., infinite K_{nano}) spherical particles, Maxwell's model further simplifies to $K_{eff}/K_{liq} = 1 + \{3\ f_{nano} / (1 — f_{nano})\}$; Lu and Kim[5631] found that perfectly conducting prolate spheroids with a/b = 10 (length/width) give theoretical and experimental values at least 10% lower than the K_{eff}/K_{liq} for spheres.

Thus for example, in the case of a ~1 cm^3 dose of spherical diamond nanorobots (~10^{12} devices at ~1 $micron^3$ each) infused into the 5400 cm^3 adult human male blood volume (f_{nano} = 1/5400), taking K_{nano} = 2000 W/m-K for diamond and K_{liq} = 0.549 W/m-K (whole blood; Table 8.12), then K_{eff}/K_{liq} = 1.00056, which is clinically insignificant. Blood heat capacity similarly is virtually unchanged. The conclusions are much the same for soft tissue emplacements of similar nanorobot populations. In augmentation scenarios[3573,4609] (Chapter 30) involving heavy loadings of the human body with diamondoid particles, the results are not much different. At 37 °C and a maximum 10% nanocrit (Section 15.6.2), blood heat capacity falls only 5%, from 3.82 MJ/m^3-K to 3.62 MJ/m^3-K for pure diamond particles, while blood thermal conductivity rises only 33%, from 0.549 W/m-K to 0.732 W/m-K for pure diamond particles —

somewhat less than the conductivity of live brain tissue (Table 8.12), hence is probably not clinically significant.* Similarly, thermal equilibration time is only modestly increased even in the case of ~1000-terabot augmentation loads of free-floating in sanguo nanorobots.

Nevertheless, changes in whole-body thermal conductivity due to massive implantation of continuous diamondoid materials can impact natural thermoregulatory mechanisms. Aside from blackbody radiation, sweating, capillary sphincter control, and behavioral thermoregulation (including respiratory cooling), the body regulates its temperature and offloads excess heat principally via two mechanisms, as follows.

First, there is passive conduction. Heat travels by pure conduction through fat and muscle from the body core out to the periphery. The thermal conductivity of human tissue is $K_t \sim 0.5$ W/m-K, so for a typical L = 10 cm path length (~half-torso thickness), heat flow $H_f \sim K_t / L = 5$ W/m^2-K, or ~10 W/K for a 2 m^2 human body. In a cold room, the mean temperature differential between core and periphery $\Delta T \sim 11$ K (Section 8.4.1.1), so $H_f \sim 100$ watts, which is approximately the basal metabolic rate. Experiments confirm that 5-9 W/m^2-K is the minimum heat flow in very cold conditions (the actual value depending largely upon the thickness of subcutaneous fat layers).[2093] In this case, the peripheral capillary blood flow has slowed to a trickle, producing the minimum thermal conductivity of the human body in cold conditions. On the other hand, in a warm room or during heavy exercise, $\Delta T \sim 1$ K, so $H_f \sim 10$ watts. Thus, paradoxically, at warmer temperatures when the human body is generating considerable surplus heat, the body's passive heat flow is actually very low because of the smaller temperature differential between core and periphery.

Second, heat is transported via the active blood flow. In warm rooms, not only are the peripheral capillary sphincters fully dilated, allowing more blood to flow through the peripheral capillaries relative to the core capillaries, but also the total volume of blood flow may increase. (During heavy exercise, total blood flow volume may rise by a factor of 4 or 5.) Diathermy experiments suggest that the active blood flow mechanism alone may carry off 100-200 watts of heat before core temperature starts to rise (Section 6.5.2). In cold rooms and in the absence of heavy exercise, peripheral capillary sphincters are maximally contracted, thus minimizing blood flow (and hence heat transport) to the periphery.

To summarize: The passive conduction mechanism can throw off ~100 watts of waste heat when the human body is in a cold room but only ~10 watts when the body is in a warm room, while the active conduction mechanism can throw off negligible heat in a cold room but up to 100-200 watts in a warm room. Thus as the external environment warms up, the human body shifts from passive conduction to active conduction via increased blood flow and capillary sphincter widening.

The presence of even a maximum 10% Nct of diamondoid nanorobots in the circulation will not significantly alter the heat capacity of the blood, hence the active conduction mechanism in human thermoregulation should be largely unaffected. However, in augmentation situations where vascular fluid flow is completely replaced by nonfluidic transport systems (and including capillary sphincter inhibition) as in the vasculoid[4609] (a whole-body diamond-plated artificial vasculature; Chapter 30), the active conduction mechanism in thermoregulation is essentially disabled.

This leaves the passive conduction system. Heat flow in a natural biological-tissue body is $H_{f,biol} = K_t / L = 5$ watts/m^2-K. For a human body shape composed entirely of pure diamond ($K_t \sim 2000$ watts/m-K at 310 K[5632]) and again taking L = 10 cm, then $H_{f,diam} = 20{,}000$ watts/m^2-K. For a diamond-envasculoided human body, taking a mass of ~1.7 kg of diamond thoroughly interwoven with 68.3 kg of mostly aqueous biological tissue mass (for a standard 70 kg male body), as a worst-case estimate** the effective heat flow becomes $H_{f,vasc} \sim (1.7 / 70)\ H_{f,diam} \sim 500$ watts/m^2-K, or ($H_{f,vasc} / H_{f,biol}$) ~ 100 times more thermally conductive than before. For comparison, a pure metal human form would have $H_{f,metal} \sim 170$ watts/m^2-K for stainless steel, ~350 watts/m^2-K for lead, ~780 watts/m^2-K for iron, or ~3800 watts/m^2-K for copper. Hence a diamond-envasculoided or augmentation-loaded human body, in the worst case,** could have passive conduction properties similar to those of solid metal.

This has implications for the maximum ΔT that can be maintained between core and periphery. Consider a human-shaped tissue-mass with half-thickness L ~ 10 cm and surface area A ~ 2 m^2, sufficiently heated from the inside to cause P ~ 100 watts (human basal rate) to flow via passive conduction from core to periphery, establishing a temperature differential $\Delta T \sim P\ L / A\ K_t \sim 10$ K for natural human tissue with $K_t = 0.5$ watts/m-K. Upon switching to diamondoid-envasculoided tissue, mean tissue thermal conductivity would rise to $K_t \sim 50$ watts/m-K and so ΔT would fall to ~0.1 K. In effect, the entire human body would become isothermal to within 100 millikelvins; even at the peak power output of 1600 watts for the human body (Table 6.8), ΔT rises to just ~1.6 K. Thus a diamond-envasculoided human body would tend to become isothermal with its surroundings very quickly (although partially resisted by intervening subcutaneous fat), a possible hazard to normal human health especially in very hot or very cold environments. The thermal equilibration time is approximately $t_{EQ} \sim L / v_{thermal} \sim 0.1$ millisec, where $v_{thermal} \sim K_t / h_{plate}\ C_V = 1000$ m/sec for neighboring vasculoid plates in good thermal contact with each other and having thickness $h_{plate} \sim 1$ micron, with $K_t = 2000$ watts/m-K and $C_V = 1.8 \times 10^6$ joules/m^3-K for diamond at 310 K, and taking L = 10 cm as before. This is far shorter than the typical 1-10 sec thermal response time of the purely-biological human vasculature.

** Most studies of the thermal conductivity of suspensions have been confined to those containing millimeter- or micron-sized (i.e., nanorobot-sized) particles, but nanometer-sized particles have a still larger surface area-to-volume ratio and thus might be expected to exhibit higher thermal conductivity because heat transfer takes place at the surface of the particle.[6003] Accordingly, experiments on "nanofluids" by Choi and Eastman[6000-6004] revealed that even a small volume fraction $f_{nano} = 0.003$ (0.3%) of 10-nm metallic copper particles suspended in ethylene glycol produced a 40% increase in thermal conductivity of the composite fluid (i.e., $K_{eff}/K_{liq} = 1.4$) — roughly an order of magnitude larger increase in conductivity than the classical Maxwell theory predicts. Alumina-particle nanofluids have also been investigated experimentally.[6005]*

*** This calculation pessimistically assumes that the continuous diamond implant is proportionally represented in conductive channels oriented normal to the body surface. B. Wowk notes that one can also consider the opposite extreme in which the diamond implant is wholly oriented as parallel rods running through tissue parallel to the body surface. The thermal conductivity enhancement between body and external environment would then be much smaller, for the same reason that highly conductive particles that occupy a small volume fraction in solids or liquids don't significantly enhance conductivity (see above). The reality of an artificial diamondoid vasculature would lie somewhere between these two extremes. A proper quantitative thermophysical assessment of the vasculoid[4609] would require an analysis of the effect of fractal tortuosity on thermal conductivity calculations. Wowk notes that evacuated aerogels demonstrate phenomenally low conductivities (0.005-0.01 W/m-K)[6006] for their glass content and their study might provide some rough quantitative guidance on the effect of fractal tortuosity on thermal conductivity, but a more accurate result will require thermal modeling on numerically-generated random vascular trees. Mathematical models of thermal tortuosity have been explored in other contexts,[6008,6009] and fractal tortuosity has found its way into the reaction chemistry,[6007] fluidized-bed engineering[6008-6013] and hydrogeology[6014] literatures, but fractal thermal tortuosity apparently has not yet been extensively studied.*

The substitution of sapphire for diamond in these augmentation applications should significantly improve thermal performance. The thermal conductivity of synthetic sapphire may be as low as K_t ~ 2.3 watts/m-K for sapphire at 310 K,[5633] roughly a thousandfold lower than for diamond, when measured in the direction normal to the symmetry or optic axis (c-axis); heat capacity (C_V = 2.9 x 10^6 J/m^3-K) and density (3970 kg/m^3) of sapphire are slightly higher than for diamond. Thus for a sapphire-envasculoided human body, taking a mass of ~1.9 kg of sapphire (at 25 watts/m^2-K for L = 10 cm) thoroughly interwoven with 68.1 kg of mostly aqueous biological tissue mass (at 5 watts/m^2-K), the total heat flow is just $H_{f,sapph}$ ~ 5.5 watts/m^2-K, which differs insignificantly from natural biological tissue.[5635] At P = 100 watts, ΔT falls to 2 K compared to 10 K for natural tissue and 0.1 K for diamond-envasculoided tissue; t_{EQ} ~ 1 sec for sapphire vs. 10^{-4} sec for diamond.

Two complications regarding sapphire require additional research. First, the thermal conductivity of sapphire can vary significantly with both composition and crystallographic orientation, a fact which may impose additional and unknown constraints on the various designs. For instance, one source reports heat flow values interpolated to 310 K of 21 watts/m-K normal to the c-axis and 23 watts/m-K parallel to the c-axis;[5632] minor extrapolations of other sources to 310 K (i.e. slightly outside the exact temperature ranges measured experimentally) imply values of 2.0[5634] and 2.3[5633] watts/m-K for heat flows normal to the c-axis. However, all reported values for sapphire are at least two orders of magnitude more insulating than diamond.

Second, much like diamond, the thermal conductivity of sapphire varies with temperature. For example, at ~200 K (near dry ice temperature) sapphire's thermal conductivity rises to 5 watts/m-K. At liquid nitrogen temperature (77 K), K_t soars to ~1000 watts/m-K; the peak is ~6000 watts/m-K at 35 K.[5632-5634] (Diamond's conductivity also rises as it cools.[5632-5634]) At the other temperature extreme, sapphire's thermal conductivity rises to 3.9 watts/m-K by 523 K. Diamond thermal conductivity also varies significantly with isotopic composition (e.g., ^{12}C vs. ^{13}C);[5636,5637] in 2002, it was unknown whether similar opportunities might exist for the engineering of desired levels or patterns of thermal conductivity in isotopically-controlled sapphire-based nanorobotic devices.

CHAPTER 15.4

Systemic Nanorobot Distribution and Phagocytosis

Traditional biocompatibility focuses on the implant-host interface. But a human patient is an interconnected structure with various mechanisms permitting physical exchange among all of its tissues and organs. Of particular interest in nanomedicine is the movement of solid bodies and particulate matter through the various systems of the body. Intact motile nanorobots that can travel purposively inside the human body (Chapter 8 and 9) and can avoid geometrical trapping, phagocytosis, and granulomatization can achieve indefinite persistence without clearance by the natural immune system. The analysis here primarily concerns the fate of free-floating nanorobots (or their material ejecta or fragments), stationkeeping nanorobots such as internal communication (Section 7.3.2) or navigation (Section 8.3.3) networks, or motile nanorobots that have malfunctioned and lost their mobility, and are moving passively through the body or are being driven by cell-mediated processes.

Section 15.4.1 reviews the movement and fate of very large particles in human tissues. This is followed by a lengthy discussion of the potential for geometrical trapping (Section 15.4.2) or phagocytic trapping (Section 15.4.3) of microscopic medical nanorobots in the human body, and how nanorobots may actively avoid this fate. The Chapter concludes with a brief discussion of the biocompatibility of nanorobot fragments in vivo (Section 15.4.4).

15.4.1 Large Particle Movement

Large immotile macroscopic particles can migrate through soft tissue on their own if they possess a certain degree of asymmetry.[234] A sphere, such as a buckshot pellet, tends to stay in place for an indefinite time. But an asymmetric object such as a sewing needle or porcupine quill can move point first and may travel for long distances due to the action of natural tissue movements and the muscular forces acting upon it.[234] Various implants used for internal fixation of fractures and for adjunctive tissue immobilization during placement of permanent implants may also become dislodged and migrate.[234] Smooth pins and wires[2600-2622] are more likely to be reported as migrating than threaded objects such as screws[2601] or staples,[2600,2601] although screws,[2623-2625] threaded pins,[2626] and staples[2627] are occasionally reported as having migrated. For instance, of 47 occurrences reported in one survey,[2601] eight patients died, six suddenly, due to damage to the heart or to the blood vessels near the heart by the migrating implants, with migration typically occurring within 8 months of implantation. Migrating device or wire fragments have entered the lungs,[2602-2604] heart,[2601,2625] aorta,[2610-2613] pulmonary artery,[2615-2618] small bowel,[2628] abdominal wall,[2629] spinal canal,[2630] and knee joint.[2608] Migrating fragments have moved as far as from hand to elbow;[2622] from pelvis to heart;[2620] from hip bone to ureter[2631] or bladder;[2632] from cervical vertebra to lungs;[2604] from right hip to left lung;[2633] and from the neck or shoulder down to the heart,[2621] aorta,[2610,2611] thorax,[2606,2609] lung,[2602] pulmonary artery,[2615] diaphragm,[2635] spleen[2605,2607] (in one case, reaching the spleen in only 12 hours[2607]), liver,[2634] and lower abdomen.[2636] Incompletely absorbed dissolvable subdermal sutures can work their way back to the surface of the skin[2637] (Section 7.3.3) – suture[2638-2640] and ICD patch[3936,6080] migration is well known.

Large material particles can also become involved in blood circulation, as illustrated by four occurrences of shell fragments transported into the cerebral circulation,[2641] Kirschner wire migration through the great vessels into the heart,[2620] intrapelvic migration of a Knowles pin through the external iliac vein,[2642] and catheter fragments removed from the central circulation in children.[2643] Smaller wear particles from vascular prostheses will move downstream until trapped by reduced vessel diameters on the arterial side of capillary beds, or in the lungs on the venous side of the circulation.[234] Bloodborne cholesterol crystal emboli typically occlude 50- to 500-micron diameter arteries[2644] when cholesterol crystals flake off from the proximal arterial wall during medical procedures (e.g., angioplasty) or in the natural course. Such pathological cholesterol crystals[2647-2653] are usually found in the vasculature of kidney,[2652-2658] gastrointestinal tract,[2645-2647] muscle,[2655,2663] skin,[2654,2655] eye,[2659] penis,[2660,2661] brain,[2662] or the extremities.[2663-2665] More common is the presence in animals[2666,2667] and in human patients[2670-2673] of extracellular particles that are too large to be phagocytosed. These particles include wear debris, precipitated corrosion products, mineral dusts, fibrillar fragments from tendon prostheses, or even 4- to 100-micron Teflon paste particles (Section 15.3.4.4). They ultimately appear in the lymphatic drainage, in regional lymph nodes, or in remote medullary locations or organs.

Relatively large nanorobots and nanoorgans lacking powered locomotive capability (Chapter 9) but having a proper shape or dynamic surface geometry (Chapter 5) could exploit the natural propulsive forces in the tissues to achieve a slow, biologically-assisted histomigration throughout the body. However, nanomedicine usually demands more rapid, precise, and controlled movement. Appropriate tissue anchoring normally will be the paramount concern for nanorobotic organs, as in the case of implanted macroscale communication (Section 7.3.4), navigation (Section 8.3.6), or computational (Section 10.2.5) nodes.

15.4.2 Geometrical Trapping of Bloodborne Medical Nanorobots

The fate or "clearance" of small immotile particles injected intravenously (IV) into the human bloodstream has been widely investigated. IV injection of, say, 15-micron radiolabeled microspheres is a standard blood flow measurement technique in animal research. The number of spheres that become trapped in a histological tissue

slice is proportional to the blood flow through that tissue.[2674-2676] However, particles larger than most capillaries (i.e., 10-, 15-, 25- and 35-micron diameter microspheres) injected into pigs have revealed that there are a considerable number of arteriovenous anastomoses present in the ears and skin, large enough to allow microspheres up to 25 microns to bypass the local capillary bed.[2677] The IV injection of a small number (2-3 million) of 15- to 20-micron microspheres for purely diagnostic purposes in humans is also considered a clinically safe procedure.[2678] (The acute toxicity of 3-micron latex microspheres has been measured in rats;[2679] Section 15.6.2.)

Human capillary vessels average 8 microns in diameter but may be as large as 15-20 microns and as narrow as 4 microns in diameter (Section 8.2.1.2). A rigid particle cannot easily traverse a vessel narrower than the particle's diameter. Experiments confirm that particles resembling inert nanorobots larger than ~7 microns in diameter are trapped by purely geometrical filtration in the capillary beds.[2764] This trapping usually occurs the first time the microparticles pass through any capillary bed in the body. For example, in one study,[2680] 97% of all 15-micron radiolabeled microspheres reaching the canine eye were trapped during the first pass. The trapping of natural red blood cells in capillaries was discussed in Section 8.2.1.2, and the vascular trapping of natural white blood cells[5415-5418] with the possibility of leukergy[4142] or leukoembolization[4143] has also been described in the literature. (There are a few decades-old reports[5419-5421] of leukoembolization in the retina where capillaries are the smallest, and a handful of other reports or suggestions of possible leukoembolization,[3890,5422-5424] but these appear to have minimal clinical significance.[4143]) Of course, still-functioning nanorobots can use active motility mechanisms (e.g., microbivores,[2762] and see Section 9.4.3) to locomote through narrow vascular passages; localized emissions of vasodilator substances such as NO (nitric oxide)[5884,5885] could also facilitate such journeys despite efficient scavenging,[5886-5888] though NO[5889] and related substances[5890] have many complicating effects which must be carefully considered before they are employed in these circumstances.

At the lower end of the size scale, particles less than 0.1 micron in diameter have the possibility of slipping out of the systemic circulation through fenestrations in the cells lining the blood vessels.[2764,2833] The fenestrations differ in size for the specific capillary beds present in each organ. For example, the capillary endothelium of pancreas, intestines, and kidney[2681] has fenestrations of 50-70 nm. Exocrine glands also have endothelial walls with 60 nm fenestrations, though these are normally covered by a thin membrane and the basement membrane still presents an intact barrier.[2682] The endothelium of the liver, spleen, and bone marrow has fenestrations of ~100 nm, and the underlying basement membrane is not intact, allowing particles of this size or smaller to escape the vessel lumen. Capillaries in tumor regions may have abnormally high permeability due to tissue inflammation.[2764]

Our examination (below) of specific locations where circulating nanodevices might possibly become geometrically trapped suggests that medical nanorobots in the 0.2- to 2-micron size range should have little problem remaining in circulation, if only geometric factors are considered.

15.4.2.1 Geometrical Trapping in Lung Vasculature

The opportunity for nanorobot trapping via simple geometrical filtration is significant because the lung has the highest specific blood perfusion rate of any organ, typically 90 mm^3/sec-gm (~4500 cm^3/min) up to a maximum of 490 mm^3/sec-gm (~24,000 cm^3/min) (Table 8.4). Following IV injection, venous blood flows directly to the heart (Section 8.2.1.1), so the first capillary bed normally encountered by bloodborne injecta is in the lungs. Certainly the injection of large 77- to 125-micron[2683] or 200-micron glass beads[2684] causes vascular embolization. But in general all IV bloodborne particles >7-8 microns are preferentially trapped in the pulmonary capillary bed[2685,2764] (when this is the first capillary bed through which the bloodborne particles must pass). For instance, 7.4-micron and 11.6-micron diameter polystyrene microspheres administered IV are filtered out by the pulmonary capillary network, mostly during the first pass, with no hemodynamic effect.[2679,2686] Radiolabeled microspheres administered intravenously to beagle dogs showed that 8- to 25-micron spheres stay in the lung at least 1 month.[4495] 3-micron spheres are rapidly cleared from the lung (most having left after 2 hours[2679]) and are found in liver and spleen after 1 month.[4495,4498] This effect has long been exploited in radiodiagnostic imaging using albumin microspheres and in the delivery of anticancer agents.[2687] Some large particles, depending on their reactivity, can cause pulmonary granulomas.[2685]

Inert particles smaller than 7 microns in diameter can pass through the lung capillary bed without being trapped unless they are aggregated or are very hydrophilic, in which case the pulmonary bed deposition of somewhat smaller particles can be significant.[2688] For example, some 1- to 2-micron diameter engineered liposomes containing negatively charged amphiphiles have optimal deposition in the lung;[2689] accumulation at extrahepatic sites such as the lungs is influenced by liposome size, charge, and composition.[5692]

15.4.2.2 Geometrical Trapping in Liver Vasculature

Among the major organs, the liver has the fourth-highest specific blood perfusion rate, typically 10-14 mm^3/sec-gm (~1000-1400 cm^3/min) up to a maximum of 55 mm^3/sec-gm (~5400 cm^3/min) (Table 8.4). In the liver, the capillary beds have a high microvasculature number density (Section 8.2.1.2) with the usual vessel diameters. The injection of 15- and 80-micron microspheres directly into the portal vein in rat liver induces embolic portal hypertension, causing venous pressure to elevate 15 mmHg and 24 mmHg, respectively.[2690] One study[2691] found portal vein- and hepatic artery-injected 15-micron microspheres were all trapped in rat liver in both normal and cirrhotic rats. It was claimed that this ruled out intrahepatic shunts larger than 15 microns, but apparently a few ~20-micron intrahepatic shunts from portal vein to hepatic veins, bypassing the sinusoids, are found in cirrhotic human patients.[2692] Another study[2693] found that microspheres at least 40 microns in diameter are required for complete embolization of rat liver.

There are two interesting features of the blood filtration system in the liver that are of potential relevance to medical nanorobot geometrical trapping.

First, the portal venules that supply the liver with blood to be filtered open onto venous sinusoids (Section 8.2.5) measuring 10-13 microns in mean diameter,[2725] though varying somewhat with position in the organ.[2694,2697] This sets a rather large upper limit for clear passage by medical nanorobots. (Mean blood flow velocity through rat sinusoids is 144 (range 54-245) microns/sec, or 197 microns/sec after acute ethanol ingestion,[2695] and the varying pressure profile along human liver sinusoids has been modeled.[2696]) If sinusoids comprise ~10% of liver volume, then there are ~1000 sinusoids per lobule or ~10^9 sinusoids in the entire liver, of total tubular length ~1500 km assuming a mean ~100-$micron^2$ cross-section. Sinusoids in periportal areas are narrower, more tortuous, and slightly less porous (5.96% hole area) than the wider, straighter, and more porous (7.94% hole area) centrolobular ones.[2697] Micron-size nanorobots should be able to navigate safely through these passages.

Second, the endothelial cells comprising the sinusoid walls are fenestrated with numerous (5-20 per micron^2) small (mean diameter 0.175-micron, range 0.1- to 0.3-micron) openings and fairly rare (<0.1 per micron^2) large (0.3- to 1-micron diameter) openings[2697-2700] (Section 8.2.5). These fenestrae are not occluded by diaphragms or basal lamina, hence act as sieve holes through which small nanorobots could possibly be drawn into the 0.5-micron deep Disse space[2701] and thence into the lymphatic drainage. Alternatively, nanorobots could be drawn into direct contact with the microvilli lining the hepatocyte plasma membrane (Section 8.2.5), becoming trapped and possibly endocytosed. Of course, even simple nanorobots equipped with gas concentration sensors (Section 4.2) could probably detect an impending passage into the Disse space because the sinusoid-to-hepatocyte oxygen gradient is 5 mmHg.[2702] Such impending passage may be actively resisted using manipulatory appendages[2762] or by other means (Section 9.4), if required by mission design.

In the narrower periportal sinusoids, red blood cells in transit are forced against the endothelial wall, helping to drive small particles through the holes via "forced sieving" and stirring the fluid in the Disse space via "endothelial massage".[2703,2704] The main purpose of the fenestrated endothelium appears to be that of a sieve. The sieve allows the passage of particles <100 nm out of the blood while preventing larger particles, such as ~7-micron-wide red cells and nanorobot-sized ~1-micron chylomicrons, from contacting the hepatocytes.[2705-2707] Chylomicrons are protein-lipid aggregates produced by the intestine and carried by the lymph system into the blood. Their lipids are gradually stripped off by enzymes and their proteins are slowly removed or changed. This causes them to shrink from ~0.5-1 micron in diameter to ~70-80 nm whereupon they can finally pass out of the liver sinusoid through the fenestrae, thence to be absorbed by hepatocytes. The half-life of chylomicrons in the blood is 6-7 minutes,[2519-2521] up to 9 minutes in smokers.[2520] The fenestrae thus act to keep the chylomicrons in circulation until they have lost most of their lipid.[2707] Plasma concentration of chylomicrons of various sizes are estimated to range from ~0.5 x 10^6/mm^3 while fasting up to ~50 x 10^6/mm^3 after a large meal, but typically are ~5 x 10^6/mm^3, about the same particle count as red cells. While flowing through blood vessels, chylomicrons are marginated toward the walls[2522] along with the other smallest "flow units" in the blood (Section 9.4.1.3), including nanorobots.

Medical nanorobots larger than 0.3 microns in at least two dimensions are extremely unlikely to be removed from circulation by filtration through the hepatic sinusoidal fenestrae. For smaller nanorobots, it must be noted that the endothelial fenestrae are dynamic cytoskeleton-rich structures[2708] that respond to hormones,[2709] viral infection[2710] and cytoskeletal inhibitors,[2711-2715] and can be affected by various disease states and local inflammation. It is possible that the size and number of fenestrations[2716-2722] and even the width of sinusoids[2723-2726] could be manipulated via purposeful local biochemical secretions from neighboring medical nanorobots or from other sources.

15.4.2.3 Geometrical Trapping in Spleen Vasculature

The spleen has the third-highest specific blood perfusion rate in the human body, typically 48 mm^3/sec-gm (~450 cm^3/min) with a wide range of 10-130 mm^3/sec-gm (~100-1200 cm^3/min).[2727-2731] It is probably the most likely site in the blood circulation where geometrical trapping of medical nanorobots may occur, because its microcirculation is probably the most complex of any organ in the body.[5610] The spleen serves as a sieve or filtration bed which is especially important in the clearance of rigid or less-deformable particles such as plasmodial-parasitized malarial erythrocytes,[2732] red cells containing Heinz bodies,[2733] poorly opsonized encapsulated bacteria[2734] (which are typically 0.6-0.8 microns in size[2735]), "sickled" cells found in sickle cell anemia patients, and colloidal particles.[2736]

The spleen is a soft, purplish organ about the size of a fist whose primary role is to remove damaged, fragile or abnormal erythrocytes from the circulation. It consists of two histologically distinct areas, the white pulp (5-20%) and the red pulp (~85%).[2737-2741,5610] The white pulp collectively constitutes a large lymph node that performs various immunological functions such as the production of antibodies and the maturation of B- and T-lymphocytes and macrophages. Indeed, the spleen is the largest single lymphoid organ in the body – it is estimated that ~250 trillion lymphocytes/day may recirculate through the spleen of a young adult male, ~8 times more than through all lymph nodes.[5616] The red pulp acts as a blood filter to cull damaged, worn-out, or potentially dangerous cells from the blood. Most importantly, the red pulp strains out fragments of broken-up red blood cells (hemoconia or "blood dust," probably lipid material associated with fragmented RBC stroma) and removes stiff or misshapen red cells, spherocytes (e.g., caused by IgG attachment to red cells in autoimmune hemolytic anemia,[2484),] or malaria-parasitized erythrocytes.[2732] The spleen is a major site of red cell destruction in the body. It is also one of the few "dispensable" organs because mammals can survive reasonably well without one. (Because of the immune functions of the spleen, asplenic patients do have a higher risk of bacterial infections, especially from encapsulated bacteria such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis*,[5609] sometimes producing overwhelming post-splenectomy infections (OPSI)[5610] — life without a spleen is not quite as benign as life without an appendix or gallbladder.)

Blood to be filtered by the spleen enters the organ via the splenic artery. This artery ramifies into progressively smaller branches as it passes through the splenic capsule (the outer wall of the organ, comprised of collagenous connective tissue interspersed with smooth muscle).[2739] As an arteriole enters the interior volume of the spleen, it acquires a continuous coating of lymphocytes – a thick sleeve of cells called the periarteriolar lymphocyte sheath or PALS.[2742,2743] Arterioles continue to break into smaller and smaller vessels with thinner PALS, finally dividing into a tuft of "penicillar" arteries (so-called because of their resemblance to paintbrush bristles).[2744] The PALS is almost wholly gone by this branching level. All of the PALS, collectively, constitute the anatomical white pulp. Upon reaching the red pulp (see below) and losing the last of the PALS, some of the penicillar arteries become sheathed capillaries whose walls are comprised of fusiform (spindle-shaped) cells. These cells are oriented parallel to the vessel axis something like a cylindrical birdcage, and are surrounded by a sheath of reticulocytes and macrophages bound together by reticular fibers.[2739,2745] (Sheathed capillaries can in very rare cases be embolized by natural fat globules;[2746] similar embolization by a large enough population of indigestible medical nanorobots might induce clinically significant loss of function or even necrosis.) Past the sheath, these capillaries return to the normal tubular configuration and empty, along with the other capillaries, into the red pulp.[2739]

The red pulp[2737,2738] comprises most of the splenic volume and consists of pulp cords (Billroth's cords) and the venous sinuses (sinuses are ~30% of red pulp volume[5610]). The pulp cords make a continuous sponge-like reticular tissue, which crisscrosses between fenestrated walls of splenic venous sinuses. The cords contain erythrocytes, lymphocytes, macrophages, granulocytes, and plasma cells. The venous sinuses are 10-150 microns wide[2747] and are lined by elongated endothelial cells that resemble barrel staves ringed by hoops

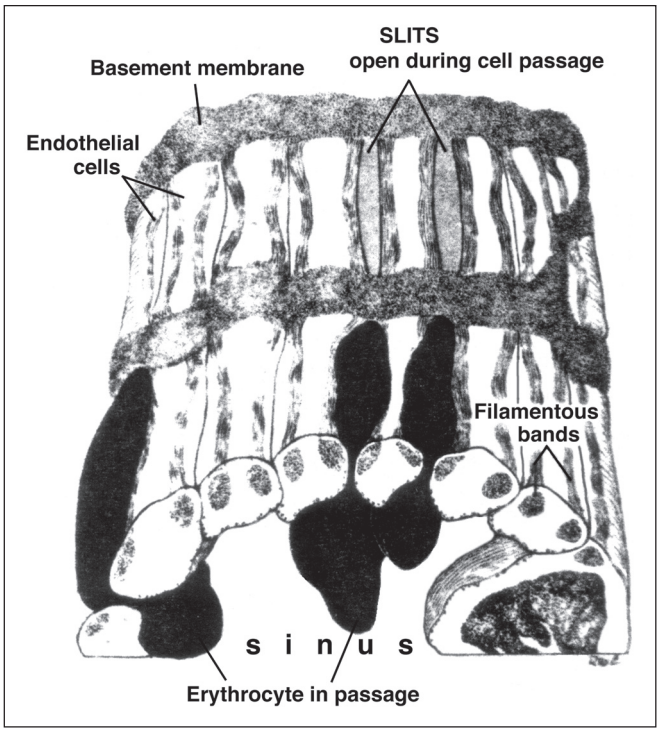

Fig. 15.12. Unique arrangement of filamentous bands in sinus endothelial cells of splenic red pulp (courtesy of Li-Tsun Chen and Leon Weiss;[4645] © 1973 Grune & Stratton, Inc.).

of reticular fibers, forming the hollow cylindrical shape of a sinus. There are tiny slits (fenestrations in the sinus wall) between these endothelial cells. (Figure 15.12). The basal membranes contain actin and myosin and can probably contract to vary endothelial cell tension and thus the dimensions of the slits.[5611]

The spleen filters blood via two physical pathways – "closed" and "open." In the "closed" pathway, some capillaries terminate near the outer surface of a sinus, forcing blood to pass directly into the venous sinuses. (Arteriovenous shunts have been observed in the human spleen that are as large as 7-10 microns.[2748]) In the "open" pathway, some arterioles empty blood through one or two end-pores, 3-4 microns in diameter,[2749] into the pulp cords and reticular cell meshes, but not directly into the sinuses. Blood cells must then pass by open circulation through the additional barrier of the network of reticular fibers which make up the pulp cord before they can attempt to squeeze through the endothelial slits and enter the venous sinuses.[2750] Blood cells that enter a venous sinus using either pathway return to the general blood circulation, ultimately exiting the organ via the splenic vein. In humans, 90% of the blood entering the spleen takes the "closed" pathway (~2 minute transit time, directly from arteriole to venous sinuses) and only 10% goes via the "open" circulation;[2751] ~5-10% of resting cardiac output continuously passes the spleen.[5612] (The histology and microanatomy of the human spleen differs from animal spleens.[5613-5615]) The slits between endothelial cells are normally closed, but widen when cells pass through them.

How large are the interendothelial slits (Figure 15.12) through which cells must pass? Fujita[2737] and Irino et al[2749] observed dumbbell-shaped erythrocytes passing through side-pores 1-2 microns in diameter, Linker[2484] gives slit width as 2 microns, and Cokelet[2752] reports that the sinus wall slits are roughly 1 micron x 6 micron rectangular openings, and about 2 microns deep.* Although red cells cannot pass through a long tube of diameter <~2.3 microns without plugging the tube (Section 8.2.1.2), careful experiments have revealed that normal human erythrocytes can traverse a rigid micropore with a diameter as small as 1 micron if the pore depth is very shallow (e.g., 0.4 micron[2753]) with a driving pressure of only ~1.5 mmHg differential,[2754] or even as small as 0.5 micron during erythrocyte diapedesis.[2755] Transit through the slit is slow, ~10 sec or longer for healthy red cells,[2752] somewhat slower in rat.[2756] The mean residence time of a human erythrocyte in the red pulp is ~66 sec with an average velocity of ~0.25 micron/sec.[2752] Because the percolation of blood through the reticular meshwork between capillary endings and venous sinuses is so slow, the red pulp concentrates blood to twice the normal arterial hematocrit, e.g., an intrasplenic hematocrit of ~78%.[2757]

In the red pulp, deformed or injured red cells cannot navigate the splenic sinusoids successfully, leading to sequestration and phagocytosis (Section 15.4.3.2.4). For instance, red cells containing Heinz bodies (granules due to hemoglobin damage) have difficulty traversing even shallow pores ~3 microns in diameter,[2733] and relatively rigid spherical *Staphylococcus aureus* bacteria of diameter 2-3 microns have been found trapped in mouse spleen.[2758] In this manner, the spleen monitors for abnormal cells in blood by geometrical sieving in venous sinuses and by surveillance of surface antigens by mononuclear phagocytes. Experiments show that polystyrene microspheres 5 microns in diameter injected into rat splenic artery are trapped mainly in the red pulp.[2759] One possible additional minor complication is the observation that rat and mouse spleen capillaries apparently can experience spontaneous cyclic contractions of capillary walls to as narrow as 1 micron in diameter.[2760] Cycles average 1 minute in length (range 12-180 sec), with closure occurring in 2-12 sec during the cycle, lasting for <1-60 sec. However, the author is unaware of any reports of such contractions in human spleen.

Can medical nanorobots pass through the venous sinus slits? These slits are optimally designed to trap rigid particles. For instance, Heinz body fragmentation occurs when rigid particles of oxidized hemoglobin are torn from affected red cells as they circulate through the spleen.[2761] Thus the simplest device design rule would be that non-organic nanorobots should possess at least one physical dimension of ~1 micron or less, or should employ mechanical assistance[2762] or a metamorphic surface (Section 5.3) capable of deforming the entire device to a width of ~1 micron or less in at least one dimension during slit passage.

It may be useful for bloodborne nanorobots larger than ~1 micron in any dimension to incorporate explicit splenic passage protocols and splenofenestral motility mechanisms in their design.[2762] The situation that such a nanorobot may face in traversing the spleen might best be understood by analogy to the recorded journey of a typical healthy erythrocyte through the red pulp. In one experiment, an analysis of three 70-micron RBC paths through open red pulp showed characteristic stop-and-go motion, with RBCs spending 0.015-9.71 sec in any 7-micron segment, despite steady perfusate velocity.[2757] At some locations RBCs adhered to reticular cells or fibers by point attachment, and at others they became caught

** An early oft-cited electron microscopy study by Chen and Weiss[4645] reporting an interendothelial slit size of 0.2-0.5 micron in width, 2-3 microns in length, and 3-5 microns in thickness was for phenylhydrazine-poisoned Sprague-Hawley albino rat spleen, not healthy unpoisoned human spleen. Human erythrocytes have a much larger mean cell volume (MCV) of 94 micron^3 (Section 8.2.1.2) than the reported MCV of 59.7 micron^3 for rat erythrocytes,[4646] and phenylhydrazine can dramatically affect cell volume[4646] and thus, quite likely, measured absolute slit width as well.*

over fibers. But in general RBCs were detained in the reticular meshwork more by surface interactions rather than by narrow channel restrictions.[2757] Appropriate splenofenestral passage techniques for medical nanorobots might range from relatively simple motile semaphoric surface arrays (Section 9.4.5.3) over individual step lengths perhaps equivalent to the 8-nm kinesin motor molecule steps (Figure 9.32), to more complex brachiation mechanisms[2762] (Section 9.4.4.2). Lymphatic-return pathways might also be feasible from the spleen.[2743] A more aggressive solution would be to deploy in advance a small number of specialty nanorobots to selectively block the entrance to the splenic artery during the nanomedical procedure, physically denying entry to therapeutic nanorobots while simultaneously allowing other blood components to pass normally. One such nanorobotic "vascular gate" (see Chapter 19 for details) installed across a 6-mm diameter artery could be established using a sheet of ~10^7 nanorobots each having a (~2 micron)^2 patrol area. The gate would allow non-nanorobotic particulate matter to pass, selectively filtering out only nanorobots; if the vascular gate aggregate consists of vasculomobile nanorobots, then at mission's end the aggregate can disassemble itself and "walk away" without creating a large nanorobotic embolus that could infarct the spleen. (Vascular gates seem workable for nanorobots on short-term missions but might not be appropriate for long-term missions where nanorobots are performing surveillance functions such as early disease detection.) This avoids the even more radical (though survivable) conventional options of splenic embolization[2763] or splenectomy followed by autologous splenic reimplantation.

Some blockage of the reticular meshwork by insoluble particles is tolerable and presents only minor health risks. For example, experiments with 3-micron latex spheres in rats found these particles to be safe imaging agents or drug delivery systems for spleen or liver,[2679] even though 3.4-micron microspheres pass readily through the lungs and are trapped in the spleen with bloodstream half-lives of 1.62 minutes and 1.72 minutes in venous and arterial circulation, respectively.[2686] Acute hemodynamic toxicity as a result of vascular occlusion is a function of total microsphere volume administered, with an inverse relationship between sphere diameter and hemodynamic toxicity.[2679] Additionally, there is some evidence that up to 90% of the blood flowing into the spleen may pass through a region bordering the white pulp known as the perimarginal cavernous sinus plexus (comprised of large flattened open spaces up to 300 microns x 1000 microns in area and 30-100 microns thick), bypassing the narrow-gauge filtration beds of the red pulp.[2745]

15.4.2.4 Geometrical Trapping in Kidney Vasculature

The kidney has the second highest specific blood perfusion rate of any organ, typically 70 mm^3/sec-gm (~1300 cm^3/min) up to a maximum of 100 mm^3/sec-gm (~1800 cm^3/min) (Table 8.4). Nevertheless, geometrical filtration of medical nanorobots from the renal blood flow is unlikely because the capillaries of kidney (also pancreas and intestine) have 50-70 nm fenestrations in the renal endothelium covering the mesangium,[774,2764-2766] far too small to allow either the formed blood elements or micron-scale medical nanorobots to pass through. The size, number, and density of these fenestrae are not markedly changed in human patients with acute renal failure[2767] although the fenestrae are smaller in spontaneously hypertensive rats,[2768] and the diameter and number density of endothelial fenestrae may be purposely reduced by administration of aminoglycosides[2769,2770] or certain perfusion chemicals.[2771]

Experiments with microspheres using various animal models have investigated the largest sizes of inert spherical particles that can pass the kidney capillary bed without being trapped. In cats, microspheres 0.3-, 1.8- and 3.5-microns in diameter readily passed through feline kidney.[2772] In dogs, one experiment found that 3-30% of renally-injected microspheres <7 microns in diameter reached the renal vein, whereas microspheres >10 microns in diameter were completely trapped within the preglomerular or glomerular circulation.[2773] Other studies found that 9-micron microspheres are not entirely trapped in canine renal cortex,[2774-2776] and that previously trapped 9-micron microspheres can be released due to subsequent vasodilation caused by the presence of the particles themselves.[2774,2775] (Sepsis also results in renal vasodilation[2777] which could in theory allow slightly larger particles to pass — an important point to note when performing a nanomedical procedure on a patient with sepsis.) Progressively larger microspheres may pass during hypotension due to vasodilation, but microspheres >~15 microns in diameter are trapped in canine[2778] and rat[2779] renal arterioles. Canine renal vasa rectae vessels are typically 10-20 microns in diameter[2780] and the average kidney afferent arteriole diameter is ~16 microns.[2781] In one study,[2781] the mean diameter of spheres trapped in the interlobular arteries was ~26 microns. Finally, injections of 40- to 150-micron and 100- to 300-micron dextran microspheres caused canine renal embolism with dramatic occlusion of blood vessels using even small quantities of particles.[2782] In rats, 8- to 12-micron microspheres were completely extracted from the bloodstream by the kidney,[2783-2785] though in one study not all 15-micron spheres were trapped in renal glomeruli[2786] and in another study 15-micron microspheres injected intracardially proved capable of locally dilating preglomerular vessels and slowly migrating towards the glomeruli.[2787] In rabbits, 15-micron microspheres lodged in renal glomerular capillaries and 25-micron microspheres blocked interlobular arteries causing intrarenal hemorrhage.[2788] Renal clearance of creatinine was unaffected at a total injection dose of 1 x 10^5 15-micron particles but was detectably decreased at 2 x 10^5 particles and markedly decreased at 5 x 10^5 particles.[2788]

Arteriovenous shunting around the renal filtration bed could in principle allow the continuous circulation of somewhat larger nanorobots, but such shunting is generally not available in the kidneys of healthy subjects. Some arteriovenous renal shunting,[2789] marked by the passage of 10- to 30-micron microspheres, is seen in rats[2790] and humans[2791-2796] but only in connection with renal transplants,[2790,2791] renal biopsies,[2792,2793] and renal carcinomas,[2794-2796] the latter producing volumetric shunt rates ranging from 15-57%.[2795]

15.4.2.5 Geometrical Trapping Elsewhere in the Circulation

Most capillary beds in body tissues will permit smooth-surface ~4-micron diameter nanorobots to pass easily. However, passively circulating nanorobots might become trapped, at least temporarily, at several other sites:

1. *Heart.* Early therapeutic drug-containing microspheres 75-150 microns in diameter implanted directly in the heart during open heart surgery caused extensive myocardial necrosis.[2797] A particle trapping experiment in cat and rabbit hearts using 7.9-, 8.6-, and 14.6-micron microspheres found that only the largest spheres were completely trapped, whereas significant quantities (7-8%) of the smaller spheres were found in perfusate leaving the heart.[2798] Complete trapping of 14.4-micron spheres proved there were no leaks or arteriovenous shunts nearby.[2798] A few nanorobots also might become trapped in eddies immediately downstream of the four heart valves — specifically, in the mural cusps on the ventricular side of the tricuspid and mitral valves,[2799-2802] and in the sinuses of Valsalva[2818,2821] on the arterial side of the aortic and pulmonic valves,[2803-2805] where flow can temporarily stagnate in hydrodynamic vortices, or in cases of cardiac regurgitation.[2806-2809]

2. *Vein Valves*. Nanorobots might become caught in the sinuses behind vein valves (Figure 8.3) where there may exist pressure traps[2810] or semi-stagnant pockets.[2811]

3. *Hemodynamic Anomalies*. Nanorobots could get caught in eddy vortices immediately downstream from vessel constrictions (Figure 9.18A), as might be caused, for example, by atherosclerotic partial occlusions, stenoses, or various vascular lesions. Other unusual flow reversal conditions caused by partial occlusions in particular locations may trap nanorobots in specific branches of the circulation for extended periods of time, as in the "steal syndrome" (tends to refer to subclavian steal syndrome and is significant because of the neurological effects seen due to vascular insufficiency to the vertebral artery and all the branches it supplies)[2812-2816] where blood reverses its flow direction, in some cases simultaneously in two anastomosed arteries (e.g., "double steal" near the circle of Willis[2815]) or even in three arteries (e.g., "triple steal"[2812]). Steal syndrome can cause cerebral ischemia and stroke.

4. *Vascular Aneurysms and Fistulas*. Passively circulating nanorobots, like microbes,[2817] could become trapped in concave vascular caverns such as cardiac aneurysms,[2818-2824] arterial aneurysms,[2821-2824,4603-4606] infectious aneurysms,[2825-2827] drug-induced aneurysms,[2828] venous aneurysms,[2829,2830] and giant vascular fistulas[2831] The fate of particles trapped in this manner could be phagocytosis (Sections 15.4.3.2 and 15.4.3.4) or foreign body reaction (Section 15.4.3.5).

15.4.3 Phagocytosis of Medical Nanorobots

A phagocyte is a cell that has the ability to ingest and degrade particulate substances such as bacteria, protozoa, cells and cell debris, dust particles, colloids, and, in principle, medical nanorobots. This process of ingestion and destruction is called phagocytosis.[2832,2867]

This Section opens with a general description of phagocytes, phagocytosis, and the reticuloendothelial system (Section 15.4.3.1), and then describes the phagocytic clearance of microparticles from the blood (Section 15.4.3.2), from the nonsanguinous spaces (Section 15.4.3.3), the lymphatics (Section 15.4.3.4), and by foreign body reaction (Section 15.4.3.5). We conclude with a discussion of techniques for phagocyte avoidance and escape by medical nanorobots (Section 15.4.3.6).

15.4.3.1 Phagocytes, Phagocytosis, and the RES

There are two broad classes of "professional" phagocytes. First, there are the granulocytes or polymorphonuclear leukocytes ("PMNs" or "polys"), having horseshoe-shaped multi-lobed nuclei, that circulate in the blood. The PMNs include the neutrophils (the most common granulocyte), basophils, and eosinophils. Second, there are the agranulocytes or mononuclear phagocytes ("MNPs"), which have only one nucleus. The mononuclear phagocytes include the monocytes (in the bloodstream), lymphocytes (mostly resident in lymphatic tissues[5670]), and macrophages (monocytes that have left the bloodstream, transformed, and settled in the tissues). Many other cells in the body, such as endothelial cells,[2833-2836] fibroblasts,[778] osteoclasts,[2837] pericytes,[2833,2834] and platelets[775,868,875,881-883,885] have some phagocytic activity, and even thyroid and bladder epithelial cells phagocytize erythrocytes in vivo.[2867] But only the neutrophils and macrophages are good enough particle scavengers to be considered professional phagocytes.[2838]

Phagocytic cells are normally inactive until an apoptotic (see refs. 5765-5767, 6065; Section 10.4.1.1) cell* or a foreign cell or particle is encountered, which activates them.[234,647] Activation is characterized by a change in metabolic activity (e.g., an increase in oxidative metabolism or "respiratory burst"**) and in cell shape. When contacting and recognizing a foreign particle through antigen (opsonin)-membrane receptor binding, the phagocyte plasma membrane develops a dimple (invagination). The particle is drawn inside and the dimple closes, often pinching off to form a small vacuole or phagosome. This traps the particle inside the cell, surrounded by everted cell wall membrane. The phagosome then forms a phagolysosome by merging with a lysosome, whose contents (including degradative lysozymes) are released into the smaller vacuole, attacking the enclosed foreign or denatured proteins.[234] There are ~200 cytoplasmic lysozyme-containing granules per neutrophil.[2839] The ensuing oxidative burst[2875,2877] produces hydrogen peroxide and superoxide anions[2840] which act nonspecifically to digest nonproteinaceous foreign materials that cannot be digested by lysozymes.*** Afterwards the phagolysosomal vacuole may be absorbed or released to the outside at the cell's outer surface (exocytosis; Section 8.5.3.7), producing a large membrane flow. For example, in cultured macrophages an amount of membrane equal to the entire surface area of the cell is replaced in ~1800 sec,[2841] and macrophages may ingest up to ~25% of their volume per hour.[526] For macrophages ranging from 25-30 microns in diameter,[2844] these numbers imply a maximum particle-wrapping phagosomal membrane recycling rate of 1.1-4.4 micron^2/sec and a maximum volumetric ingestion rate of 0.6-4.6 micron^3/sec, which in turn suggests a theoretical maximum particle phagocytosis rate of one ~1-micron^3 particle per second, per macrophage.

Of course, the normal rate of phagocytosis is low in relation to this theoretical maximum capacity.[2845] If the chemical composition of foreign particles allows their degradation, they are destroyed. But if the particles are resistant to digestion, they are retained within the phagocyte in isolated phagosomes[2842] and thus are effectively removed from further interaction with the host.[2843] Typically:

1. internalized albumen is digested inside macrophages with a half-life of 13-23 minutes;[2846]

2. rat macrophage digestion of opsonized red cells and ghost red cells is complete in 24 hours and 3 hours, respectively;[2847]

3. Kupffer cells digest organelle membrane proteins with a half-life of 1.5-2 hours and lipid components with a half-life of 2.0-3.5 hours;[2848]

4. surface-bound immune complexes are digested by macrophages with a 15.5-hour half-life at 37 °C;[2849]

5. the digestive half-life for mitochondria by rat liver Kupffer cells is 3-4 hours, and 8 hours for microsomes;[3664]

** Interestingly, phagocytes can also induce apoptosis (cell death) in seemingly healthy cells[5262] (or at least in cells whose unhealthy state is too subtle for us to detect today).*

*** Respiratory burst refers to an increase in oxidative metabolism, including oxygen consumption, that occurs after the phagocyte ingests the opsonized particle. The major products of respiratory burst in cells are superoxide anion, singlet oxygen, hydrogen peroxide, and hydroxyl free radical.[5617]*

**** However, at least one recent study[4629] suggests that activated proteases could be mainly responsible for bacterial destruction inside neutrophils, with toxic reactive oxygen species and myeloperoxidase-catalyzed halogenation (iodination) playing lesser roles.*

6. tooth amoebas digest human erythrocytes with a 2-hour half-life;[2850] and
7. ribosomes require >24 hours to be fully digested inside rat Kupffer cells.[2851]

Neutrophils, typically 8-10 microns in diameter, are specialized to find and phagocytize bacteria. They can also detect and become activated by foreign particles such as splinters and wear debris. The process of inorganic particle detection and PMN activation remains incompletely understood, but appears to be guided by several mechanisms including particle chemical composition (chemotaxis); local pH differences; electrochemical factors associated with the particle and its surroundings; opsonization (e.g., by complement; Section 15.2.3.2) of the particle;[234] and most importantly by the availability of excess plasma membrane area.[2852] However, medical nanorobots can probably be engineered to avoid PMN activation. This is because micron-size diamond particles do not activate complement,[1642] do not produce neutrophil chemotactic activity,[222,633,639] and do not stimulate lysozyme degranulation in neutrophils.[640] Diamond particles are ingested by PMN cells (Section 15.3.1.4) — admittedly, an event that could be significant enough to prevent a diamondoid nanorobot from completing its mission — but there is no significant further biological response after such ingestion. In one experiment,[640] 4- to 8-micron diamond crystals present at up to ~0.2% Nct (nanocrit, % by volume; Section 9.4.1.4) in culture were ingested by PMNs without negative effect. In another experiment,[633] 3-micron diamond crystals at 2 mg/cm^3 (~0.06 % Nct in culture) were phagocytized by 21% of the neutrophils present at 7250 cells/mm^3 after 45 minutes, but again no chemotactic activity was generated. Eosinophils are similar in structure and function to the neutrophils, and can also phagocytize antigen-antibody complexes,[234] but no antibodies have yet been raised to diamond (Section 15.2.3.3). Neutrophils and eosinophils are the first active line of defense against foreign material in tissue — an "emergency squad" whose duties are later supplanted by monocytes.[234] Leukocytes are end-state cells that cannot replicate by division (mitosis). They have a lifespan of a few hours in blood or few days in tissue, and the cells die rapidly after fulfilling their phagocytic function.[234] Heat production rises from 9 pW/cell in unstimulated human neutrophils up to 28 pW/cell during phagocytosis, with the rise proportional to the number of particles ingested.[2853]

The monocyte is the largest freely-circulating leukocyte, up to 12-15 microns in diameter,[2844] which transforms into a macrophage upon its permanent migration into tissue. There is also a pool of transformable monocytes already present in the tissues.[234] The estimated basal whole-body monocyte production rate is ~11,000 cells/sec for the average adult human.[2854] Monocytes circulate in the bloodstream for 8-70 hours.[2854] During this time they enlarge, migrate into the tissues, and after 8-12 hours differentiate into specific tissue macrophages.[2855] MNPs can actively phagocytize and digest foreign materials,[2856] and can also synthesize and release a wide range of biochemical factors to mediate the local activities of other cells such as lymphocytes and fibroblasts.[234] Macrophages have a maximum lifespan of several months,[2004] replacing themselves at the rate of ~1%/day.[2855] They typically measure 25-50 microns in diameter.[2844] Some macrophages can multiply by mitosis, or can fuse to create the multinuclear foreign body giant cell (FBGC) as a direct response to larger foreign particles.[2857,2858] FBGCs can reach up to 80 microns in diameter and are found primarily in foreign body (Section 15.4.3.5) or implant sites.[234]

The mononuclear phagocyte system (MPS)[2859] — classically known as the reticuloendothelial system (RES)[2860] — is the primary active system in the human body responsible for the removal of old and damaged cells, cellular debris, pathogens and other foreign particles from the circulation.[2861] The RES is composed mostly of fixed, but some wandering, cells, derived from the original bone marrow monocyte.[2862] RES phagocytes are found in large quantities in the spleen (sinusoidal cells), lymph nodes (lymphocytes), and lungs (dust cells or alveolar macrophages). But the Kupffer cells in the liver represent about 50% of all macrophages in the human body. Other macrophages are present in smaller numbers in the blood (monocytes), brain (microglia), kidney (mesangial cells), bone marrow, adrenals, thymus, mucous membranes, serous cavities, breast, placenta, and connective tissue (histiocytes). The human RES consists of at least 200 x 10^9 phagocytic cells.[2863]

Table 15.1 Effect of Particle Size on Phagocytosis by 1150 μm^3 Guinea Pig Polymorphonuclear Leukocytes (PMNs) (modified from Black[234])

Particle Diameter	Number of Particles per PMN	Volume of Ingested Particles	Particle Fraction of PMN Volume
0.088 μm	24,000	8.6 μm^3	0.7 %
0.264 μm	3,600	34.7 μm^3	3.0 %
0.557 μm	360	32.6 μm^3	2.8 %
0.871 μm	102	35.3 μm^3	3.1 %
1.305 μm	34	39.6 μm^3	3.4 %
3.04 μm	3	44.1 μm^3	3.8%
> 7.0 μm	0	0 μm^3	0 %

The presence and activity of phagocytes is particularly related to the presence of small particles. For example, 0.325-micron PMMA particles stimulate cytokine release in vitro by human macrophages at concentrations exceeding 10^{10}-10^{11} particles/cm^3.[2864] Maximum stimulus occurs at average particle sizes in the 0.1-2.0 micron range,[234,2865-2868] though phagocytosis is often said primarily to involve the uptake of particles >0.5 micron in size.[2867]

At the larger sizes, murine bone-marrow macrophages which are 13.8 microns in diameter can ingest IgG-opsonized beads >20 microns in diameter.[2876] Ingestion of an opsonized 15-micron particle requires 30 minutes to reach completion,[2876] whereas ingestion of a lymphocyte by a macrophage was observed to require only 3 minutes (with dramatic shape changes, including formation of a pseudopod 155 microns in length).[2869] Maximum neutrophil pseudopod extension speed is ~50 microns/minute.[2870] Another experiment[784] with cultured murine macrophages found that inert carbon fiber-reinforced carbon particles up to 20 microns in diameter are phagocytosed. Larger particles are not phagocytosed but become surrounded by aggregations of macrophages, some of which migrate onto the particle surfaces.[784] Presented with these larger particles, several macrophages can fuse to form a giant cell, which subsequently may be cleared into the lungs via the lymphatics and expectorated or passed into the intestines for elimination.[2871] Still larger particles (>50 microns) generally don't excite a reaction greater than bulk materials[234] unless they possess a dimension in the smaller size range — e.g., long slender fibers.[2878] The largest particles that neutrophils can ingest are somewhat smaller than those for macrophages. For example, Table 15.1 shows that guinea pig PMNs cannot absorb particles >~7 microns in diameter. Human blood monocytes readily ingest inert 0.39-micron particles, rarely ingest 1.52-micron particles, and never ingest 5.1-micron particles.[2868] Individual macrophages rarely ingest particles larger than ~5 microns:[1074,2864] such particles are ingested by FBGCs (foreign body

giant cells). Ingestion may proceed differently in larger cells. For instance, in amoebas, larger particles are taken up singly while smaller particles are accumulated outside the cell. When a critical volume is reached, the small-particle aggregate is absorbed all at once.[234,2872,2873]

A phagocytic cell can become activated by a failure to digest indigestible or toxic particles (e.g., silica crystals absorbed by alveolar macrophages[175]). This results in the external release of lysozymes and oxidative products, a process called frustrated phagocytosis.[2874-2879] When this occurs, the offending particle is often expelled unchanged from the dying macrophage, followed by ingestion by another macrophage which itself will be killed. This process produces a continuous inflammation with masses of dying and dead neutrophils or macrophages, as well as a cellular debris accumulation (caseation) or "pus" resembling that which accompanies massive bacterial infection.[234] Fortunately, as with neutrophils, 2- to 4-micron diamond particles can be ingested in large quantities by macrophages without harmful effect on the cells.[652] Phosphatase enzyme discharged into diamond-containing phagosomes does not escape into the macrophage cytoplasm or nucleus.[652] In another study, 2- to 15-micron diamond particles in serum-free suspension at 0.5 mg/cm^3 (~0.01% Nct in culture) induced no change in monocyte morphology, indicating no phagocytic activation by the diamond.[641]

Mean rates of phagocytosis up to 2.5 particles per hour were observed for cultured murine macrophages ingesting 8- to 20-micron inert carbon particles.[784] A second experiment[1074] found only 10% mortality among murine macrophages that had ingested up to 2500 0.6-micron alumina ceramic particles (~10% of cell volume), but >30% mortality for particles >2 microns in diameter at high concentrations.* Aggregated serum albumin is cleared at rates similar to rates for metal, dye, and other inert particles. The whole-body maximum clearance rate of aggregated albumin by the human RES has been determined to be ~1.07 mg/kg-min, or ~1.25 mg/sec for a 70-kg man.[2863]

In the natural course, inert particles, once ingested, are retained in isolated phagosomes for the life of the phagocyte. Phagocytes that have ingested too many inert particles lose their phagocytic function, a process called blockade[872,873,1391,3631-3634] (Section 15.4.3.6.10), and shorten their lifespan. Thus massive tissue overloads of chemically inert nanorobots might blockade or even kill large numbers of phagocytic cells if the internal accumulation of foreign matter volume becomes too great (perhaps ~10-20% of total phagocyte volume; Section 15.6.3). In the experiment using carbon particles,[784] cells presented with a large excess of inert particles became rounded and detached from the substrate, and some cells underwent lysis. Inert particles released into the intracellular space due to the lysis of a blockaded phagocyte will either be re-ingested by another phagocyte, or will be swept into the lymphatic filtrate and eventually sequestered in lymph nodes (Section 15.4.3.4) or granulomatized (Section 15.4.3.5).

As a general rule, phagocytic response is decreased with increasing particle size,[2880] producing differences in histological reaction[644] and cytokine production.[645] For instance, particles of hydroxyapatite larger than 15 microns are not taken up intracellularly by monocytes[641] and thus appear relatively inert.[2881] But <15-micron particles of similar composition, when added to serum-supplemented cultures, stimulate monocytes to produce bone resorptive cytokines,[2882,2883] which has been corroborated under serum-free conditions.[2884]

The influence of surface charge on phagocytosis is less clear. One study found no significant difference between anionic and cationic surfaces.[2865] Other experiments with polystyrene microspheres having macromolecule-modified surfaces produced different clearance and organ deposition patterns for negatively or positively charged particles,[2688] and suggested that positive charges increase phagocytic uptake while negative charges reduce uptake.[2880] Positively-charged particles tend to accumulate in the lungs, whereas negatively-charged particles tend to accumulate in the liver, with very few found in the lungs or spleen.[2688] But total RES distribution is not changed, relative to non-RES tissues, despite these differences in organ distribution, so the end result of surface charge alteration is mainly a redistribution within the RES.[2885]

Hydrophilic particles are phagocytosed less.[2880] For instance, microspheres with hydrophobic surfaces are more readily phagocytosed than those with hydrophilic surface in murine peritoneal macrophages.[2865] Surface hydrophobicity appears to be a critical determinant in the opsonization process and in the subsequent uptake of particles by the RES.[2886] Particles with hydrophilic surfaces are rendered more hydrophobic by the adsorption of IgG and can then become phagocytized by macrophages.[2874] In contrast, hydrophobic particles are taken up by macrophages without the need for opsonization.[2764] In one experiment, the least phagocytosis was observed for cellulose microspheres with non-ionic hydrophilic surfaces.[2865] Since all these properties are readily controlled by design, medical nanorobots probably can be given the ability to evade, or if necessary, to escape from (Section 15.4.3.6), the RES.

Particles smaller than 0.5 microns in diameter that are hydrophobic — such as aggregated LDL, microcrystalline cholesterol, polystyrene microspheres, or hydrophobic gold — may trigger "patocytosis." Patocytosis is a unique macrophage endocytosis pathway in which external particles induce and enter a labyrinth of internal membrane-bound compartments that remain connected to the phagocytic cell surface.[2887] Hydrophobic polystyrene microspheres larger than 0.5 microns enter macrophages in the usual manner, via phagocytosis.[2887]

Interestingly, tissue cells contain endogenous adjuvants in their cytoplasm that when released (e.g., due to cell injury or death by apoptosis) markedly augment the generation of CD8 cytotoxic T lymphocyte responses to particulate and cell-associated antigens but not to the same antigens in soluble form.[5047] This is a different mode of action than a classical immunostimulant or bacterial adjuvant such as Freund's. Experimental co-injection of cytosol and fluorescent particles increases the accumulation in the draining lymph node of dendritic cells and macrophages that contain phagocytosed particles and that express high levels of costimulatory molecules.[5047] As a result, attempts by phagocytes to trap immune-visible medical nanorobots may become more urgent in the immediate locale of cell trauma or apoptosis, unless the endogenous adjuvant molecules are extracted or metabolized by the nanorobots.

15.4.3.2 Phagocytosis of Bloodborne Microparticles

Measurement of the phagocytic capacity (ingestible particle volume) of an animal's RES is traditionally accomplished by determining the rate of disappearance of stable, inert, uniform particles such as gelatin-stabilized carbon particles. Upon intravenous injection of such particles, about 90% are taken up by the liver, most of the remainder by the spleen.[2888] One-micron diameter fluorescent beads administered IV to rats are preferentially cleared by the spleen, liver, and lungs[2889] through a complex interaction of geometric and phagocytic influences. Another experiment with amino-modified 0.1- to 1-micron polystyrene particles in mice found that blood elimination half-life ranged from 80-300 seconds.[2890] Aside from purely

** Interestingly in macrophages, as in PMNs, maximum phagocytic capacity appears to be limited by the amount of available membrane rather than by the number of surface receptors.[2876]*

geometric considerations (Section 15.4.2), once inert medical nanorobots have been opsonized (Section 15.4.3.2.1) they may subsequently be phagocytized by phagocytes resident most importantly in the liver (Section 15.4.3.2.3) and spleen (Section 15.4.3.2.4), and also in some cases in the lung (Section 15.4.3.2.2) and kidney (Section 15.4.3.2.5).

The smallest particles <0.1 micron in diameter (e.g., 30-100 nm technetium particles[2891]) that remain in circulation distribute primarily to the bone marrow,* [2891,2892] where mononuclear phagocytes[2893-2897] and phagocytic bone marrow fibroblasts[2898] have been shown to ingest various particles such as polystyrene microspheres[2898] and polyacrylamide microparticles.[2893] Microspheres and lipid nanoparticles are also frequently employed to carry antitumor agents into tumors.[2491,2900,2901] For instance, cationic magnetic aminodextran microspheres 1-2 microns in diameter preferentially accumulate in brain tumors as compared to neutral magnetic dextran microspheres.[2902]

The ultimate fate of inert microparticles phagocytized from the blood varies but may involve transport into specific organs, the lymphatic flow (Section 15.4.3.3.4) or the cerebrospinal flow,[2903] or may involve granulomatogenesis in situ (Section 15.4.3.5).

15.4.3.2.1 Phagocytosis and Opsonization in Blood

The first critical event that occurs upon injection of a particle into the bloodstream is the rapid and efficient process of conditioning through the interaction of plasma proteins with the particle surface.[2904] The rate and extent of particle uptake and the nature of the conditioning material depend both on particle size and on the nature of the particle itself.[2905,2906] Hydrophobic particles such as unmodified pure diamond may become coated with a variety of blood components (Sections 15.2.2 and 15.3.1.1) in a process known as "opsonization." This renders the particles more recognizable by phagocytes within the blood compartment, and particularly by the macrophages in the liver (Kupffer cells; Section 15.4.3.2.3) and in the spleen (Section 15.4.3.2.4). Opsonization also may promote particle (e.g., nanorobot) aggregation.

Important opsonic materials can include complement[2907] (Section 15.2.3.2) and immunoglobulins (Section 15.2.3.3). Organ-specific opsonins for liver and spleen macrophages have been found.[2908] However, if particles are hydrophilic and present a steric stabilizing barrier to the external environment, the extent of particle conditioning can be minimized and altered (Section 15.2.2). For example, it is well established that certain surfaces can encourage the uptake of dysopsonic factors that will render the particle less recognizable by resident macrophages.[2886,2909,2910] Opsonic and dysopsonic processes are dynamic in nature with a competition for the surface and continuous phases of uptake and displacement. Albumin is often the first component to be adsorbed because it is the most abundant blood protein. Other components are present at lower concentrations but higher affinity for the surface, and compete for adsorption subsequently (Section 15.2.2.1). Note however that macrophages can bind and engulf some particles even in the absence of specific opsonins.[2911]

Medical nanorobots should attempt to avoid being unintentionally phagocytosed by neutrophils and monocytes in the circulation, prior to extravasation or transformation of these cells in response to chemotactic signals from injured tissues. For example, one experiment studied the phagocytosis of three types of 1.5-micron polymeric particles with different surface wettabilities that were incubated with blood taken prior to a cardiopulmonary bypass procedure.[2906] One of the three particle types, PMMA, adhered well to phagocytes and was readily ingested (14 particles/monocyte and 11 particles per neutrophil), whereas the other two particle types, MMA/HEMA and PMMA/PVAL, showed almost no adhesion or phagocytosis — although after the bypass procedure the leukocytes evidently became activated and could then phagocytose all particle types.[2906] Stealth liposomes (Section 15.2.2.1) also show a marked decrease in phagocytosis by macrophages.[5281]

15.4.3.2.2 Phagocytosis in Lung Vasculature

Besides geometrical filtration in the lung vasculature (Section 15.4.2.1), in some mammals, such as (but not exclusively) ruminants, particles may also be removed from blood passing through the pulmonary vasculature by active pulmonary intravascular mononuclear phagocytes (PIMPs) or macrophages (PIMs) residing in the pulmonary capillaries.[2912-2919] PIMs are large (20- to 80-micron diameter) mature macrophages bound to the pulmonary capillary endothelium. These cells have an irregular shape, an indented nucleus, lysosomal granules, pseudopods, phagosomes and phagolysosomes, tubular micropinocytosis vermiformis structures, and a fuzzy glycocalyx.[2913,2920] PIMs attach preferentially to the thick portion of the air-blood barrier,[2913,2921] thus minimizing potential interference with gas exchange at the air-blood barrier.[2919] Histologic experiments on the rat found that the lung microvasculature contained ~1 mononuclear phagocyte (half of them active) per alveolus and ~0.3 active neutrophils per alveolus.[2922] About 15 m^2 of the sheep lung capillary endothelial surface is covered with PIMs.[2920]

In 13 nonhuman animal species, 20-nm gold particles clearance half-lives ranged from 1-2 minutes, with 90% clearance after 10 minutes in all species.[2919] 0.5-micron iron oxide particles were cleared during the first lung pass in sheep and calves.[2919] In sheep injected IV with 1-micron latex microbeads, 70% of the beads were caught in the phagosomes of pulmonary intravascular macrophages after 1 hour.[3317] Warner et al[2923] showed >90% uptake of IV injected *P. aeruginosa* bacteria in sheep lungs.

Do humans have PIMs? Dehring and Wismar[2924] reported large mononuclear cells with phagocytic vacuoles in clinical human lung biopsy specimens. But a morphometric study of human lung[2925] showed no macrophages or macrophage-like cells in the pulmonary capillaries and particle uptake studies suggest that humans do not normally have resident PIMs.[2919] (Humans do have pulmonary alveolar macrophages; Section 15.4.3.3.3.) In humans, IV-injected radiolabeled colloid is usually taken up by hepatic (Section 15.4.3.2.3) and splenic (Section 15.4.3.2.4) macrophages — the basis of liver-spleen scans used clinically[2926] — and detectable lung uptake has occasionally been seen, usually in cases of severe liver damage.[2926] It may be that pulmonary uptake in humans is enhanced when Kupffer cells are compromised,[2927] or when organ injury results in monocyte margination in lung capillaries and in the subsequent differentiation of these monocytes into mature macrophages.[2928,2929]

15.4.3.2.3 Phagocytosis in Liver Vasculature

It is well known that if particles consisting of carbon (India ink[777,2930]) or vital dyes are injected into the blood, the macrophages (Kupffer cells) of the liver (along with the phagocytic cells of the spleen) ingest most of them.[2888] Kupffer cells are ~15- to 20-micron stellate phagocytic cells with a 70 nm thick fuzzy coat including a

** Interestingly, in one experiment,[2899] carbon-particle laden bone marrow macrophages in chickens migrated from the erythropoietic sinus through the sinus wall to the extravascular area (the granulopoietic region) 1-3 days post-injection. After 7 days almost all the carbon-laden macrophages accumulated in macrophage islets mainly around the lymphatic nodules in the extravascular area.[2899]*

15 nm thick glycocalyx,[2931] mechanically attached to the sinusoid (Section 15.4.2.2) endothelial cells of the liver. Kupffer cells partially occlude the sinusoid lumen but have no functional attachments to the endothelial cells or to the underlying hepatocytes, and are partially motile.[2932] Their customary positioning, predominantly at the periportal end of the sinusoids, confirms that they monitor arriving blood, looking for particles to remove from the flow.[2845] Distribution in liver lobules (Figure 8.26A) is 43% periportal, 28% midzonal (midacinic), and 29% in the central area (perivenous), with periportal cells larger and more active than central cells.[2704] Kupffer cells can phagocytize particles of dirt, worn-out blood cells including red cells and platelets, and bacteria — and, presumably, inert nanodevices. The cells possess internal inventories of rolled-up spare membrane. This allows a more rapid ensnarement of particulate matter.[2932] Kupffer cells can internalize 5-micron diameter IgG-coated sheep erythrocytes (SRBCs) at a peak rate of 3-4 SRBCs/minute, and C3b complement-coated SRBCs at a peak rate of 5-6 SRBCs/minute.[2845]

The Kupffer cell population constitutes ~31% of liver sinusoidal cells,[2704] with a mean of 14-20 x 10^6 cells/gm liver tissue[2704] or ~25 billion Kupffer cells in the entire organ.[2845,2933] Long-term observations reveal that the mean number and distribution of cells is unchanged over 3 months, indicating that these resident macrophages represent a long-living (i.e., many months) and self-renewing population. Population turnover is slow, with a cell-cycle of ~52 hours including an S-phase of ~7 hours.[2934] About 75% of Kupffer cell population growth comes from cell replication, while the remaining 25% of population growth results from extrahepatic recruitment of macrophage precursors.[779,2930,2934]

A colloidal particle that undergoes opsonization is usually removed rapidly and efficiently by liver macrophages.[2904] The particles are trafficked to the lysosomal compartment of the cell where a battery of enzymes can degrade labile structures.[2904] The half-life of the uptake process can be less than 1 minute for small (e.g., <100 nm) opsonized particles, with more than 90% of the administered colloid being sequestered inside the cells.[2682]

The first nanorobotic line of defense against Kupffer cell phagocytosis is to reduce or to avoid opsonization by blood proteins that would make nanorobots visible to the RES. It may be possible to devise proteophobic coatings (Section 15.2.2.1) to accomplish this objective. For example, particulate matter not coated with blood proteins does not adhere to the 70-nm fuzzy coat lining the cells of hepatic sinusoids.[2935] Under normal conditions, formed elements of the blood and lipid droplets like chylomicrons also do not adhere to the wall of sinusoids.[2935] If diamondoid surfaces can be rendered unwetted or unwettable by fibrinogen and other blood proteins, or can be appropriately masked or pegylated[2904] (Section 15.2.2.1), then physically intact nanorobots might not be efficiently recognized and phagocytosed by the Kupffer cells or the other phagocytic cells of the liver (see below).

If nanorobots are recognized as foreign objects suitable for phagocytosis, uptake and distribution of nanorobots will depend to some degree upon their size. Studies of uptake and distribution as a function of particle size have been done. In one experiment,[2936] polystyrene microspheres 0.05 microns and 0.5 microns in diameter were administered IV to rats. Both particle sizes were mostly distributed to the liver, with small but significant amounts distributed to lung (in the case of the 0.05-micron particles) and spleen (for the 0.5-micron particles). In the liver, uptake of the smaller 0.05-micron particles went 59% to Kupffer cells, 28% to parenchymal cells (e.g., hepatocytes), and 13% to endothelial cells; uptake of the larger 0.5-micron particles went 71% to Kupffer cells, 24% to endothelial cells, and only 5% to parenchymal cells.[2936] Passively circulating inert nanorobots would likely be similarly distributed.

Another experiment[2836] using chemically inert latex particles also found that uptake by a particular phagocytic cell type was determined by particle size. Sinusoidal endothelial cells can internalize particles up to 0.23 microns in size under physiological conditions in vivo, while larger particles normally are taken up by Kupffer cells. However, when Kupffer cell uptake is impaired (e.g., by alcohol), endothelial cells can uptake particles up to 1 micron in diameter after the injection of an excess amount of latex particles.[2836] Splenic macrophages (Section 15.4.3.2.4) can also do this.[2937] Endothelial cells thus constitute a second line of defense in the liver, removing foreign materials from the blood when Kupffer cell phagocytic function is totally disturbed. The total cellular plasma membrane surface area of each cell type, per cm^3 of liver parenchyma, is 1160 cm^2 for hepatic sinusoidal endothelial cells and 325 cm^2 for Kupffer cells.[2938]

A similar study[2939] of the endocytosis of latex particles 0.33-, 0.46-, and 0.80-micron in diameter by sinusoidal endothelial and Kupffer cells in rat liver found that after 10 minutes all three sizes were incorporated by the luminal cell surface of the perikarya or thick portion of the endothelial cells in vitro (bicarbonate-perfused liver) but in numbers far less than in the Kupffer cells. However, in vivo endocytosis of these particles was observed in Kupffer cells but not in endothelial cells. A particle ingested by an endothelial cell was surrounded by a large patch of bristle coat, whereas in Kupffer cells the particle was engulfed by the ruffled membranes or sank into the cytoplasm without a large patch of bristle coat, suggesting different endocytotic mechanisms for the two cell types.[2930,2939]

If Kupffer cells cannot break down ingested particles — as would most likely be the case for diamondoid medical nanorobots — what is the ultimate fate of these cells? (For the fate of phagocytosed nanorobots, see Section 15.4.3.6.) Fujita and colleagues[777] studied the long-term changes in Kupffer cells in mice that were given intravenous India ink. Aggregates of Kupffer cells containing many vacuoles stuffed with 10-100 nm carbon particles appeared in the sinusoidal lumen, Disse space and interlobular connective tissue space 3-4 days after ink injection. After 1 month, large clumps of aggregated Kupffer cells containing numerous carbon-filled vacuoles up to 9 microns in diameter were distributed in the Disse space and other connective tissue, with cells in close contact and partly fused with one another. After 3-6 months, large multinucleate foreign body giant cells (Section 15.4.3.5) with numerous large vacuoles containing densely-packed ink particles were visible throughout the liver tissue, probably formed by fusion of particle-stuffed Kupffer cells. Some endothelial cells also stored ink particles in cytoplasmic vacuoles for as long as 6 months after injection.[777] Particle doses were evidently too low to produce clinically observable pathological effects on mouse liver function.

In a subsequent experiment by the same group,[2940] mouse Kupffer cells in vivo took up 0.2- and 2.0-micron polystyrene latex particles and most cells were stuffed with the particles after 2 days. After 1 month, large Kupffer cell clumps or aggregates (which the researchers called granulomas) 80-120 microns in diameter were observed in the liver connective tissue spaces (i.e., Disse, interlobular and subperitoneal) composed mostly of cells heavily laden with latex particles. Hepatic sinusoidal endothelial cells, attenuated in shape, also took up 0.2-micron particles (but only very rarely a 2-micron particle) into their cytoplasm.[2940] After 8 months, numerous large granulomas were distributed throughout the liver in the interlobular or subperitoneal connective tissue spaces.[2940]

These results suggest that medical nanorobots should be designed first to avoid recognition and uptake by phagocytic cells, and second to actively escape (Section 15.4.3.6) from such cells during or after hepatic phagocytosis, in order to forestall significant foreign body giant cell and granuloma formation (Section 15.4.3.5) in the liver, or unintentional RES blockade (Section 15.4.3.6.10).

15.4.3.2.4 Phagocytosis in Spleen Vasculature

The spleen is an "immunological conference center"[2941] that may be thought of as two distinct organs[361] — (1) an immune organ (the white pulp[2942]) consisting of periarterial lymphatic sheaths and germinal centers comprised mainly of 40- to 200-micron^3 splenic lymphocytes;[2943,2944] and (2) a phagocytic organ (the red pulp) consisting of granulocytes (e.g., neutrophils and eosinophils), NK cells (~25% of splenic lymphocytes[2945]), and macrophages either lining the vascular spaces (i.e., the splenic cords and sinusoids; Section 15.4.2.3) or resident in the perifollicular and marginal zones.[2946]

Splenic macrophages resemble Kupffer cells (Section 15.4.3.2.3) in morphology and functional properties.[2947] These macrophages remove from passing blood, via phagocytosis, certain parasites,[2948] bacteria,[2949] worn out blood cells (red cells,[2950-2952] white cells,[2950], platelets[2950,2953]), and other particles.[2950] Splenic macrophages also break down red cell hemoglobin into the pigment bilirubin,[2954,2955] which is released into the blood plasma and subsequently removed by liver, marrow and kidneys. (The spleen clears mildly damaged erythrocytes from the circulation, whereas more severely damaged red cells are removed mainly by the liver.[2863]) Approximately 10^{11} erythrocytes/day are phagocytized by macrophages in the red pulp cords[2956] Mean turnover time for murine splenic macrophages is 6 days, with 55% of the macrophage population supplied by monocyte influx and 45% by local production.[2957]

There have been relatively few direct investigations of the propensity of splenic macrophages to ingest inert particles that might be analogous to medical nanorobots, though the results should be similar to Kupffer cells. One line of experiments found that uncoated 0.1-micron polystyrene microspheres experience only ~1% uptake by rat spleen after 24 hours in circulation, whereas 0.22-micron particles have ~5% splenic uptake and 0.5-micron microspheres experience ~30% uptake within 24 hours of IV administration.[2904] If the same microspheres are coated with poloxamine-908 surfactant, and if particle injection is preceded by 1-3 hours with a predosing of free poloxamine-908, then splenic uptake of these larger microspheres is dramatically reduced, but this is due to increased accumulation in hepatic Kupffer cells[2958,2959] and not to altered affinity of splenic macrophages for microspheres. Indeed, without the predosing, splenic uptake is dramatically increased.[2735]

Another experiment found that challenging mouse RES with colloidal carbon produced only an increase in the population of splenic lymphocytes, although the thymus underwent acute cortical atrophy followed by post-challenge cellular replenishment.[2960] Phagocytosis of colloidal carbon by splenic macrophages takes place within 20-30 seconds of IV injection, mostly by macrophages from the Billroth's cords and not by sinus-lining endothelial cells. After 24 hours, the particles are still mostly in the red pulp, with a small number in the periphery of the white pulp but never diffusely throughout this area.[2961] Percoll microspheres 20-30 nm in diameter can also reach the thymic cortex from the murine intestinal lumen, there to be absorbed by perivascular thymic macrophages.[2962] Hydrophilized nanospheres <0.1 microns in diameter show negligible uptake by splenic or hepatic macrophages; increasing particle size or hydrophobicity increases RES uptake.[2963]

Assuming that completely passive nanorobots are ingested by splenic phagocytes, what might be the fate of these particles? Once again, experimental studies are few. Macrophages heavily laden with inert carbon particles, when injected into rat splenic artery, were found to slowly migrate from the red pulp marginal zone to the periphery of the white pulp, into the deeper white pulp, and finally into the germinal centers.[2964] Limited numbers of macrophages made the journey in 12-24 hours, but most had completed their journey into the lymphatic tissue after 10 days.[2965] Latex microspheres do not induce granuloma formation in murine spleen cells in vitro, but dextran microparticles do.[2966] Granulomatogenesis apparently can be suppressed by the addition of dexamethasone, PGE2, or certain T cell-derived lymphokines such as IL-4 and IFN-γ.[2967] Massive overdoses of 0.05-micron magnetite-dextran nanoparticles have produced splenomegaly in mice,[2968] and IV injections of metallic tin powder particles in rats have produced up to six-fold splenomegaly and epithelioid granulomas.[2969] Clearly an active phagocyte escape protocol (Section 15.4.3.6) would provide a useful capability for medical nanorobots in transit through the spleen. Particle clearance from the lymphatics is briefly discussed in Section 15.4.3.4.

15.4.3.2.5 Phagocytosis in Kidney Vasculature

The normal human kidney contains blood monocytes mostly in the glomerular and intertubular capillaries, with wide variation in the numbers present in different glomeruli but up to 14 monocytes present in a single glomerulus.[2970] Not more than 1% of monocytes reside within the mesangium.[2970] Macrophages normally are not found in the tubules and are virtually never seen in the interstitium, except in areas of scarring;[2970] possibly in areas of oxalate crystal deposition in nephrolithiasis;[2971] in fetal kidneys;[2972,2973] and in diseased kidneys[2974,2975] when macrophages can be found in the Bowman's space and the mesangial area of the glomeruli,[2974] and leukocyte infiltration is also seen.[2976] Macrophages found in the kidney generally behave much like macrophages elsewhere in the body.

The mesangium is the core of the renal glomerulus and the preferred destination of the induced migration of monocytes during inflammation.[2977] Mesangium consists of the matrix (mucopolysaccharides and glycoproteins) and two cell types — at least 85% contractile mesangial cells, which resemble smooth muscle cells, and up to 15% resident mesangial phagocytes, derived from bone marrow[2978] and belonging to the family of mononuclear leukocytes.[2977] Mesangial phagocytes ingest proteins and particulate material[2979,2980] including zymosan particles,[2981] apoptotic cells,[2982] and of course the familiar colloidal carbon,[2983-2989] internally releasing reactive oxygen species like other phagocytes.[2995] In one interesting experiment, monocytes that had previously ingested inert latex microspheres migrated into rat kidneys whose glomeruli had been denuded of mesangial cells and occupied the vacant cell sites (after 24 hours), transforming first into macrophage-like cells (after 4-6 days) and later into cells indistinguishable from normal mesangial cells (after 2-4 weeks).[2996]

However, there have been relatively few investigations of the details of particle ingestion by kidney-resident or kidney-infiltrating phagocytes.[2989-2994] For example, BSA-coated colloidal gold particles injected IV into ducks were mostly trapped in the mesangial channel system, phagocytized by mesangial cells, exocytosed back into the mesangial channels, transported extracellularly towards the vascular hilus, rephagocytized by macula densa cells, then expelled into the tubular lumen.[2992] Another study found that during glomerulonephritis, macrophages accumulate at sites of inflammation and subsequently migrate to the draining kidney lymph nodes.[2997] This suggests one possible fate of renal macrophage infiltrates after their ingestion of large quantities of completely passive medical nanorobots.

15.4.3.3 Particle Clearance from Nonsanguinous Spaces

This Section describes the phagocytic clearance of microparticles such as nanorobots that are injected into the tissues (Section 15.4.3.3.1), or are ingested (Section 15.4.3.3.2) or inhaled (Section 15.4.3.3.3).

Inert particles should normally be cleared from the bladder via mechanical fluid movements. Some phagocytic presence in the urine is normal,[5455] but pyuria or leukocyturia (>10/mm^3) is considered a pathological condition often observed in diabetic patients,[5456] the elderly,[5457] and other groups. Partial urinary tract blockage by nanorobots could produce some symptoms in common with oliguria,[5458] prostatic obstruction, experimentally-induced chronic partial outlet obstruction,[5459] or crystalluria[2145] (treatable by increasing urine flow, traditionally with diuretics[5460]).

Inert particles should also be cleared, though more slowly, from vaginal cavities via mechanical fluid movements. Lymphocytes and macrophages are present only infrequently in cervicovaginal secretions of healthy women except during menses,[5461] infections,[5462] or histologic chorioamnionitis,[5463] though phagocytic Langerhans cells have been observed in the epithelium of the murine vagina and cervix.[5464]

15.4.3.3.1 Clearance of Particles from Tissues

Immobile nanorobots found in extravascular tissues are susceptible to being phagocytized either by resident tissue macrophages and other phagocytic cells such as fibroblasts, or by newly arriving phagocytes such as neutrophils and monocytes that have immigrated from the blood by passing through blood vessel walls via diapedesis (Section 9.4.4.1) into the adjoining tissue. Sell[2888] notes that if particles are injected into connective tissue, the local phagocytes will ingest them; if particles are injected into the brain, the microglia will absorb them.

For example, macrophages patrol or readily enter the tissues of the peritoneum[2998] and thorax.[2999] The capture of polystyrene particles 0.3-3 microns in diameter by rat peritoneal macrophages was studied in vitro.[3000] The most efficient accumulation by the macrophages was of 0.6-micron particles, yielding an endocytic index of 4.56 micron^3/cell-sec. Hydrophilized (via hydroxymethylation) 3-micron particles had a tenfold higher rate of capture, an endocytic index of 37.9 micron^3/cell-sec.[3000] Upon injection into rat peritoneum, 3-micron particles showed selective accumulation in the omentum whereas 0.8-micron particles were better able to leave the peritoneal compartment.[3000] After 5 hours, most particles (72-86%, depending on particle type) still remaining in the peritoneum had been endocytosed by cells.[3000]

Other similar experiments found that:

1. 1- to 5-micron microspheres were efficiently taken up by macrophages both in culture and after intraperitoneal injection into mice, with saturation of phagocytosis after 3 hours;[3001]
2. peritoneal phagocytes from striped bass ingested ~3-micron latex beads during a 30-minute incubation time, giving a phagocytic capacity of ~4 beads/phagocyte;[3002]
3. sterically stabilized (coated) polystyrene microspheres with thicker coatings are decreasingly phagocytosed by mouse peritoneal macrophages;[3003]
4. 30- to 120-micron microspheres injected intraperitoneally in rats were large enough to be retained more or less permanently in the peritoneal cavity, whereas microspheres with diameters <24 microns were cleared from the peritoneal cavity through fenestrations in the diaphragm, and eventually were observed in the lymphatic system;[3004]
5. for peritoneally-injected microspheres in mice, 1.4- and 6.4-micron PMMA particles and 1.2- and 5.2-micron polystyrene particles were engulfed by macrophages, but 12.5-micron polystyrene particles were not;[5050]
6. fused aluminosilicate microparticles injected into beagle dog peritoneal cavities were translocated to mesenteric, left sternal and right sternal lymph nodes, with a small percentage also going to the left tracheobronchial lymph node;[3005] and
7. inert tungsten particles instilled into the pleural space of dogs were translocated to the thoracic lymph nodes in 1-7 days.[3006]

Colloidal carbon particles injected intravitreously into chicken eyes were actively ingested by hyalocytes (the resident macrophages) by the second day, without significant leukocyte recruitment.[771] Noted the researchers: "In the second stage (at 7-14 days), a large number of macrophages infiltrated the ciliary body and emigrated into the vitreous chamber. In the third stage (at 30 days), the infiltration by macrophages into the ciliary body was complete. The carbon-laden macrophages disappeared from the vitreous body but accumulated on the pecten oculi and retina. They were exclusively drained through the scleral venous sinus in the iridocorneal angle." Another experiment in which 0.02- to 0.07-micron carbon particles were injected into the vitreous humor of monkeys produced cellular proliferation of mononuclear phagocytes and inflammatory cells after 1 week, continued macrophagic response along with fibrovascular proliferation into the vitreous after 3 weeks, deposition of extracellular fibrous material and traction retinal detachment after 4-5 weeks, and carbon-laden macrophages aggregated over the optic disk and fovea, along with prepapillary neovascularization and cystoid macular edema after 10 weeks.[3007]

But there are other phagocytic cells in the eye besides macrophages. The trabecular meshwork is a specialized tissue in the anterior chamber of the eye that regulates aqueous humor outflow and pressure.[3008] Meshwork cells are actively phagocytic and may operate to keep the drainage pathways free of cellular debris, pigment, and other particulate material.[3009,3010] When meshwork cells are exposed to latex microspheres, within 4 hours the cells exhibit a short-term loss of cell-matrix adhesiveness and an increase in cellular migratory activity, returning to normal after 24 hours.[3008] Ingestion rates are 3-4 beads per phagocytic cell.[3009] However, Buller et al[3011] reported that the presence of a foreign particle does not always induce a phagocytic response by human trabecular cells, because free particles were observed in the intertrabecular spaces and in Schlemm's canal. Latex microspheres injected into rabbit corneal stroma were endocytosed by keratocytes (corneal fibroblasts) and stored for >800 days in the keratocyte cytoplasm.[3012]

As another example, consider the phagocytes in brain tissue. One experiment[3013] demonstrated the ability of rat astrocytes to ingest 0.05- to 0.2-micron fluorescent polystyrene microspheres. In another experiment,[773] colloidal carbon injected into the cerebral cortex of neonatal rats was ingested in membrane-bound vacuoles and sequestered in lysosomes of young astrocytes (phagocytic star-shaped neuroglial cells with many branching processes). Carbon-laden astrocytes were seen in the immediate vicinity of the site of the injection after 4 days (and in abundance after 10-21 days), in the surrounding (apparently normal) neuropil, and in the perivascular regions. This showed that young astrocytes could engulf foreign particles injected into the developing brain.

In adult brains, however, it appears that astrocytes are involved in phagocytosis[3014] of cell debris and foreign particles only as a second line of defense.[3015] The microglia[3016-3021] appear to be the first line of defense, distributed, unlike astrocytes, throughout the brain

in non-overlapping territories.[3019] Microglia belong to the RES and are the resident macrophages in brain tissue, in the spinal cord, and in the retina.[3019] In one experiment[3022] involving implantation of polystyrene microspheres in rat brain, both microglial cell and non-specific astrocytic (proliferative) brain tissue reactions were seen in the first few days, similar to that found after damage to the CNS. Some foreign-body giant cells (Section 15.4.3.5) were also observed. After 9 months, the microspheres appeared to be engulfed by histiocytic cells, with microsphere clusters surrounded by a non-necrotic sheath of collagen and astrocytic cells.[3022] Additional phagocytic cells found in the brain include macrophages[3023,3024] such as pericytes,[3025] perivascular[3026,3027] cells, and meningeal[3027] cells. Researchers also have studied: (1) the passive displacement of 6- to 10-micron microspheres throughout the brain parenchyma;[3028] (2) the drainage of particles in cerebrospinal fluid directly from the subarachnoid space into the nasal lymphatics in the rat[3029] and in man[3030-3032] (up to 20-30% of CSF may drain by this route[3033]); and (3) the intracellular transport of latex microspheres inside peripheral nerve cells in both anterograde and retrograde directions.[3034]

Phagocytes which have ingested foreign particulate matter present in tissues may persist at the site of ingestion if they are unable to solubilize the material. Indeed, some cells have been shown to persist for years at the site of particulate insoluble foreign bodies.[1841] Tattoos[3035] are an excellent example of this persistence. In one experiment,[778] the fate of India ink particles and of polystyrene latex beads injected into the murine dermis and subcutis of the skin of the auricle and back was observed with the naked eye and by light microscopy and electron microscopy. Ink particles injected as tattoo patterns remained essentially unchanged for life, to the naked eye. Microscopic examination revealed that both India ink particles and latex beads were endocytosed by fibroblasts and macrophages in the dermis and subcutis. In fibroblasts, numerous ink particles or small latex beads (0.22 micron in diameter) were packed into vacuoles 0.1-10.0 micron in diameter, occupying a large volume of the cytoplasm of the cell body and pseudopods. In macrophages, numerous particles and larger beads (both 0.22 micron and 2.0 microns) were taken up into the cell body. Dermal and subcutaneous fibroblasts that take up and store ink particles and latex beads move poorly after particle ingestion, and thus are almost fixed in the connective tissue, lending persistence to tattoos. The researchers[778] note that this represents "a specific non-inflammatory defense mechanism that protects the living body, without immune reactions, against injuries and invasions by non-toxic foreign agencies." This description would likely apply equally well to inert medical nanorobots.

15.4.3.3.2 Clearance of Ingested Particles

The possible mechanical toxicity of ingested diamond particles and related objects has already been examined in Section 15.1.1. The discussion here concerns the likely fate of immobile nanorobots or other inert particles that have been ingested into the alimentary canal (Section 8.2.3). Because of the tremendous commercial interest in creating orally-administered microparticle-based and microencapsulated pharmaceutical agents, there is a vast literature on this subject, the comprehensive review of which lies well beyond the scope of this book. There is space here to discuss only a few of the many relevant experiments and results. Most of these experiments examined the types and sizes of particles that can traverse the gut wall and the subsequent fate of the migrating particles. Our focus here is on possible particulate analogs to medical nanorobots.

In 1980, LeFevre et al[3047] administered 5.7-micron and 15.8-micron polystyrene microspheres orally to mice. They found that the larger particles did not accumulate in intestinal Peyer's patches, mesenteric lymph nodes, or other organs of the reticuloendothelial system or in the blood, even after the maximum dosage of 8×10^6 particles/day for 60 days. However, the smaller particles were found in Peyer's patches (Section 8.2.3), mesenteric lymph nodes, and lungs after the maximum dosage of 4.5×10^8 particles/day for 60 days. 77 days after terminating ingestion, the 5.7-micron particles were still present in these tissues but were not found in spleen or liver.[3047] The site of uptake for the smaller particles, which were capable of penetrating the intestinal mucosa, was the Peyer's patches. Absorbed particles were sequestered in Peyer's patch macrophages. Particles that escaped this sequestration were transported by lymph rather than by portal blood.[3047] Related experiments with carbon and iron oxide particles suggested that surface properties (Section 15.2.2) as well as particle size govern accumulation in Peyer's patches.[780]

Subsequent work has largely confirmed and extended this picture. Particulate matter passing through the gut lumen is continuously sampled in the gut-associated lymphoid tissues (e.g., Peyer's patches[3036-3038]) to immunologically survey the gut content and to elicit appropriate immune reactions.[3039,3040] In 1989, Eldridge et al[3041] found that orally administered biodegradable poly(DL-lactide-co-glycolide) microspheres of diameter 10 microns or larger were unabsorbed by the gut walls whereas microspheres smaller than 10 microns were specifically taken up into the Peyer's patches of the gut-associated lymphoid tissue. Microspheres between 5-10 microns in diameter remained fixed in the patches for an extended period (up to 35 days) while microspheres smaller than 5 microns were disseminated within macrophages to the mesenteric lymph nodes, the blood circulation, and the spleen.[3041] Kofler et al[3042] later found that translocation of orally-administered PLG microspheres into murine Peyer's patches was much more efficient for 0.8-micron microspheres than for 2-micron microspheres. Carr et al[3048] found that while more 2-micron particles are taken up (particularly by epithelial tissues), a greater total particle volume is translocated to lymph nodes via 6-micron particles.

In 1989-90, Jani et al[3043] fed by gavage 0.05- to 3-micron polystyrene microspheres to rats for 10 days (1.25 mg/kg dose). They confirmed the uptake of particles across the gastrointestinal tract at the Peyer's patches and their subsequent passage via the mesentery lymph supply and lymph nodes to liver and spleen. Heart, kidney and lung showed no uptake. The smallest 0.05-micron particles were 34% absorbed; 0.1-micron particles were 26% absorbed, of which 7% (at 0.05 micron) or 4% (at 0.1 micron) was in the liver, spleen, blood and bone marrow; particles larger than 0.1 micron did not reach the bone marrow; and microspheres larger than 0.3 micron were absent from blood.[3043]

In 1996, Tabata et al[3050] administered biodegradable poly (D,L-lactic acid) microspheres from 0.6-26 microns orally to mice and found that the amount of microspheres taken up into Peyer's patches increased with size up to 11 microns, then decreased at larger sizes, falling to zero at 21 microns or larger (the next lowest size tested being 15 microns). After being taken up into the Peyer's patches, particles larger than 5 microns remained trapped there whereas particles 5 microns or smaller were transported to the spleen. Also in 1996, Damge et al[3044] injected microspheres of size 1-5 microns (1.44×10^9 particle dose) and 5-10 microns (0.183×10^9 particle dose) into the ileal lumen of adult rats. The number of microspheres found in the mesenteric vein increased rapidly, reaching a maximum after 4 hours for both sizes, then decreasing more rapidly for larger particles. A total of 12.7% of small particles and 0.11% of large particles were ultimately absorbed, mainly after crossing the intestinal mucosa at the site of the Peyer's patches.[3044] A few small microspheres were occasionally found in the epithelial cells, and only the smallest particles were recovered in the liver, lymph nodes, spleen, and basement membranes.[3044] In another 1996

study,[3045] 6-micron microcrystalline cellulose particles exhibited no translocation through the intestinal wall at doses up to 5 gm/kg-day (~10^{10} particles/kg-day) for 90 days.

In 1997, Porter et al[3046] injected 0.2- to 20-micron microspheres into chicken intestinal lumens. No uptake of 6-, 10- or 20-micron microspheres was observed in any intestinal segment, into epithelium and lamina propria, after 1 hour. Microspheres 2 microns or smaller were taken up equally by most intestinal segments. After 1 hour, 0.2-, 0.5- and 2-micron microspheres were oriented along the brush border of epithelial cells and microsphere uptake into the epithelium and lamina propria was observed in the duodenum, ileum, cecum, cecal tonsil, and colon.[3046] Peyer's patch tissue had 2-200 times higher microparticle uptake than in adjacent non-patch tissue, and the uptake efficiency for 0.1-micron particles was 15-250 times higher than for 1- to 10-micron particles.[3049] Mathiowitz et al[2592] also found that 0.3- to 2-micron copolymer-coated microspheres could slip between mucosal epithelial cells, entering the lymphoid tissue of Peyer's patches, the bloodstream, and eventually both spleen and liver.

In 1998, Beier and Gebert[3039] injected 3.4-micron yeast particles into pig gut lumen at Peyer's patches. They found that the particles were transcytosed out of the lumen through the gut epithelium via membranous (M) cells in a few hours, without significant phagocytosis by intraepithelial macrophages. The particles then migrated down to and across the basal lamina in 2.5-4 hours, whereupon they were quickly phagocytosed and transported out of the Peyer's patch domes.[3039]

Aside from particle size[3047-3050] and surface modifications,[3043,3051] other important factors in the absorption of microspheres in the gut include particle dosage,[3052,3057] dosage duration,[3053,3054] the age of the animal,[3055-3057] and diet.* [3058-3060] LeFevre et al[3055] administered 1.8-micron latex microspheres orally to young and old mice for 25 days and found that old mice accumulated more particles in Peyer's patches, and fewer in lungs, than young mice, though all mice contained measurable particles in mesenteric lymph nodes and Peyer's patch-free intestinal segments (cf. Simon et al[3056]). A similar study by Seifert et al[3057] using 1-micron polystyrene microspheres counted the number of particles present in thoracic duct lymph (since particles are preferentially transported in the lymph), and found a larger particle uptake by older than younger animals. Uptake was also dose-dependent in Seifert's study: the thoracic lymph contained 5 particles/cm^3 of lymph after an intraduodenal administration of 3.7 x 10^5 particles, rising to 221 particles/cm^3 for a total duodenal dose of 3.7 x 10^9 particles.[3057] Diet also matters. Simon et al[3060] found that the number of 2-micron polystyrene microspheres retained in the gut lumen of rats fed a liquid diet was greater than the number of particles retained when rats were fed a solid diet. Larger volumes of water given with 0.87-micron particles increased the rapidity of appearance and number of particles in the bloodstream.[3058] A quantitative study of the translocation of latex microparticles across the epithelium of the rat small intestine and the microsphere uptake rate to internal organs, also by Simon's group,[3053] found that particle number increased with time in spleen, kidney, lung, liver, and brain, but decreased with time in mesenteric lymph node and heart tissues. Uptake and translocation of 1.82-micron latex particles may begin as early as 5-10 minutes after administration in the gut.[3054,3061] Micron-sized intestinal bacteria are also readily translocated from the gut to mesenteric lymph nodes by macrophages.[3062]

15.4.3.3.3 Clearance of Inhaled Particles

The possible mechanical toxicity of particle inhalation, normal environmental dust levels, the clearance of particles from the lungs via the mucociliary escalator (Section 8.2.2), and the role of alveolar macrophages in respect to crystalline particles, especially diamond, has been described in Section 15.1.2. To review, most micron-size particles (similar in diameter to proposed medical nanorobots) that reach the alveoli are quickly cleared by the mucociliary escalator.[3064-3070] This process of clearance is influenced by particle surface chemistry[3087] and by total particle surface area.[3088] Pure mucociliary particle transport has a mean half-life of 2-3 hours,[3089] which can be slightly accelerated by oral, or IV, administration of aminophylline.[3090] Particles cleared in this manner are swallowed and exit the body through the alimentary canal unless they are reabsorbed in the gut (Section 15.4.3.3.2) or stomach (which in the case of coal dust particles can lead to an increased risk of gastric cancer[3091]).

Those microparticles not immediately cleared by the escalator are ingested by phagocytes, mostly the pulmonary alveolar macrophages (PAMs)[3092-3094] residing in the alveolar airspaces. (Lavages typically reveal a total of ~10^9 macrophages present in the human lungs[3095] and a burden of resident particles 0.5-1.2 microns in size;[3096,3097] in the non-exposed lung, 1-2 macrophages reside in each alveolus in a near-sterile environment.[6061]) This process is also, in part, a function of both chemical and physical particle surface properties,[767,3098,3099] though no comprehensive analysis has yet been done (which will be essential for serious nanorobot design).

Fibroblasts[3103] and leukocytes[766,3104,3105] can become involved in clearance as well. In one experiment,[3104] intratracheal instillation of rat lungs with 0.5 x 10^9 microspheres caused an influx of PMN leukocytes from tissues into the pulmonary airspaces. Nevertheless, after 1 day, 77% of the microspheres recovered in bronchoalveolar lavage fluid had been ingested by pulmonary alveolar macrophages and only 19% by PMNs, with 4% of the particles still free.[3104] After 2 days, 95% of the microspheres were inside the macrophages, and ~100% were still present after 4-7 days.[3104] After particle internalization, macrophages generally exit the lungs either: (1) by migrating to the nearest bronchiole and availing themselves of the mucociliary escalator,[179,3099-3102] or (2) by passing into the interstitium (or in the case of interstitial macrophages, accumulating interstitial-resident particles[3106]) and exiting via the blood vessels or lymphatics, often accumulating in regional lymph nodes.[3071-3076] Alveolar macrophages can ingest 1.5-micron diameter glass fibers that are up to 5 microns long, but not fibers that are 60 microns in length.[758,2493] Fiber inhalation can affect the subsequent lung clearance of microspheres.[3107]

How fast are the lungs normally cleared of particles? In a series of studies by Falk et al,[3108,3109] 6-micron monodisperse chemically-inert Teflon particles were inhaled slowly (depositing in small ciliated airways) or normally (depositing in large bronchi and alveolar region) by healthy nonsmokers. About 60% of the particles deposited in the conducting airways during the slow inhalation were cleared after 24 hours. Of the remaining particles, 35% cleared with a half-life of 3.6 days and 65% with a half-life of 170 days.[3108] After the normal inhalation, 14% of the particles retained after 24 hours cleared with a half-life of 3.7 days and 86% cleared with a half-life of 217 days.[3108] A related study of Teflon and polystyrene 6.05-micron and 4.47-micron particles also found ~50% clearance in 24

** Interestingly, food-ingested foreign DNA is not completely degraded in mouse gut and segments up to 976 bp can reach peripheral blood leukocytes, liver cells, and cells from spleen including B cells, T cells, and macrophages.[3063]*

hours.* [3110] Investigations by Langenback et al[3064,3065] of 2.85-micron diameter carbonized insoluble polystyrene particles instilled in sheep lungs found rapid clearance in 44 hours for tracheobronchial deposition via the mucociliary escalator. This included 2-4 hour clearance of particles deposited in bronchi down to 1 mm in diameter, with slower mostly alveolar clearance over next 30 days. Alveolar deposited particles were sequestered by macrophages and there was no interstitial penetration by alveolar-deposited particles. Macrophages engulfing these particles at low particle burden per cell normally travel only in one direction, from interstitium to alveolus and then to the escalator.[3065] Clearance efficiency generally increases with increasing particle size.[3112] Numerous mathematical models of lung clearance as a function of particle size have been devised.[3078-3086] Clearance of carbon particles from the lung is briefly described in Section 15.3.3.5.

Phagocytes may also transport particles from lungs to lymph nodes for presentation to T lymphocytes.[3070-3077] For example, fused aluminosilicate microparticles injected into beagle dog lungs were translocated by alveolar macrophages to left mediastinal, left and right tracheobronchial (TBLN), and left middle and right middle TBLN lymph nodes.[3005] Microparticles of calcium tungstate sprayed into dog lungs are carried by pulmonary macrophages to the regional lymph nodes, with the first particles arriving after 24 hours and peak arrivals at 7 days.[3113] Neutrophils in dogs can make similar journeys.[3114] Lymph nodes may become enlarged due to the arrival of particle-laden alveolar macrophages and particles phagocytosed in resident hyperplastic histiocytic cells.[3115]

A small amount of particulate matter escapes primary phagocytosis by the alveolar PAMs and PMNs and penetrates the respiratory epithelium, lodging in the interstitium (Figure 8.15) between cells.[3116] In one experiment, 12 hours after carbon particle overloading in mouse lungs some free carbon crossed the type I cells to reach the interstitium and was later observed in peribronchial and perivascular interstitial cells.[772] This triggered a proliferative burst among free interstitial macrophages,[772] which can absorb these particles and transport them back across the epithelium and into the alveolar spaces for removal in the usual manner. Particulate matter that avoids this recovery process is later removed from the interstitium along the lymphatic capillaries (initial lymphatics)[180] to the draining lymph node via the lymphatic circulation, particularly the pleural, hilar, or more distant nodes.[3117-3120] 21-50 nm carbon particles instilled into the nasal mucosa generally cannot pass through the epithelial basement membrane unless inflammatory cells (eosinophils) have preceded them. Even then, inert particles might not penetrate further since the interstitial fluid flows outwardly from the mucosa during allergy.[3121]

As noted earlier (Section 15.1.2), 2 hours after exposure ~2% of small alveolar-resident particles may penetrate the airway lining and enter the pulmonary interstitium and the phagocytic vacuoles of lymphatic endothelial cells. At 24 hours, these particles are detected in the peribronchial lymphatics and lymph nodes,[173,180,766] but overall lymphatic clearance is low.[766] For example, in the study by Snipes et al[3111] cited earlier, 1.7% of 3-micron polystyrene microspheres instilled in beagle dog lungs translocated to tracheobronchial lymph nodes during the 128-day study, whereas only 0.2% of the 7-micron particles and none of the 13-micron particles accumulated in tracheobronchial lymph nodes. A related study[3122] found that 1% of 3-micron latex microspheres inhaled by rats and guinea pigs were translocated from lung to lung-associated lymph nodes, whereas none of the similarly-inhaled 9-micron or 15-micron microspheres were found in these lymph nodes. Up to 6% of very small particles, such as are found in diesel exhaust (typically ~0.2 micron median aerodynamic diameter[5933]), make their way to the mediastinal lymph node in rats after 28 days.[3123] 4% of lung burden in dogs exposed to 1.8-micron coal dust was translocated to the tracheobronchial lymph nodes after ~1 year.[3124] Rat-inhaled cristobalite (silica) aerosol particles accumulate in the mediastinal lymph nodes and thymus,[3125] and rat-inhaled coal fly ash particles <2.3 microns in diameter are transported to the bronchopulmonary lymph nodes.[3126]

Conventional fiber biocompatibility analysis commonly focuses on particle dose, dimension, and durability, with durability determined by inhalation biopersistence (e.g., fiber retention in lung and clearance half life after 5-day animal exposure) and laboratory dissolution rate (e.g., fiber dissolution rate k_{dis} measured in ng/cm^2-hr).[6061]

15.4.3.4 Particle Clearance from the Lymphatics

Aside from the mucociliary escalator (Section 15.4.3.3.3), human biology includes no systematic mechanism by which foreign particles, once internalized in blood or tissues, can be physically ejected from the body.** Rather, physiological systems circulate particles through various "clearance" systems until one of two things happens: (1) the particles are chemically broken down, digested, or dissolved, with the remains subsequently metabolized or excreted (or for some fluorocarbons, exhaled as a vapor through the lungs[3127]), or (2) the particles are trapped somewhere in the body, more or less permanently. For insoluble, inert particles such as immobile diamondoid medical nanorobots, the first option is not available. Ultimately, these particles are either granulomatized in place or in bone (Section 15.4.3.5), or are swept into the lymphatic circulation and finally sequestered in the lymph nodes.

The lymphatic circulation collects foreign particles from all over the body — including tissue spaces such as the peritoneum,[2998] dermis,[3128,3176] footpads,[3129,3130] and organs such as the liver,[2670,3131,3132] spleen,[2670] heart[3133] and lung.[3134] For example, metallic and polyethylene wear particles, mostly <1 micron in size, in patients with hip and knee replacement prostheses can migrate to liver, spleen, and abdominal paraaortic lymph nodes.[2670] Crystalline silica particles in a lipstick cream can enter the body through a recurring angular cheilitis (lip sore) and migrate to the submasseteric lymph node, forming a silica granuloma there.[3176] Inhaled silica particles can translocate from lung to hilar lymph nodes, enlarging the nodes with many granulomas containing silica and macrophages.[3134] Dodson et al[3135] suggest that lymph nodes

** An older and apparently inconsistent study by Snipes et al[3111] of 3-, 7-, and 13-micron polystyrene microspheres instilled in the lungs of beagle dogs reported that only 2-3% of all particles cleared in a few days via the mucociliary escalator. Of the remaining particles, 3-micron microspheres cleared with a retention half-life of 820 days while the 7- and 13-micron microspheres cleared with a half-life in excess of several thousand days.[3111]*

*** Some phagocytic cells can transport small particles from elsewhere in the body to the lungs, from which it is then possible to extrude the particles through the lung wall and exhale them through the airway.[2871] There is at least one report of 0.5- to 5-micron alumina particles originally implanted subcutaneously and intraarticularly in mice that were later observed in the interstitium of the lung,[1050] and similar observations have been reported for ingested 5.7-micron polystyrene particles internalized through Peyer's patches[3047] and for Teflon particles[1392] injected into humans for the treatment of urinary incontinence[1277,1280,1286-1288] and vesicoureteric reflux[1312,1401,1403] that were subsequently transported to the lungs. However, while it is well known that particles which have crossed from the alveolar spaces into the lung interstitium can be ingested and returned to the alveolar spaces by arriving neutrophils or interstitial macrophages, the author has found no confirmation in the medical research literature that systematic long-range particle scavenging by migrating phagocytes followed by discharge in the lungs has been directly observed.*

"may be better indicators of lifetime exposure to dust than lung tissue" because the nodes permanently sequester indigestible particles like asbestos and retain this particle burden for the lifetime of the organism.

The lymphatic system (Section 8.2.1.3; Figure 8.8) is an auxiliary circulatory system in which interstitial fluid is drained off into tiny open-ended vessels, the lymphatic capillaries, whose walls are comprised of endothelial cells with a resting intercellular gap (Figure 8.5) normally ranging ~0.1 micron to several microns.[4597] However, Allen[4596] intraperitoneally injected particles up to 22.5 microns in diameter and all sizes later appeared in the diaphragmatic lymph. This suggested that the peritoneal mesothelium and the lymphatic endothelium on either side of the fenestrations of the basement membrane can open at least this wide to admit stray particles. Median lymph flow rate as measured by 1-micron latex microspheres in mouse tail skin lymphatic capillaries is 4.7 microns/sec, with pulsations synchronized with the murine respiration rate of 2 Hz.[3136] In supine humans,[3137] the median resting flow velocity is 9.7 micron/sec in a 54.8-micron diameter lymphatic capillary, but this varies greatly with many factors including body orientation and vessel size (Table 8.5). The lymphatic capillaries gradually combine into larger and larger tubes until the largest are the size of veins (Table 8.5). Most lymph collects into the largest lymphatic of all, the thoracic duct, which leads into the left subclavian vein in the upper chest (Figure 8.6), thus returning the lymph to the blood circulation. (The lymphatics on the right side of the head, neck, heart, and thorax, and the right arm and lung, drain into the right lymphatic duct and thence to the right subclavian vein; see Figure 8.7.)

Interposed throughout the lymphatic tree are ~450 lymph nodes (Figure 8.9), lymphatic organs that serve as bacterial and particulate filters and as a final resting place for indigestible particles. Each lymph node has a blood supply representing ~0.01% of cardiac output or ~24 ml/gm-hr of blood.[3138] One in every four lymphocytes that enters a node in the blood supply exits the blood and enters the efferent lymph, and every five days ~60% of the entire blood pool of lymphocytes passes through each lymph node's blood vessels.[3138] Despite the slow lymph velocity, filtration of lymph through the nodes can take place fairly rapidly. For example, in one experiment the subcutaneous injection of 0.15- to 0.167-micron carbon particles into murine footpads blackened regional lymph nodes in just 1-8 minutes.[3129] The very smallest particles such as ~0.05-micron liposomes generally are not retained in nodes, but larger particles such 0.5- to 0.7-micron liposomes[3139] are retained by lymph nodes.[3139]

Lymph node tissue is a loosely structured material consisting of a spongelike stroma and free cells in the meshes of the stroma. There are phagocytic fixed cells (lymph node histiocytes) in the sinuses that serve as filters to scavenge from the lymph, and destroy, such particles as red blood cells, bacteria, viruses, and larger dust particles imported by the respiratory tract and collected by macrophage cells of the bronchial nodes. A 5-mm lymph node probably contains a population of ~10^8 cells,[3140] including mostly lymphocytes and both fixed histiocytes and free phagocytes. Nucleated cells in the prenodal lymph are typically 85% lymphocytes, 13% monocytes and macrophages, and 2% neutrophils (Section 8.2.1.3).

Particles injected intravascularly (e.g., intravenously) distribute rapidly to systemic lymph nodes.[3141] In one experiment,[2834] colloidal carbon injected IV into mice was preferentially trapped immediately by postcapillary venules (PCV) and migrated easily out of the PCV either through the intercellular space of the PCV endothelium or by phagocytic processes as soon as 1 hour post-injection. The colloid particles were taken up by pericytes and macrophages around the PCV during the next 24 hours, conveyed to local nodes, distributed throughout the node cortex and medulla, and finally carried to the medullary lymphatic sinuses to be phagocytosed by nodal endothelial cells.[2834] Some redistribution of particles via the lymphatic sinuses from the regional lymph was observed 10-14 days after injection in different lymph nodes. In another experiment,[3132] gelatinized carbon particles injected into the hepatic portal vein revealed a new pathway of liver lymphatics. Heavily carbon-laden macrophages migrated from the liver sinusoid into the interlobular connective tissue within 6 hours of the IV injection, and then entered the lymphatic vessels of the portal tract. By 9-12 hours, these macrophages began migrating into the celiac nodes via the two lymphatic pathways. From the marginal sinus in the celiac nodes, they moved into the interfollicular area of the superficial cortex, then accumulated in the paracortex after 12-24 hrs, finally ending up in the corticomedullary junction.[3132] In yet another experiment,[3131] lymph-borne particles of tantalum coming from rat liver lymph entered hepatic hilar lymph nodes 7-8 hours after IV injection and were subsequently redistributed from marginal, trabecular and medullary sinuses to the paracortex (at 12-24 hours), and finally to medullary cords.

Particles injected extravascularly are distributed primarily to the lymphatic sinus, follicle and paracortex of regional lymph nodes draining from the injected sites. There is a systemic distribution of a smaller amount to distally located nodes and to liver, spleen, and bone marrow.[3141] In one study,[3130] after injection of Pelikan ink into mouse footpads the macrophages that took up carbon particles in the peripheral tissue reached the regional lymph nodes via the afferent lymphatics. The particles then entered the germinal centers, mainly through the medullary pole of the lymph follicles, after migrating along their immediate exterior from their marginal sinus to their medullary pole.[3130] In another study,[3142] ~0.25-micron India ink particles were subcutaneously injected into guinea pigs. A small number of fixed macrophages that were scattered throughout the germinal center (tingible body macrophages) of the popliteal lymph nodes ingested a few particles within 15-20 minutes, and there the particles remained. A larger number of itinerant ink-packed macrophages migrated from the peripheral tissues and were found preferentially in the medullary portion of the germinal center, together with many lymphoblastoid cells. The ink-packed phagocytes all exited the node after a short stay, carrying the particles away with them to another destination.[3142]

Lymph nodes that become heavily overburdened with particles develop serious lesions. In one case study, a man was exposed to <0.1 mg/m^3 quartz dust over a period of 30 years, leading to hilar lymph node fibrosis and calcification. Subsequently, he was exposed to 2 mg/m^3 quartz dust for 5 years, which proved fatal since all alveolar-trapped dust was retained in his lungs in part because his lymph nodes were saturated with particles.[3143] A second man who had been exposed to 1.5 mg/m^3 of quartz dust for 6 years experienced hilar node enlargement and subsequent calcification. When lymph nodes get overloaded with dust imported from the lungs — particularly silica, a potent lymphotrophic material — says Seal et al:[3144] "dust, accumulating in central lymph nodes, leads eventually to spread throughout the capsule and rupture into bronchi or pulmonary vessels, thereby sending dust laden activated cells back into the lungs to produce progressive massive fibrosis."

As of 2002 there had been no studies of the behavior of diamond or sapphire particles instilled into lymph nodes, either for short-term or long-term exposures, and there had been no good studies of diamond dust inhalation risk (Section 15.1.2). Therefore at this time the possibility cannot be ruled out that indigestible

diamondoid particles, accumulating in lymph nodes, might act like indigestible silica* in the same locale. However, a serious risk seems unlikely because diamond dust[652] and sapphire dust[2496] provoke no significant cytochemical reactions in macrophages, unlike quartz dust which is generally highly cytotoxic.[652,2496] Perhaps diamond particles may act more like mica dust, which is also readily transported from lungs to lymph nodes, but once in the nodes, results only in "swollen dust-laden macrophages that retained their normal structure" for at least 1 year post-exposure,[3145] with "fibrotic lesions limited to the formation of thick reticulin fibers."

Retention of microbial or other foreign particles produces swollen lymph nodes, e.g., from a normal ~0.5 cm size up to a node diameter of 0.7-1 cm in response to vaccination.[3147] But inhaled and translocated dust particles produce the most dramatic enlargements. For example, rat lungs instilled with volcanic ash produced mediastinal lymph nodes 8-18 times larger than normal "due to abundant cellular microgranuloma formation and early fibrosis".[3148] Following an eight-day inhalation exposure in rats, silica particle-laden macrophages arrived at the posterior mediastinal lymph nodes and accumulated in granuloma-like structures without degeneration or apoptosis, increasing the weight of the lymph nodes progressively from 3.5-fold up to 35-fold at 52 weeks post-exposure.[3149] Tin particles also cause swelling in the regional draining lymph nodes,[3150] and mercury produces threefold swelling in rat lymph nodes.[3151]

In 2002, the maximum safe dust capacity of human lymph nodes was still unknown. However, an examination of the dust content and composition of fibrotic lung lesions and hilar lymph nodes from the lungs of British coalworkers found that the highest mean dust concentration in nodules and massive fibrosis was ~20%, mostly coal dust mixed with some fly ash which is composed of quartz, kaolin, and mica.[3152] Quartz was preferentially transported to the nodes. Dust taken from miners' lymph nodes was 20.3% quartz but only 6.1% quartz in dust taken from the lungs.[3152] Nodes with dust-related lesions were typically 1-9 mm in diameter; only the most severe lesions were >10 mm in diameter.[3153] In a more recent study, diseased lungs from patients undergoing surgical lung resection were found to have pathological particle burdens in thoracic lymph nodes of 10^{10}-10^{11} particles per gram of dry node tissue, with particles of mean diameter 0.5-0.9 microns.[3096] This implies a volumetric nodal particle burden ranging from 0.07-4%. Adopting ~1% particle burden as a reasonable maximum and assuming an initially unswollen 0.5-cm diameter lymph node, each node could safely retain ~10^9 particles of volume 1 micron^3 per particle. Thus the entire human body could tolerate at most ~10^{12} of these particles (~1 cm^3) if evenly distributed (the ideal case) throughout all the ~450 lymph nodes of the body. This estimate is crudely consistent with particle retention models which predict mean lung and lymph node particle burdens of 12 gm and 1.9 gm, respectively, after exposure to respirable coal mine dust at 2 mg/m^2 during a 45-year working lifetime, at age 75.[5048] (Some alternative measures of lung overload[781] suggest more conservative maximum particle burdens of only ~0.1%.[781])

The spleen could also be used for particle storage, but may be susceptible to granuloma and swelling (splenomegaly) when exposed to the same materials as those that similarly affect lymph nodes,[3154] e.g., talc dust or tin particles in spleen[2969,3155] and nodes.[3150,3156] For instance, up to sixfold volumetric swelling has been provoked in rat spleens using IV inoculations of metallic tin particles.[2969] Assuming a ~1% maximum safe volumetric particle burden in the splenic white pulp to avoid granuloma and splenomegaly, the spleen could safely store at most another ~1 cm^3 (~10^{12} particles) of 1-micron^3 particles, producing no swelling. Despite the likely inertness of diamondoid materials, these maximum safe particle storage limits seem surprisingly low compared to likely nanomedical diagnostic and therapeutic doses. This points to the necessity for reliable phagocytic avoidance and escape protocols for medical nanorobots (Section 15.4.3.6).

15.4.3.5 Foreign Body Granulomatous Reaction

As a general principle,[1841] the human body reacts to insoluble foreign bodies placed within it either by extruding them (if they can be moved and an external wall is close at hand) or by walling them off by exactly the same process as wound granuloma formation** (Chapter 24). Willert[3157] has pointed out that while small amounts of indigestible particles can be stored locally or transported away through the lymphatic drainage (Section 15.4.3.4), large quantities of particles can overwhelm the normal process and produce (1) a histiocytic granulation tissue with accompanying fibrosis, which results from attempts to encapsulate and isolate the reaction, and (2) progressive tissue loss through necrosis and attempts at remodeling,[234] a phenomenon sometimes called "small particle disease"[234,2669,3157] or "nano-pathology".[5638]

As an example, in one experiment up to 7.5 mg/kg of glass fibers (~0.2 cm^3/70 kg) instilled peritoneally in rats were taken up by peritoneal organs in 1-2 days. But at higher doses, the excess foreign material formed clumps of fibers (nodules) that were either free in the peritoneal cavity or loosely bound to peritoneal organs. The nodules displayed classic foreign body reactions with an associated granulomatous inflammatory response.[3158] The granulomatous reaction of the body to Teflon particles has been exploited therapeutically (Section 15.3.4.4), and granulomatous foreign body reaction has been reported for a diverse range of materials including colloidal carbon,[3159] cholesterol,[3160,3161] collagen,[3162] cotton and other surgical textiles,[3163-3165] fish bone,[3166] gallstone,[3167] glass,[3168] graphite,[2513,2514] hair,[6166-6169] mercury,[3169] metal particles,[3170,5824] plastics,[3171-3173] silica,[3174-3177] silver needle,[3178] sutures,[3179,3180] swabs,[3181] talc,[3182] thorns,[3183-3185] and wood.[3186-3188] The possibility of nanorobotic foreign-body carcinoma is discussed in Section 15.2.8.

Studies of silica-induced fibrosis[3134] suggest that activation of macrophages by foreign materials[3189,3190] is a prerequisite for release of chemotactic factors (which summon other phagocytes to the site) and cytokines.[3191] The chemical activity of phagocytosable particles does not seem to be primarily responsible for their cellular stimulatory effect.[234] Activated macrophages that encounter foreign particles larger than a few microns in size can multiply by mitosis or be stimulated to merge with other macrophages[2857,2858] to form a relatively sessile multinuclear foreign body giant cell (FBGC).[2668,3192] Reaching up to 80 microns in diameter, the FBGC cell can more aggressively phagocytize larger particles than individual neutrophils, eosinophils, or macrophages alone can attack. For example, inhaled short inorganic fibers (<5 microns) are phagocytized by alveolar macrophages, but long fibers (>10 microns) are phagocytized by FBGCs in rats, hamsters and guinea pigs.[3193] Also, a macroscopic

** There is some evidence that the body can slowly transport (in some as yet unknown manner) small amounts of silica, as evidenced by the occurrence of nondietary silica in human urinary calculi.[3146]*

*** This process is relatively slow, with mostly neutrophils arriving during the first 6-24 hours, replaced by monocytes after 24-48 hours.[1841]*

ocular lens implanted in mice produced multi-macrophage FBGC aggregates.[3194] Fibroblasts then surround the FBGC aggregate and form a fibrous wall around the object. Encapsulation or marsupialization (see below) could well be the fate of an immobilized medical nanorobot that is unable to avoid triggering phagocyte activation (Section 15.4.3.6).

As a general principle, granulomas are proximately mediated by the local release of interleukins such as IL-1beta[4650] and other interleukins,[4651,4652] and by proinflammatory C-C cytokines such as monocyte chemotactic proteins MCP-1 and MCP-2[4650] and other cytokines.[4653-4656] These cytokines help to recruit new leukocytic cells to the site. Granulomas display characteristic cytokine profiles with coordinated expression that is under cytokine-mediated regulation.[4656] Medical nanorobots may be equipped with molecular sorting rotors to absorb some or all of these recruitment or key mediating cytokines,[4657] thus reducing their local concentration to near-background levels and effectively short-circuiting the granuloma-formation process. The effects will be similar to the results in knockout mice lacking critical chemokine receptors whose ability to form granulomas is thereby artificially impaired.[4658-4660] A less elegant alternative would be to release anti-interleukin antibodies which have been shown to partially abrogate pulmonary granuloma formation and to inhibit leukocyte recruitment in mice in vivo,[4661] or to release a receptor antagonist for IL-1.[2157] Other granuloma inhibition strategies might also be pursued.[4662-4664,5367-5379] In the case of long-term nanorobot missions or augmentations (Chapter 30), a key design issue will be whether granuloma inhibition can be achieved locally without blocking the function systemically, or alternatively, how to replace the lost function served by granuloma formation, using artificial means, once the natural means have been permanently systemically suppressed.

As Peacock[1841] pithily describes the process of granuloma formation: "In granulomatous reactions, the macrophage is usually found immediately adjacent to the inciting material or it may actually have phagocytosed it. Fibroblasts move into the area and surround the cluster of macrophages. Collagen is laid down, eventually enclosing the lesion in a dense fibrous capsule. These hard spheres of fibrous tissue constitute the granuloma."

Granulomas can be comprised of macrophages (foreign body reaction), epithelioid cells (immune granulomas of sarcoidosis, tuberculosis), or skin macrophages or Langerhans' cells (histiocytosis X)[3195] that have ingested foreign material but cannot digest or exocytose it. Activated macrophages and tissue monocytes release cytokines such as angiogenic growth factors that induce the invasion of capillaries into the granulation tissue.[234] Large amounts of mucopolysaccharides and collagen are synthesized and formed into a scaffold for cellular reconstruction and remodeling in this tissue, a process called fibroplasia.[234,3196] Similar processes (granuloma formation) in latex-bead- and ink-particle-stuffed fibroblasts that become trapped in the connective tissue of the dermis are responsible for the long-term persistence of tattoos.[778] By one month after implantation, the granuloma has become a relatively acellular[3197] fibrous capsule that is maintained by the presence of the implant.[234] If the foreign body is then removed, the capsule may collapse into a residual scar or be completely remodeled.[234] The potential for encapsulation may apply to isolated particles such as medical nanorobots, aggregates of such particles such as communicyte (Section 7.3.2) or navicyte (Section 8.3.3) arrays, or to the outer surfaces of macroscale implants such as artificial nanorobotic organs. Trapped nanorobots can still communicate chemically with the external environment even in the absence of transgranulomatous mechanical penetration[6140] by nanorobot appendages, e.g., via simple chemical diffusion (Section 3.2) of small molecules through granuloma walls.[6141-6144]

Many factors can influence the thickness of the fibrous capsule. Chemically active materials such as corrosible metals or leachable polymers will mediate formation of a capsule whose thickness is directly proportional to the rate of release of these constituents.[234,3201] Besides concentration, the chemical nature of the released materials or surface composition may be cytotoxic, inhibitory, or neutral.[3199-3201] For example, pure titanium may elicit a minimal fibrous encapsulation under some conditions, whereas stainless steel implants can induce a thick fibrous layer up to 2 mm deep.[3201] In experiments with rats,[3200] polyethylene implants coated with RGD (a tripeptide) or poly-L-lysine had thicker capsule formation than RGE-coated implants. Active medical nanorobots should be able to control these emissions and surface characteristics. Even disabled devices, if constructed of diamondoid materials and physically intact, should remain chemically inert and not corrode (Section 15.3.3.6) or leach (Section 15.3.7).

Besides chemical inertness, mechanical factors are also important in mediating capsule formation.[234] For example, an absolutely smooth surface discourages extensive fibrosis, although a slight roughness of the surface (even microscopic irregularities), particularly if the roughness is ordered as in linear scratches or in the weave of a fabric, leads to increased fibrous reaction.[1841] Formation of a fibrous capsule around a nanorobotic organ implant will be markedly aided if very fine lines are etched on the surface of the implant because fibroblasts show directional movement on an oriented substrate by a process called "contact guidance" (Section 15.2.2.3).

Capsules also become thicker with increased relative motion between implant and tissue,[234,3201-3207] sometimes[1841] but not always[3202] as a result of mild injury to adjacent tissue. Variation in the distribution of strain between implant and tissues can alter the spatial pattern of fibrous tissue thickness surrounding the implant.[3211] In extreme cases, a painful fluid-filled bursa mimicking a synovial capsule may form around the implant.[234] One study[3207] found that cylindrical implants inserted into dog femur bone and laterally oscillated in vivo for 8 hours per day produced stable bone ingrowth up to 20 microns of oscillation, but not at 40-150 microns of oscillation, which produced excess fibrous ingrowth. When implanting a material, caution should be taken that the implanted material has roughly the same mechanical properties as the surrounding tissue.[3207-3210] A significant mismatch (Section 15.5.3.4.1), such as a difference in Young's modulus between the implant and the surrounding tissue, could induce the formation of a relatively thick capsule. This factor may be most relevant to such nanomedical systems as in vivo tethers (Sections 6.4.3.6), fiber networks (Section 7.3.3), pressure ulcer resistant nanorobotic garments (Section 15.5.1.3), vasculomobile nanoaggregates (Section 15.5.3), transdermal portals (Chapter 19), and nanoorgans (Chapter 14) employing external mechanical effectors.

Implant shape[5728] may also affect the thickness of the fibrous capsule.[234,3212-3215] Capsules will become thicker over edges and sharp changes in surface features. For example, the capsule surrounding a rectangular slab of reactive material will be dogbone or club-shaped, a phenomenon called "clubbing".[3212] All else equal, cylindrical implants form stronger soft-tissue attachments than flat rectangular implants.[3214] Implants with features offering a reduced solid angle to surrounding tissue reduces the accessibility of that nearby tissue to microbe-killing neutrophils if it ever becomes infected.[234] Similarly, implants having corners with the most acute angles produce higher inflammatory response in the absence of infection — in one study,[3216] otherwise similar implants having a

triangular shape showed the highest enzyme activity and cellular response, pentagon shapes showed less, and circular rods showed the least activity. The existence of "dead spaces" — volumes filled with cell-free fluid rather than tissue — is a special geometric hazard because this fluid can act as an in vivo culture medium for bacteria.[234] Thus in nanorobotic organs, adherence of soft tissue to the implant will usually be desirable in order to eliminate these fluid-filled cavities, thus helping to decrease the risk of infections. Other characteristics of implants that may lead to surface infection and the spread of biofilms have already been reviewed in Section 15.2.1.4.

Electrical currents, such as those emanating from an implanted stimulatory electrode, can also produce capsules[3217-3219] whose thickness is sometimes related to current density[234] although sometimes there is little or no fibrous reaction.[3220] Electrodes can release corrosion products while also mediating changes in local pH and pO_2, so effects due to direct electrical (faradic) and indirect electrochemical (electrodic) stimulation can easily be confused.[234]

Fibrous tissue capsule thickness is also influenced by implantation location within the body. In one series of experiments with rats,[3198-3200] intraperitoneally-placed implants had a more extensive fibrous and vascular tissue formation and more numerous associated inflammatory cells than subcutaneously-placed implants. In another experiment with dogs,[3218] intramuscular-placed electrodes produced thicker fibrous capsules than epimysial-placed electrodes.

Finally, thickness tends to increase with duration of the implant in the body. For instance, the external fibrous capsule surrounding one implant reached 4-5 mm in thickness, 19 years post-implantation.[3221]

Black[234] notes that implant "resolution" — a final state after which no further progressive biological changes occur — can have four possible outcomes:

1. *Resorption*. A resorbable implant[3222] eventually resolves to a collapsed scar, or in the case of bone, may entirely disappear. Most medical nanorobots probably will not be resorbable. However, if nanorobots retain mobility after encapsulation they could later migrate away from the site, producing a similar outcome.

2. *Extrusion*. The local host response to an implant in contact with epithelial tissue will be the formation of a pocket or pouch continuous with the adjacent epithelial membrane, a process called "marsupialization"[3223,3224] due to the structural similarity to a kangaroo's pouch. In the case of the external epithelium (skin), marsupialization results in the extrusion of the implant from the host unless the implant is anchored in the deep connective tissue or other deep tissue.[3223] Nanorobot control and mobility systems should prevent this outcome, unless it is desired.

3. *Integration*. In a very few cases such as the implantation of pure titanium in bone,[3225] a close, possibly adhesive, approximation of nearly normal host tissue to the implant is possible without an intervening granulomatous capsule, although inflammatory cells may persist in small numbers. With proper surface engineering (Section 15.2.2), good tissue integration is a very real possibility for medical nanorobots or nanoorgans.

4. *Encapsulation*. This is the most common response to, for example, implant wear particles,[2668-2670] carbon particles,[902] or cosmetic microimplant particles:[3171-3173] formulation of granulation tissue with a fibrotic capsule surrounding the foreign body. If an implant is placed in a location where bone may form (e.g., within a medullary space) and does not achieve osseointegration, then the fibrotic capsule may become mineralized in which case the granuloma is called a "sequestrum." Small particles also can elicit the release of cytokines that stimulate large phagocytic cells called osteoclasts to resorb bone.[3226] Such particles may even inhibit bone formation by osteoblasts,[254] resulting in overall bone loss and a loosening of the implant at the implant-bone interface, possibly with some local tissue necrosis. Selective absorption or emission of appropriate factors (e.g., cytokines to stimulate osteogenesis[5618-5620] or revascularization via angiogenesis,[5621-5623] or bone morphogenetic proteins[5624]) by nanomedical implants could reduce or eliminate these negative effects. If encapsulation is inevitable, nanorobots can be designed to accommodate this natural reaction. For example, an encapsulated nanorobot could extend sensor-tipped telescoping stalks through the capsule, enabling collection of sensor data outside the capsule's outer wall. Once sufficient readings have been taken, the sensor stalks could be retracted back into the nanorobot without further disturbing the capsule.

"Whether each of these resolution outcomes represents success or failure of the implant depends on the circumstances [and] the desired consequences of the insertion of the implant," observes Black.[234] "This is the basic idea of biocompatibility: biological performance in a specific application that is judged suitable to that situation."

15.4.3.6 Phagocyte Avoidance and Escape

Invading microbes that readily attract phagocytes and are easily ingested and killed are generally unsuccessful as parasites. In contrast, most bacteria that are successful as parasites interfere to some extent with the activities of phagocytes or find some way to avoid their attention.[3302] Bacterial pathogens have devised numerous diverse strategies to avoid phagocytic engulfment and killing. These strategies are mostly aimed at blocking one or more of the steps in phagocytosis, thereby halting the process.[3302]

Similarly, phagocytic cells presented with any significant concentration of medical nanorobots may attempt to internalize these nanorobots. How often will such an opportunity arise? There are an average of one ~730-micron^3 granulocyte or PMN in every ~3 x 10^5 micron^3 of human blood, one ~1525-micron^3 monocyte in every ~2 x 10^6 micron^3 of blood, and one >1525-micron^3 macrophage in every ~2 x 10^5 micron^3 of human tissues. By random thermal motions in a quiet fluid, a 2-micron nanorobot would trace out a volume containing one PMN in ~70 sec at 37 °C (Eqn. 3.1), or would diffuse the ~40-micron mean free distance (Eqn. 9.72) between nanorobot and the nearest macrophage in quiet watery tissue in ~4000 sec (Eqn. 3.1). In a small (1 mm diameter) artery with blood flowing at 100 mm/sec, each 2-micron nanorobot, in a total bloodstream population of 10^{12} such nanorobots, would collide with a PMN cell once every ~3 seconds near the periphery of the vessel but only once every ~300 seconds near the center of the vessel (Section 9.4.2.2). This rheological disparity will be amplified by phagocyte margination (Section 9.4.1.3) and nanorobotic vascular plasmatic zone locomotion (Section 9.4.2.6). Studies of macrophage particle-ingestion kinetics show that the number of particles ingested by each phagocytic cell may rise tenfold as the local particle concentration rises from 5 particles per cell to 150 particles per cell.[1074]

From these crude estimates — which neglect the effects of variable blood flow rates (Figure 8.30), large-vessel turbulence (Section 9.2.5), and other factors — it becomes apparent that virtually every medical nanorobot placed inside the human body will physically encounter phagocytic cells many times during its mission. Thus all nanorobots that are of a size capable of ingestion by phagocytic cells

must incorporate physical mechanisms and operational protocols for avoiding and escaping from phagocytes.[26,27] Engulfment may require from many seconds to many minutes to go to completion (Section 15.4.3.1), depending upon the size of the particle to be internalized, so medical nanorobots should have plenty of time to detect, and to actively prevent, this process.*

The basic strategy is first to avoid phagocytic contact (Section 15.4.3.6.1), recognition (Section 15.4.3.6.2), or binding and activation (Section 15.4.3.6.3), and secondly, if this fails, then to inhibit phagocytic engulfment (Section 15.4.3.6.4) or enclosure and scission (Section 15.4.3.6.5) of the phagosome. If trapped, the medical nanorobot can induce exocytosis of the phagosomal vacuole in which it is lodged (Section 15.4.3.6.6) or inhibit both phagolysosomal fusion (Section 15.4.3.6.7) and phagosome metabolism (Section 15.4.3.6.8). In rare circumstances, it may be necessary to kill the phagocyte (Section 15.4.3.6.9) or to blockade the entire phagocytic system (Section 15.4.3.6.10).

Of course, the most direct approach for a fully-functional medical nanorobot is to employ its motility mechanisms to locomote out of, or away from, the phagocytic cell that is attempting to engulf it. This may involve reverse cytopenetration (Section 9.4.5), which must be done cautiously (e.g., the rapid exit of nonenveloped viruses from cells can be cytotoxic[5356]).

It is possible that frustrated phagocytosis may induce a localized compensatory granulomatous reaction. Medical nanorobots therefore may also need to employ simple but active defensive strategies to forestall granuloma formation (Section 15.4.3.5).

15.4.3.6.1 Avoid Phagocytic Contact

One simple avoidance method employed by a few pathogens that may occasionally be practical for medical nanorobots is to confine all activities to regions of the human body that are inaccessible to phagocytes. For example, certain internal tissues such as the lumens of glands, the urinary bladder and kidney tubules, and various surface tissues such as the skin are not regularly patrolled by phagocytes.[3302] The heart and muscle tissues also are relatively macrophage-poor.[2854]

If reliable methods can be found for the remote (noncontact) detection of nearby phagocytes, akin to the detectability of bacterial metabolic chemical plumes (Section 8.4.3), then most motile nanorobots should also be able to outrun any "pursuing" phagocytes. For example, activated phagocytes emit various telltale substances[3227] such as cytokines,[3228-3234] enzymes,[3235-3237] histamine,[3238] taurine,[3239] and so forth. Lipoxins[3240] recruit healthy macrophages to phagocytose apoptotic neutrophils, another cautionary chemical plume to avoid. Of course, nanorobots must be able to distinguish all these emissions locally from background concentrations normally present.

If remote phagocyte detection methods** cannot be made reliable, then nonmotile nanorobots must employ contact avoidance techniques. One potentially useful approach is to make use of the natural mediators of cellular chemotaxis (movement along a spatial gradient or directed cell locomotion) and chemokinesis (general random movement or nondirected cell locomotion).[3241,3242] Specific chemicals are known to be chemorepellents, chemotaxis antagonists, chemotactic factor enzymes or antibodies, or negative chemokinesis agents for various cell types. Alternatively, emission of decoy chemoattractants followed by a quick course change by nanorobots could also frustrate phagocytic pursuit.

Repelling pathogens from normal cells is of great medical interest, so it is not surprising that a great deal of research has been done on inducing negative chemotaxis in pathogenic microbes, which we shall now briefly summarize. Among the bacteria, *E. coli* moves away from chemorepellent molecules produced by stimulated phagocytic leukocytes including peroxide, hypochlorite, and N-chlorotaurine.[3245] Chemorepellents indole and benzoate induce motor-direction switching,[3246] and lipophilic weak acids, decreases in extracellular pH, and nigericin also induce chemorepellent response.[3275] Short-chain alcohols or DMSO are chemorepellents for the Gram-negative bacterium *Myxococcus xanthus*,[3247] and phenol is a chemorepellent for the flagellate bacterium *Vibrio alginolyticus*.[3248] Known chemorepellents for the bacterium *Bacillus subtilis* include chlorpromazine (a CNS depressant), local anesthetics, and tetraphenylboron (a lipophilic anion).[3249] Of course, some of these substances are toxic to human cells and thus would not be appropriate chemorepellent molecules for medical nanorobots.

Among the protozoans, *Trichomonas vaginalis* exhibits negative chemotaxis to peroxide,[3250] with significant chemorepulsion by the spermicide Nonoxynol-9 and by nitroimidazoles such as metronidazole.[3251] Some chemorepulsion has also been seen in response to the antifungal imidazoles such as ketoconazole and miconazole.[3251] Lysozyme is a chemorepellent for *Paramecia* at 0.5-1.0 μM[3252,3253] and also for the unicellular eukaryotic ciliated protozoan *Tetrahymena thermophila*.[3254] Pituitary adenylate cyclase activating peptide (PACAP-38) is a peptide hormone chemorepellent for *Tetrahymena* with an EC50 at 10 nM concentration,[3253,3255] and leukocyte N-t-BOC-Norleucine-Leu-Phe (maximized at ~1 pM) is also chemorepulsive to *Tetrahymena*.[3256] Other nontoxic chemorepellents to *Paramecia*, effective in nM to μM concentrations, include GTP, the oxidants NBT and cytochrome c, the secretagogues alcian blue and AED, and the dye cibacron blue;[3253] all but AED and cytochrome c are chemorepulsive to *Tetrahymena*.[3253]

Chemorepellents are known for neural cells and include semaphorins,[3257-3264] netrins,[3263-3266] slit ligand,[3267,3268] and other neural factors.[3269,3270] Chemotaxis of murine spleen cells was decreased in the presence of the lipoxygenase inhibitors azelastine and ketotifen.[3271] Interestingly, negative necrotaxis (movement away from dead cells[3272-3275]) has been observed in the motile unicellular green algae *Euglena gracilis*.[3275] The colorless cryptomonad *Chilomonas paramecium* and the ciliate *Tetrahymena pyriformis* exhibit negative necrotaxis following lysis of same-species cells or of *Euglena* cells, and the cellular content of *Euglena* lysed by laser irradiation heating or by mechanical means acts as a chemorepellent to intact *Euglena* cells.[3275]

What about chemorepellents for phagocytes? Neutrophils can respond to spatial concentration gradients as small as 1%,[2870] and some research has been done on inhibiting chemotaxis in phagocytic cells. For example, monocyte migratory inhibition factor (MIF)[3276] inhibits macrophage migration, with a maximum inhibitory effect at 1 ng/ml for both unchallenged and particle-challenged macrophages.[3276,3277] Human alveolar macrophages can release a

** Detection by a medical nanorobot that it is being engulfed by a phagocyte may be accomplished using (1) hull-mounted chemotactic sensor pads equipped with artificial binding sites that are specific to phagocyte coat molecules, (2) continuous monitoring of the flow rates of nanorobot nutrient ingestion or waste ejection mechanisms (e.g., blocked glucose or 0_2 import), (3) acoustic techniques (e.g., Section 4.8.2), (4) direct measurement of mechanical forces on the hull, or (5) various other means.*

*** Interestingly, it should be possible to detect from the outside of a phagocytic cell that the cell has already ingested even a chemically inert nanorobot. For example, the decrease in capacitance of a cell that has ingested latex particles has been measured experimentally — a change of -250 fF/particle for 0.8-micron latex beads and -480 fF/particle for 3.2-micron beads.[3243] Monocytes that have ingested latex microspheres also display different surface markers.[3244]*

noncytotoxic factor that inhibits neutrophil chemotaxis and random migration.[3278] Excess zinc immobilizes macrophages,[1841] and mononuclear cells cultured from hyperimmunoglobulin-E (HIE) patients produced a ~61 kD protein factor that nontoxically inhibited normal neutrophil and monocyte chemotaxis[3279] while serum from those patients contained a 30-40 kD inhibitor of PMN and monocyte chemotaxis.[3280] A heat-stable inhibitor of neutrophil chemotaxis was demonstrated but not chemically isolated in 1975,[3281] and it is now known that phospholipase A2 inhibitors[3282] and a ubiquitin-like peptide[3283] inhibit PMN chemotaxis. Lymphocyte-specific protein 1 (renamed leukocyte-specific protein 1 or LSP1) is a negative regulator of neutrophil chemotaxis.[3284] Polyamines such as putrescine at 1 mM and spermidine at 0.1-0.5 mM inhibit chemotaxis (but not phagocytosis or engulfment) by PMNs in vitro.[3285] PMN locomotion is also inhibited by diclofenac sodium, a nonsteroidal anti-inflammatory agent, at concentrations below 10 μg/ml,[3241] and eicosapentaenoic acid somewhat rigidifies the plasma membrane of human neutrophils, leading to reduced chemotaxis.[3286] Chemotaxis of PMNs is suppressed with IV concentrations of gamma globulin >~3.0 mg/ml, although adhesiveness to microbes is simultaneously enhanced.[3287]

Much phagocyte chemorepellent research occurs in the context of elucidating bacterial avoidance strategies (such as might be mimicked by medical nanorobots). Some bacteria or their products inhibit phagocyte chemotaxis. For example, Streptococcal streptolysin O (which also kills phagocytes) is a true chemotactic repellent,[3302,3288] even in very low concentrations. *Staphylococcus aureus* produces toxins that inhibit the movement of phagocytes;[3289] granulocytes are almost immobilized when administered 12 μg/ml of purified *S. aureus* lipase.[3290] Pertussis toxin, produced by the bacterium *Bordetella pertussis*, inhibits chemotaxis of neutrophils and other phagocytes;[3291] a PMN-inhibitory factor (PIF) extracted from *B. pertussis* cells shows little cytotoxicity and inhibits chemotaxis of PMNs.[3291] Fractions of *Mycobacterium tuberculosis* inhibit leukocyte migration.[3302] The *Clostridium perfringens* phi toxin inhibits neutrophil chemotaxis,[3302] and other "specific antigen" can suppress basophil chemotaxis.[3292] Phagocyte chemotaxis is generally reduced by antibiotics such as cefotaxime, rifampin, and teicoplanin.[3293] Rifampin and tetracyclines inhibit granulocyte chemotactic activity.[3294] Leukocyte, lymphocyte and monocyte chemotaxis is inhibited by methylprednisolone and azathioprine, whereas only lymphocytes are chemotactically inhibited by cyclosporine.[3295]

Phagocyte chemoattractants that serve specific signaling purposes can be counteracted by specific inhibitors. For example:

1. Formyl peptides such as fMLP (n-formyl Met-Leu-Phe) are commonly produced by bacteria and thus serve as neutrophil chemoattractants. Numerous inhibitors of fMLP chemoattraction are known: (a) recombinant human tumor necrosis factor-alpha suppresses PMN chemotaxis toward fMLP by 80%;[3296] (b) uteroglobin (a steroid-dependent secretory protein) inhibits human phagocyte chemotaxis in response to formyl peptide attractants with half-maximal inhibition at 1.2 μM;[3297] (c) monoclonal antibody to the alpha chain of the CD11b/CD18 complex inhibits PMN chemotactic response to fMLP;[3296] (d) anti-integrin-associated protein antibodies inhibit phagocyte chemotaxis in PMN and monocytes;[3298] (e) synthetic cannabinoid CP55,940 induces significant inhibition of both chemokinesis and fMLP-induced chemotaxis in rat peritoneal macrophages (typical dose ~0.4 mg/kg);[3299] and (f) human recombinant granulocyte-macrophage colony-stimulating factor inhibits human neutrophil chemotaxis towards both fMLP and the complement split product C5a, without itself having any chemotactic or chemokinetic activity.[3300]
2. Complement factor C5a (Section 15.2.3.2) enhances chemotaxis, but inhibitors are known. For example, C5a-mediated granulocyte migration towards *Streptococcus pyogenes* is inhibited by solubilized fragments of C5a peptidase,[3306] which is released by a cysteine proteinase produced by the bacterium.[3305-3307] Also, a new complement receptor antagonist (the cyclic peptide Phe-[Orn-Pro-D-Cyclohexylalanine-Trp-Arg])[3312] inhibits C5a-induced neutrophil chemotaxis.
3. Sense-antisense methodology has been used to design novel complementary peptides as inhibitors of N-acetyl-PGP neutrophil chemoattractant.[3313]
4. Chemotaxis by human neutrophils toward several common chemoattractants was inhibited by 80-95%, maximally at a concentration of ~50 μM of the protein kinase inhibitor 1-(5-isoquinolinesulfonyl) piperazine, without affecting the random migration of the neutrophils.[3314]
5. Chemokine-induced chemotaxis was generally inhibited in monkey leukocytes in the presence of mu-opioid receptor agonists such as morphine, DAMGO, methadone, and endomorphine.[3315]
6. Vasoactive intestinal polypeptide (VIP) inhibited alveolar macrophage chemotaxis to endotoxin-activated rat serum, with maximum inhibition of 46% at 0.1 μM concentration.[3316]
7. Various bacterial endotoxins inhibited neutrophil chemotaxis to chemokine IL-8 without themselves being chemotactic for neutrophils,[4607] and leukocyte migration was inhibited by a staphylococcal aggressin.[3587]
8. A specific chemoattractant for neutrophils was completely blocked in vitro, and 40% blocked in vivo, using an antagonist to the chemoattractant receptor; the antagonist itself had no chemotactic activity.[3318]
9. Gastrin-17 and gastrin-34, maximally at 0.1 nM, inhibit cell mobility in human peripheral blood neutrophils.[3319] The inhibitory effect of gastrin is similar to that obtained with EGTA, a well-known calcium chelating compound.

General-purpose chemoattractant inhibitors also are known or possible. For instance, α1-proteinase inhibitor induces chemotaxis and chemokinesis at low concentrations of 0.02-2 mg/ml (normal alveolar surface-fluid concentrations in the lung) but inhibits chemotaxis of PMNs to known chemoattractants, at higher concentrations of 2-10 mg/ml (corresponding to inflammatory blood levels).[3242] And semaphorins, originally described as neuronal chemorepellents, have now been identified in the immune system.[3320] (Human CD100 is a leukocyte semaphorin,[3320,3321] although as of this writing no chemorepulsive activity has been experimentally confirmed for CD100.) Semaphorins are also found on the surfaces of murine lymphocytes,[3322] and may be present on human lymphocyte surfaces[3323] and on human monocytes,[3324] though again there is as yet no confirmed evidence of chemorepulsive activity. It is important to note that these chemotactic inhibitors may have significant effects on other cells and on cellular activity, thus precluding their use with nanorobots.

More research is required to select, or more likely to design, an ideal chemorepellent agent that might be secreted (perhaps at nM concentrations, ~1 molecule/micron^3 or less) by, or surface-tethered to, medical nanorobots seeking to avoid contact with phagocytes. Note that bioactive substances released locally by nanorobots can later be retrieved by similar means, thus avoiding nonlocal accumulations of these substances following nanomedical treatment.

15.4.3.6.2 Avoid Phagocytic Recognition

Chemorepulsion is adequate for a few devices on simple missions of limited duration (Section 15.4.3.6.1), but large numbers of medical nanorobots on longer or more complex missions will inevitably come into physical contact with many phagocytes. The least disruption to normal immune processes is achieved if the nanorobot surface can deny recognition to the inquiring phagocyte at the moment of physical contact. Surface-bound moieties are generally preferable to free-released molecules when large populations of in vivo nanorobots are involved. For example, each nanorobotic member of an internal communication network (Section 7.3.2), stationed perhaps ~100 microns apart throughout the tissues, must continuously avoid being ingested by passing phagocytes. Any approach that relies primarily on antiphagocytic chemical releases risks extinguishing all phagocytic activity throughout the body, potentially compromising the natural immune system.

In 2002, "long-circulating" phagocytosis-resistant particles,[1450,2487,2488,2491,5051-5057] stealth drug carriers[1480,1481,2682] and stealth nanoparticles[3325,3326,5058,5059] were the objects of active research. It was well known that nanoparticle adsorption and internalization by phagocytes could be inhibited by the presence of a coating of polysaccharide (e.g., heparin or dextran) chains in a brush-like configuration,[2490,3325] or by very hydrophilic coatings (Section 15.2.2.1). Low phagocytic uptake can be achieved using a surface concentration of 2-5% by weight of PEG. This gives efficient steric stabilization (e.g., a distance of ~1.5 nm between two adjacent terminally-attached PEG chains in the covering brush[3326]) and avoids uptake by PMN cells.[3326] Experiments by Illum, Davis, et al[2682,3003] suggest that polystyrene particles sterically stabilized with adsorbed poloxamer polymer could achieve an extrapolated zero phagocytic uptake using a ~10 nm thick coating on 60 nm diameter particles or a ~23 nm thick coating for 5.25-micron diameter particles, thus eliminating nonspecific phagocytosis. Another study[421] found that pegylated sheep RBCs were ineffectively phagocytosed by human monocytes, unlike untreated sheep RBCs. Phagocytosis of polystyrene beads (as measured by cellular oxygen consumption) appears strongly dependent on surface potential and thus upon fixed surface charge,[3327] and surface charge heterogeneity across domains as small as 1-4 microns can greatly affect phagocytic ability.[3328]

Rather than coatings which phagocytes cannot recognize at all, medical nanorobots alternatively could carry surfaces that phagocytes will recognize as "self." For example, coatings that mimic natural immune-privileged cells (Section 15.2.3.5) could be used. Nanorobot exteriors could be covalently bound with essential erythrocyte coat components — a simulated RBC surface could be useful in the bloodstream, though it might provoke a response in the tissues. Similarly, immune-blind fibroblast-like surface might be useful especially in the tissues, and even in blood — while bloodborne fibroblast lysate does elicit a response,[6250] some fibroblasts may originate from peripheral blood cells[6251] called fibrocytes[6252] which have been observed to differentiate into fibroblasts,[6253] and bone marrow-derived fibroblast CFUs are also observed in blood.[6254] A metamorphic surface that alternated between these two displays, depending upon location in the body, might be feasible (Section 5.3.6). But a simulated neutrophil or monocyte surface would be better, since these cells normally migrate from blood to tissues, hence the immune system expects to see these surfaces virtually everywhere. Lymphocytes are likewise normally present in both blood and tissues, and are also adept at passing through the endothelial lining, the lymphatic processes, and the lymph nodes without being detained or trapped, eventually returning to the arterial circulation.[234] The ideal solution may be for the medical nanorobot to display a specific designed set of self-markers at its surface. These markers might include moieties such as CD47, aka. integrin associated protein or IAP. CD47 is a surface protein present on almost every cell type that provides an explicit phagocytic inhibitor signal to NK cells and to macrophages.[3329]

Microbial pathogens have employed a similar strategy to create antiphagocytic surfaces that avoid provoking an overwhelming inflammatory response, thus preventing the host from focusing the phagocytic defenses.[3302] Enveloped viruses and some bacterial pathogens can cover their external cell surface with components that are seen as "self" by the host's phagocytes and immune system, a strategy that hides the true antigenic surface (Section 15.2.3.6). Phagocytes then cannot recognize the bacterium upon contact and the possibility of opsonization by antibodies to enhance phagocytosis is minimized.[3302]

For example, Group A streptococci can synthesize a capsule composed of hyaluronic acid, the "ground substance" (tissue cement) found in human connective tissue.[2335,3302,3307-3309] The streptococcal hyaluronic acid capsule is nonantigenic and thus very effective in preventing attachment of the organism to the macrophage.[3330] Additionally, the cytoplasmic membrane of *Streptococcus pyogenes* contains antigens similar to those found on human cardiac,[3311] skeletal[3311] and smooth muscle cells, on heart valve fibroblasts, and in neuronal tissues, resulting in molecular mimicry and an immune tolerance response by the host.[3309-3311] Pathogenic *Staphylococcus aureus* produces cell-bound coagulase which clots fibrin on the bacterial surface;[1723-1727,3302] the syphilitic agent *Treponema pallidum* binds human fibronectin to its surface;[1731,3302] and a variety of bacteria cause meningitis while avoiding phagocytosis either (1) by preventing deposition of complement by sialic acid on the surface, or (2) by modification of lipopolysaccharide (LPS)[3307] (to which the immune system is unusually sensitive). Another example of antiphagocytic surfaces is presented by *Haemophilus influenza*, which expresses a mucoid polysaccharide capsule that prevents digestion by host phagocytes.[3304] A few strains resist opsonization and have become serum resistant by modifying their LPS O-antigen side chains, rendering them "invisible" to host immune defenses.[3304]

Bacteriophages, viruses first employed against bacteria by d'Herelle in 1922,[3331] are self-replicating pharmaceutical agents[3344] that can grow inside of and destroy pathogenic bacteria when injected into infected hosts during "phage therapy".[3331-3344,5758-5763,6211] Phage biocompatibility is being investigated.[5760] Even in the absence of an immune response, intravenous therapeutic phage particles are rapidly eliminated from circulation by the RES, largely by sequestration in the spleen.[3333] But Merril et al[3338] found that splenic capture could be greatly eliminated by the serial passage of phage through the circulations of mice to isolate mutants that resist sequestration. This selection process resulted in the modification of the nature of the phage surface proteins, via a double-charge change from acidic to basic, which is achieved by replacing glutamic acid (- charge) with lysine (+ charge) at the solvent-exposed surface of the phage virion. The mutant virions display 13,000-fold to 16,000-fold greater capacity to evade RES entrapment 24 hours post-injection as compared to the original phage.[3338] Similar surface modifications can be designed for use on medical nanorobots.

15.4.3.6.3 Avoid Phagocytic Binding and Activation

Once physical contact with a phagocyte has occurred, particle binding to specific cell surface receptors is the first step in the phagocytosis of a medical nanorobot. Receptors able to mediate

phagocytosis are expressed almost exclusively in neutrophils, monocytes and macrophages, and receptor clustering is thought to occur upon particle binding which in turn generates a phagocytic signal, activating the phagocytic process.[3345]

Several pathways of phagocytic signal transduction have been identified,[3345] including the activation of tyrosine kinases or serine/threonine kinase C, leading to phosphorylation of the receptors and other proteins which are recruited at the sites of phagocytosis. Monomeric GTPases of the Rho and ARF families which are engaged downstream of activated receptors, in cooperation with phosphatidylinositol 4-phosphate 5-kinase and phosphatidylinositol 3-kinase lipid modifying enzymes, can modulate locally the assembly of the submembranous actin filament system leading to particle internalization.[3345,5261] It may be possible for nanorobots to affirmatively influence, modulate, or even extinguish the phagocytic activation signal by physical, chemical, or other means, perhaps using GTPase or kinase inhibitors[3346-3353] such as genistein (50 μM),[3346,3352] herbimycin (17 μM),[3346] staurosporine and trifluoperazine.[3349] In many cases there are two or more pathways that must be simultaneously inhibited, although in a few cases these pathways may share a common inhibitor.[3348] For instance, CNI-1493 is a potent macrophage deactivator or "pacifier".[2593-2595]

Binding of particles to phagocytes may also be directly inhibited. Phagocytosis requires the internalization of a significant fraction of the plasma membrane, which results in the intracellular deposition of large particles.[3354] But this internalization does not diminish the number of receptors on the cell surface and has no effect on receptor-mediated uptake.[3354]

In the case of receptor-mediated phagocytic binding, dansylcadaverine, amantadine, and rimantadine induce inhibition of endocytosis of complement-coated zymosan particles by human peripheral PMN leukocytes. These drugs block receptor-mediated endocytosis, possibly by their actions on phospholipid metabolism[3355] or by covalent coupling to cellular membranes.[3356] Cell-bound or soluble protein A produced by *Staphylococcus aureus*[1728] attaches to the Fc region of IgG and blocks the cytophilic (cell-binding) domain of the antibody. Thus the ability of IgG to act as an opsonic factor is inhibited, and opsonin-mediated ingestion ("opsonophagocytosis"[3303]) of the bacterium is blocked.

In the case of nonreceptor phagocytic binding, medical nanorobots could emit or expose on their surfaces chemical surfactants which would repel the lipid bilayer wall, e.g., by reducing the nanorobot's coefficient of adhesion to very low or even to negative values (Section 9.2.3).

Many other substances that inhibit phagocytosis (keeping in mind the cross-talk between phagocytic receptors, the multiple signaling domains within these receptors, and the many downstream effector pathways leading to actin polymerization and particle internalization[3357]) could be further investigated for their suitability in this nanomedical context, including:

1. *Opioids and Anesthetics*. Chemokine-induced phagocytosis is inhibited in the presence of mu-opioid receptor agonists such as morphine, DAMGO, methadone, and endomorphine[3315] in murine macrophages[3358] and rat splenic macrophages.[3359] Lidocaine at 30 mM significantly inhibits phagocytosis of latex particles in bovine monocytes.[3360] The membrane-active drug procaine inhibits the phagocytosis of latex particles by normal monocytes and the proliferation of lymphocytes in an allogeneic mixed leukocyte culture.[3361] Finally, while the phagocytosis of inert latex particles by human blood monocytes is not affected by the presence of ethanol,[3362] the phagocytosis of opsonized red cells by Kupffer cells is slightly impaired by ethanol.[3363]
2. *Hormones*. Vasoactive intestinal polypeptide (VIP) inhibits alveolar macrophage phagocytosis of polystyrene beads, with maximum inhibition of 46% at 0.1 μM concentration.[3316] Dexamethasone inhibits phagocytosis by human trabecular meshwork (eye) cells in vitro, with polystyrene particle uptake reduced from 3.5 beads/cell to 1.5 beads/cell, a 57% reduction.[3364] Two cholecystokinin octapeptides (CCK-8s and CCK-8) significantly inhibit neutrophil ingestion of latex beads. This inhibitory effect is maximized at 0.1 nM concentration,[3365] and inhibition of neutrophil mobility and phagocytosis "could be carried out through an increase of the intracellular cAMP levels".[3365,3319] Gastrin-17 and gastrin-34, maximally at 0.1 nM, inhibit the ingestion of latex beads in human peripheral blood neutrophils.[3319] Prostaglandins also inhibit particle ingestion.[3366]
3. *Toxins*. Pertussis toxin decreases the phagocytosis of IgG-opsonized *Staphylococcus aureus* pathogens by human granulocytes.[3367] Many bacterial exotoxins that are adenylate cyclases such as anthrax toxin edema factor[3368] and pertussis toxin[3369] decrease phagocytic activity. The ability of rat alveolar macrophages to phagocytose *Saccharomyces cerevisiae* and *Staphylococcus aureus* microbes was significantly reduced in vitro in the presence of T-2 toxin exceeding ~0.1 μM concentration.[3370] Mycotoxins such as aflatoxin B1[3371] significantly impair Kupffer cell phagocytosis, although aflatoxin is a known genotoxin and thus would not be ideal in this application.
4. *Bacterial Factors and Enzymes*. PMN-inhibitory factor (PIF) extracted from *B. pertussis* cells showed little cytotoxicity and inhibited phagocytosis to opsonized targets by PMNs.[3291] Phagocytic activity of neutrophils was reduced by a staphylococcus aggressin,[3588] and extracellular slime produced by *Staphylococcus epidermidis* interferes with human neutrophil functions in vitro, including degranulation and phagocytosis.[3373] In the presence of 12 μg/ml of *S. aureus* lipase, almost no killing of the microbe by human granulocytes occurs, mostly due to a lack of bacterial uptake.[3290] YopH[3374] and other *Yersinia* Yop proteins[3375] inhibit the phagocytosis of *Yersinia enterocolitica* by human granulocytes[3374] and macrophages.[3375]
5. *Antibiotics*. Phagocytosis is diminished or suppressed by erythromycin, roxithromycin, cefotaxime, tetracyclines, ampicillin, gentamicin, and bacitracin.[3293,3294]
6. *Mechanical*. Colchicine (at 150 mg/kg) and cytochalasin B (at 0.15 mg/kg) greatly depress pulmonary macrophage endocytosis or "particle uptake" in hamsters,[3376] e.g., by inhibiting cytoskeletal actin microfilament polymerization. Cytochalasin B inhibits phagocytosis;[3366] Cytochalasin D, a drug that affects actin polymerization and particle internalization, also inhibits the binding stage of phagocytosis.[3388,3389] Eicosapentaenoic acid rigidifies the plasma membrane of human neutrophils, leading to reduced phagocytosis.[3286] Macroscale physical shock[3377,3378] or surgical manipulation[3379] can depress phagocytic function in Kupffer cells. A 5% cyclical strain applied to cultured peritoneal mouse macrophages at 1 Hz for 24-48 hours partially suppresses their phagocytosis of latex particles.[5331]
7. *Other*. Ammonium acetate reduces (in a concentration-dependent manner) the phagocytic uptake of mannosylated latex microspheres by human microglia and astroglioma cells[3380] — the threshold for action is >~2 mM for microglia.[3381] A variety of dissolved metal ions such as Ni^{++} and Cr^{+++} suppress phagocytic efficiency. For example, increasing Ni from 29 ppm to 58 ppm depresses phagocytic efficiency in cultured rabbit alveolar

macrophages by 78%,[234,3382] and $GdCl_3$ can prevent surface attachment of particles to Kupffer cells.[3383] However, such metal ions are probably genotoxic or cytotoxic at the concentrations necessary to suppress phagocytic efficiency. A heat-stable inhibitor of neutrophil phagocytosis has been demonstrated in sarcoma cells.[3281] Liposome particle uptake by liver endothelial and Kupffer cells is inhibited by poly(inosinic acid) and other anionic macromolecules.[3384] Kupffer cell phagocytic activity is also reduced by methylpalmitate[3385] and silica.[3386] Short-chain ceramides inhibit IgG-mediated phagocytosis by PMNs.[3387] The glycoprotein horseradish peroxidase (HRP) inhibits the binding stage of phagocytosis.[3388] Monoclonal IgM cold agglutinins (~1 mg/ml) impair various phagocytic functions of human phagocytes including adhesiveness, phagocytosis, phagocytic index and intracellular bactericidal activity of PMNs.[3390] Decreasing the pH of influent perfusate through liver RES (e.g., hepatic sinusoids) increases the uptake of carbon particles, so pH gradient across the liver lobule may be involved in the regulation of particle uptake at the sublobular level.[3391] Amantidine, an adamantane-based drug, weakly inhibits phagocytosis in PMNs.[5545] Phagocyte adhesion might also be reduced by using hydrophilic or anionic surfaces.[5507] Once again, it is important to note that many of these substances may have effects on other cells and cellular functions, suggesting caution when choosing a particular antiphagocytic substance for use in medical nanorobot designs.

Care must also be taken to avoid the use of nanorobot coatings which possess, or may induce, fusogenic conformations,[3392-3396] in which case specific fusogen inhibitors[3393-3398] might need to be simultaneously deployed.

15.4.3.6.4 Inhibit Phagocytic Engulfment

Even if a medical nanorobot has been recognized and has attached to the phagocyte outer surface (typically across a ~20 nm gap bridged by ~12 nm strands[3399]), the device can still prevent complete engulfment from taking place. Macrophages challenged with a particular type of target usually bind many more targets than they ingest.[3388] Fortunately, internalization is a relatively slow process and most particles that become bound to the phagocyte surface are not ingested.[3388] On rare occasions, phagocytosed particles are actually expelled.[2870,3400] Indeed, a recent study[5506] found that the homophilic ligation of CD31 (also known as platelet-endothelial cell adhesion molecule-1, or PECAM-1)[5764] on viable leukocytes promoted their detachment under low shear, leading to active repulsion of viable cells from macrophages, whereas such CD31-mediated detachment was disabled in apoptotic leukocytes, promoting capture and tethering, tight binding, and macrophage ingestion of dying cells. Hence CD31 is an example of a cell-surface molecule that promotes tethering of dying cells to phagocytes during apoptosis, but prevents phagocyte ingestion of closely apposed viable cells by transmitting "detachment" signals.[5506]

Phagocytosis is an uptake of large particles governed by the actin-based cytoskeleton. It is a dynamic process including actin polymerization around the particle for internalization, with phagosome maturation governed by a complex mix of proteins including actin, the Arp2/3 complex, Rho-family GTPases, filament-capping proteins, tropomyosin, Rho kinase and myosin II.[6062-6064] Complement-opsonized (CO) and antibody-opsonized (AO) particles are phagocytosed differently by macrophages[3401,3402] — CO particles sink into the cell, whereas AO particles are engulfed by lamellipodia that project from the cell surface. During the ingestion of CO particles, punctate structures rich in F-actin, vinculin, α-actinin, paxillin, and phosphotyrosine-containing proteins are distributed over the phagosome surface.[3402] These foci can be detected underneath bound CO particles within 30 seconds of cell activation, and their formation requires active protein kinase C. Complement receptor-mediated internalization requires intact microtubules and is accompanied by the accumulation of vesicles beneath the forming phagosome.[3402] By contrast, during the ingestion of AO particles (Fcgamma receptor mediated phagocytosis), all proteins are uniformly distributed on or near the phagosome surface. Ingestion of AO beads is blocked by tyrosine kinase inhibitors (e.g., which could be released from, or tethered to, medical nanorobots), whereas the phagocytosis of CO particles is not.[3402]

Phagocytic particle ingestion can require actin assembly and pseudopod extension, two cellular events that may coincide spatially and temporally but may use distinct signal transduction events or pathways.[3403] Medical nanorobots that have become bound to the extracellular phagocyte surface may attempt to inhibit either or both of these signal transduction pathways.

For example, during actin assembly, engagement of particle-bound immunoglobulin IgG ligands by receptors for the Fc portion of IgG results in receptor aggregation and recruitment of cytosolic tyrosine kinase, especially Syk.[3404] The onset of uptake is accompanied by tyrosine phosphorylation of several proteins, which persists for up to 3 minutes, is concentrated at phagocytic cups and nascent phagosomes, and is correlated with the accumulation of actin filaments.[3405] (Later, during phagosome maturation, tyrosine phosphorylated proteins and microfilaments disappear from the periphagosomal regions.[3405]) Phosphorylation of tyrosine residues occurs within immunoreceptor tyrosine activation motif (ITAM) consensus sequences found in FcgammaR subunits, which allows further recruitment and activation of Syk.[3404] Syk tyrosine kinase activity is required for FcgammaR-mediated actin assembly, which is controlled by several GTPases, including Rac1 and CDC42.[3404] Rac1 and CDC42 (two Rho proteins involved in the signal transduction through the FcRs) are required (1) to coordinate actin filament organization and membrane extension to form phagocytic cups, (2) to allow particle internalization during FcR-mediated phagocytosis, and (3) to enable the phosphotyrosine dephosphorylation required for particle internalization.[3406]

Actin assembly can be inhibited by *Clostridium difficile* toxin B, which is a general inhibitor of Rho GTP-binding proteins.[3406] Inhibition of Rac1 or CDC42 severely inhibits particle internalization but not F-actin accumulation.[3406] In laboratory tests with cells, inhibition (via knockout of gene expression in a mutant line) of CDC42 function results in pedestal-like structures with foreign particles at their tips on the phagocyte surface. Inhibition of Rac1 results in particles bound at the surface that are enclosed within thin unfused membrane protrusions.[3406] This demonstrates that Rac1 and CDC42 have distinct functions and may act cooperatively in the assembly of the phagocytic cup.[3406] Phagocytic cup closure and particle internalization has also been blocked when phosphotyrosine dephosphorylation is inhibited by treatment of the phagocytic cells with phenylarsine oxide, an inhibitor of protein phosphotyrosine phosphatases.[3406] Ceramide also inhibits tyrosine phosphorylation in human neutrophils.[3407]

During pseudopod extension, phosphatidylinositol 3-kinase (PI3K) is recruited to the plasma membrane, triggering exocytosis from an internal membrane source as is required for pseudopod extension.[3404] (Macrophage spreading on opsonized surface is accompanied by insertion into the plasma membrane of new membrane from intracellular sources.[3403]) One or more isoforms of PI3K are required for maximal pseudopod extension, though not for phagocytosis per se. PI3K is required for coordinating exocytic membrane insertion and pseudopod extension.[3403]

Pseudopod extension may be partially inhibited using wortmannin (WM) or LY294002, which are two inhibitors of PI3K.[3403] Both of these specifically inhibit phagocytosis without inhibiting Fcgamma receptor-directed actin polymerization, by preventing maximal pseudopod extension. Decreasing the size of test beads, and hence the size of pseudopod extension required for particle engulfment, de-inhibited phagocytosis (in presence of these inhibitors) by up to 80% at the very smallest submicron particle sizes. For larger (nanorobot-sized) foreign particles, phagocytosis is blocked before phagosomal closure. Both compounds also inhibit macrophage spreading on opsonized surfaces (e.g., on substrate-bound IgG).[3403]

Amphiphysin II associates with early phagosomes in macrophages and participates in receptor-mediated endocytosis by recruiting the GTPase dynamin to the nascent endosome. There is a signaling cascade in which PI3K is required to recruit amphiphysin II to the phagosome, after which the amphiphysin II in turn recruits dynamin to the phagosome.[3408] A modified amphiphysin II molecule with its dynamin-binding site ablated away inhibits phagocytosis at the stage of membrane extension around the bound foreign particles.[3408] Both phenylbutazone and chloramphenicol also have shown an inhibitory effect on the engulfment stage of phagocytosis of yeast particles by cultured human monocytes.[3409] Of course, it will be important to identify substances that produce minimal effects on other cells or cellular functions.

As might be expected, bacteria already employ a wide variety of strategies to avoid engulfment when physically contacted by host phagocytes.[3302] Some of these strategies could in principle be mimicked by medical nanorobots. Most commonly, many important pathogenic bacteria bear substances on their surfaces that inhibit phagocytic adsorption or engulfment. Resistance to phagocytic ingestion is usually due to an antiphagocytic component of the bacterial cell surface, such as:

1. *Cell Wall Substances* — polysaccharide surface slime (alginate slime[3410] and biofilm polymers) produced by *Pseudomonas aeruginosa*;[3302,3411] O antigen associated with LPS of *E. coli* (smooth strains);[3302] and K antigen (acidic polysaccharides) of *E. coli* or the analogous Vi (K) antigen (microcapsule) of *Salmonella typhi*.[3302]

2. *Fimbriae and M Protein* — fimbriae in *E. coli*,[3303] and M protein and fimbriae of Group A streptococci.[3302,3303] For example, *Streptococcus pyogenes* has M protein, a fibrillar surface protein whose distal end bears a negative charge that interferes with phagocytosis.[3307] *Enterococci* also have antiphagocytic surface proteins[3301] such as M protein.

3. *Capsules* — polysaccharide capsules of *S. pneumoniae* (unless antibody is present), *Treponema pallidum, Klebsiella pneumoniae, Bacteroides fragilis,* and *Clostridium perfringens*, and the *Enterococci* inhibit engulfment.[3301-3303] *Haemophilus influenzae* expresses a mucoid polysaccharide capsule of thickness ~1 microbial diameter which prevents digestion by host phagocytes, although many of these bacteria remain susceptible to opsonization.[3302-3304] The protein capsule on cell surface of *Yersinia pestis* resists engulfment.[3302]

Macrophages can also bind and engulf a variety of particles in the absence of specific opsonins, a process known as nonspecific phagocytosis,[3412] nonopsonic phagocytosis,[3413] or opsonin-independent phagocytosis.[3414] Polystyrene microspheres are often used to demonstrate this.[3414] For instance, during patocytosis (Section 15.4.3.1) of hydrophobic >0.5-micron particles by phagocytes, actin-independent capping of hydrophobic polystyrene microspheres on the plasma membrane precedes actin-dependent uptake of the microspheres into the surface-connected compartments.[2887] Microsphere transport from plasma membrane invaginations into spaces created by unfolding stacks of internal microvilli are inhibited by administering primaquine.[2887] Studies of non-specific endocytosis and binding of liposomes by mouse peritoneal macrophages also found that particle internalization declined markedly after anchorage of the cells to polystyrene substrate.[3415] Inhibitors are potentially available to medical nanorobots to halt these processes too. For example, staurosporine selectively inhibits nonspecific phagocytosis while having no effect on receptor-mediated phagocytosis.[3412]

15.4.3.6.5 Inhibit Enclosure and Scission

Assuming that a medical nanorobot has become partially or wholly engulfed by a phagocyte, it is likely that the vacuole can still be prevented from pinching off and separating into a free intracellular phagosome containing the nanorobot (i.e., enclosure and scission).

Cells normally internalize soluble ligands or small particles via endocytosis, and large particles via actin-based phagocytosis. The dynamin family of GTPases[3416,3417] mediates the membrane destabilization, constriction, fission (scission) and trafficking of endocytic vesicles from the plasma membrane, but dynamin-2 also has a role in phagocytosis by macrophages.[3418] Experiments reveal that early phagosomes (vacuoles) are enriched in dynamin-2, and inactive mutant versions of this molecule, if expressed, inhibit particle internalization at the stage of membrane extension around the particle.[3418] This arrest of phagocytosis resembles that seen with PI3K inhibitors, preventing the recruitment of dynamin to the site of particle binding. Dynamin is a microtubule-binding enzyme with a microtubule-activated GTPase activity; phosphorylation engages its activity.[3419] Dynamin can interact with the actin cytoskeleton to regulate actin reorganization and subsequently cell shape.[3420]

Observations suggest that dynamin mediates scission from the plasma membrane of both clathrin-coated pits and caveolae during distinct endocytic processes.[3421] For example, dynamin-1 is a 100 kD GTPase involved in scission of endocytic vesicles from the plasma membrane. It is present in solution as tetramer. Following its recruitment to coated pits, dynamin-1 undergoes self-assembly into higher-order oligomers that resemble collars around the necks of nascent coated buds. GTPase hydrolysis by dynamin in these collars is thought to accompany the pinching off of endocytic vesicles.[3422] Dynamin may use GTPase hydrolysis physically to drive vesiculation, or may act as a classical G protein switch, or both.[3423] Laboratory work shows that purified dynamin readily self-assembles into rings or spirals, suggesting that it probably wraps around the necks of budding vesicles and squeezes, pinching them off[3424-3427] — in other words, the large GTPase dynamin is a mechanoenzyme.[3428] Different dynamin isoforms may be localized to distinct cellular compartments but may provide similar scission functions during the biogenesis of nascent cytoplasmic vesicles.[3421] Once again, inhibitory tools that might be employed by medical nanorobots are potentially available. For example, anti-dynamin antibodies have been used to specifically inhibit dynamin function in cultured mammalian epithelial cells, inhibiting cellular uptake of external particles in these cells.[3421] These antibodies also have been used to inhibit clathrin-mediated endocytosis in hepatocytes.[3429] Ca^{++} inhibits both dynamin I GTPase[3430] and dynamin II GTPase[3431] and may also serve as a vesiculation inhibitor for engulfed medical nanorobots. Alternatively, butanedione monoxime,

a class II myosin inhibitor, has been shown to prevent the purse-string-like contraction that closes phagosomes without inhibiting the initial pseudopod extension.[3432]

Another approach for trapped but not yet enclosed medical nanorobots relies upon the observation[3433] that internalization of encapsulated particles via endocytosis produces a net increase in the total cell surface area of the ingesting leukocytes. This suggests that exocytosis is occurring simultaneously.[3433] If the phagocyte's ability to recycle plasma membrane to the cell surface is interrupted, endocytosis eventually halts. Accordingly, in one experiment,[3433] selective cleavage (disablement) of components of the secretory machinery using bacterial neurotoxins induced a pronounced inhibition of phagocytosis. Unlike many other cell types, macrophages lack a morphologically distinct pericentriolar recycling compartment but instead have an extensive network of transferrin receptor-positive tubules and vesicles that participate in recycling.[3434] Transferrin is recycled rapidly: the GTPase Rab11 participates in the recruitment of a rapidly mobilizable endocytic compartment to the macrophage cell surface by mediating the transferrin efflux.[3434] Chemical inhibition of Rab11[3435] or of phospholipid synthesis[3436] could therefore slow this efflux, ultimately restricting the turnover of phagocyte plasma membrane, which could greatly slow the rate of particle internalization and give the trapped nanorobot more time to escape.

15.4.3.6.6 Induce Exocytosis of Phagosomal Vacuole

Consider a medical nanorobot that has become trapped inside an intracellular vacuole or phagosome that has pinched off and now resides entirely within the intracellular space of the phagocytic cell. Without leaving the phagosome and prior to its merger with a lysosome, the nanorobot may escape by redirecting the phagosomal transport destination back to the plasma membrane, where the nanorobot can then be exocytosed, whole, from the cell.

To accomplish this, existing centripetal (endocytic) targeting proteins first must be removed from the vacuolar wall, and then new centrifugal (exocytic) targeting proteins must be embedded on the external phagosomal surface to redirect the vacuole back to the plasma membrane. One example of plasma membrane targeting (i.e., regulated exocytosis,[3437-3440] reverse endocytosis,[3441] or related processes[3442]) is the synaptic vesicle targeting protein synaptobrevin (VAMP-1 and -2). This protein binds only to the neuron-specific plasma membrane proteins syntaxin 1A and 1B, thus ensuring proper vesicle docking and fusion exclusively to the neuron plasma membrane from intracellular origins.[3443] (Fusion of two distinct lipid bilayers is energetically unfavorable in the absence of such specialized targeting proteins.) Regulated exocytosis is well known in neurons and in endocrine and exocrine cells,[3438] and even in conventional lysosomes in response to rises in the intracellular free Ca^{++} concentration.[3444] Similar centrifugal transport pathways have been identified in phagocytes,[3372,3445] wherein intracellular vesicles are targeted exclusively to plasma membrane surface receptors (e.g., CD11b, CD18).[3372] Other possible mediators of secretory vesicle regulated exocytosis[3446-3448] are being investigated. Vacuolar retargeting strategies are employed by bacteria, as for example *Legionella pneumophila*, which, once internalized into a vacuole, evidently redirects its transport to the endoplasmic reticulum.[3389] The recently-discovered actin-based motility of bead-containing macrophage phagosomes[6064] might also be purposefully manipulated. More research is required to identify specific proteins and mechanisms to aid nanorobots in escaping phagosomes.

Inert phagocytosed particles can be rapidly exocytosed by phagocytes. In one experiment,[3449] ~50% of an ingested load of inert oil emulsion particles was released from rabbit neutrophils in 2400 seconds at 37 °C. Electron microscopy confirmed an exocytic release process. Particles were extruded through a network of processes often accompanied by membranous vesicles. Neutrophils undergoing particle exocytosis remained intact. By feeding the cells differently labeled particles, the investigators showed that phagocytosis and exocytosis of the same particles can occur concurrently, and that particle ingestion can accelerate particle release.[3449]

One less-well-targeted approach is for medical nanorobots to induce their own degranulation from the phagocyte by releasing secretagogues for that cell. For example, IgA and granulocyte-macrophage colony-stimulating factor (GM-CSF) are the two most potent secretagogues for human eosinophils, and IL-5, IL-3, TNFα and RANTES also induce eosinophil degranulation.[3450,3455] C3b, IL-1, IL-6, fMLP, the divalent calcium ionophore A23187, and GM-CSF are secretagogues for human neutrophils.[3451-3455] Elevated levels of intracellular free Ca^{++} can stimulate exocytosis, and can also inhibit endocytosis that has been evoked by dynamin I vesiculation, dynamin II GTPase activity, or receptor mediation.[3431]

It is also possible that cell eversion and extrusion of contents might be triggered chemically. For instance, the nucleus of an oocyte can be ejected if the cell is treated with etoposide and cycloheximide (chemical enucleation).[3456-3458] Microtubule poisons such as colchicine, colcemid and vinblastine cause extrusion of cellular nuclei,[3459-3461] and EDDF is involved in erythroid cell denucleation.[3462] There are also a few older reports of nuclear extrusion in lymphocytes,[3463,3464] cell enucleation,[3465] extreme nuclear convolution[3466] and nuclear blebbing,[3467] though R. Bradbury notes that normal failures of the cell division process can result in the production of micro- or satellite- nuclei, which are not "normal" processes that can be biochemically invoked but rather are pathological situations that develop in pre-cancerous or cancerous cells. It's also important to note that the goal of nanorobot escape should not come at the cost of the destruction of the phagocyte.

More selective induction of localized non-nuclear cytoplasmic extrusions by medical nanorobots may be possible. Such controlled extrusions might be functionally similar to the production of lamellipodia or pseudopodia (Section 15.4.3.6.4) or a long list of related structures including giant granules;[3468] tubular vermipodia;[3469] cytoplasmic bulbous protrusions;[3470] hairy cell leukemic irregular cytoplasmic projections;[3471-3474] cytoplasmic membrane blebbing (zeiosis[3475]); and arborization during (1) apoptosis[3476] (whether chemically[3477-3482] or biologically[3483-3487] elicited), (2) cytotoxic T cell attack.,[3488] (3) viral budding,[3489-3491] (4) nonlethal bacterial challenge,[3492] (5) chemical induction,[3493-3497] (6) mechanical trauma,[3498,3499] (7) locomotion,[3500,3501] or (8) vesicular release.[3502,3503] Such extrusions would result in the ejection of a bleb of cytoplasm containing the trapped nanorobot into the extracellular space with relatively little loss of material, or diminution of viability, of the phagocytic cell. A similar process of extrusion is employed by the intracellular bacteria *Shigella* and *Listeria* (see below).

In some circumstances, efficiency may be gained if the medical nanorobot first escapes from the phagosome in which it is trapped — possibly via reverse cytopenetration (Section 9.4.5) — before pursuing its ultimate exit from the cell. Such escape is not difficult and has been mastered by many species of intracellular pathogens. For example, *Listeria monocytogenes* relies on several molecules for quick lysis of the phagosome — listeriolysin O (a pore-forming hemolysin toxin)[3504,3505] and two forms of phospholipase C.[3506,3507] *Listeria ivanovii* employs several phospholipases to similar effect.[3508]

Once free in the cytoplasm, *Listeria* induces its own movement via a remarkable process of host cell actin polymerization and formation of microfilaments within a comet-like tail[3509-3512] (Section 9.4.6). Another intracellular bacterium, *Shigella flexneri*, also lyses the phagosomal vacuole and escapes,[3513] then induces cytoskeletal actin polymerization for the purpose of intracellular movement[3514] and, eventually, cell-to-cell spreading.[3515] The bacterial factor used by *Shigella* to breach the vacuolar membrane is IpaB,[3513] one of the secreted invasin proteins it uses to invade cells.[3517-3519] *Rickettsia* also enters host cells inside phagosomes but are detected free in the cytoplasm a short time later,[3520] starting in as little as 30 seconds.[3302] In one experiment,[3521] half of the phagocytosed bacteria were freed from the phagosome after only 12 minutes. A bacterial enzyme, phospholipase A2, and other hemolysins and toxins seem to be responsible for dissolution of the phagosome membrane by *Rickettsia*.[3522,3523] The intracellular protozoan parasite *Trypanosoma cruzi* also can escape from phagocytic vacuoles into the cytoplasm,[3524,3525] assisted by a hemolysin[3527] and a phospholipase C.[3528] Experiments show that ~70% of the parasites are free, just 2 hours after infection.[3526]

Once the medical nanorobot is free in the cytosol, it has several options for final escape from the phagocyte. First, it can use presentation semaphores (Section 5.3.6) to display on its surface all necessary targeting proteins to allow it eventually to be naturally exocytosed from the cell. Second, the nanorobot, if still motile, can locomote (Section 9.4) to the cytosolic face of the plasma membrane, then directly undertake cytopenetration (Section 9.4.5), perhaps assisted by fusogens (Section 9.4.5.4) or membrane fluidizers such as n-butanol.[3296] Third, it can re-enter an intracellular vesicle already targeted for exocytosis and "ride" the vesicle out of the cell.

Once again, the bacteria have a lesson to teach. Usually when intracellular pathogens have actively replicated inside the host cell, the cell dies, often by lysis, releasing the pathogens extracellularly.[3389] However, a few intracellular bacteria that can quickly escape phagosomal confinement and enter the host cytosol can achieve cell-to-cell spreading without ever leaving the cytosolic compartments of adjacent cells. *Shigella* and *Listeria*, upon reaching the plasma membrane, induce the formation of plasma membrane protrusions that invaginate into the neighboring cell, resulting in the creation of a double-membraned vacuole containing the bacterium, whose walls are subsequently lysed, releasing the bacterium into the neighboring cell.[3389] *Shigella flexneri* requires the cell adhesion molecule E-cadherin during this process[3516] and other mediators are being studied intensively.[3515,3529] A medical nanorobot could use similar means to extrude itself into adjacent cells, or into the extracellular spaces, thus escaping the phagocyte.

15.4.3.6.7 Inhibit Phagolysosomal Fusion

Lysosomal fusion with phagosomes containing a trapped medical nanorobot — that is, the fusion of phagocytic lysosomes (granules) with the phagosome, forming a digestive phagolysosome — is not a direct threat to diamondoid nanorobot core integrity. However, digestive substances present in phagolysosomes could possibly alter the surface characteristics of nanorobots such as their "biocompatibility coatings," or could partially dissolve or digest semaphore display ligands, nanosensors, or exterior binding sites containing organic constituents. Thus it may sometimes be useful for nanorobots to directly modulate or control the phagolysosomal fusion process, which can occur in just 30 minutes following receptor-mediated uptake but may require hours (to complete phagolysosome formation) for other ingested particles such as latex beads.[2867]

Several bacteria survive while trapped in phagosomes by preventing phagolysosome formation.[3302] The simplest chemical that inhibits phagolysomal fusion appears to be ammonia (e.g., ammonium chloride).[3537] *Mycobacterium tuberculosis*[3530-3532] produces ammonia at high levels, thus interfering with phagolysosomal fusion[3533] and the saltatory movement of lysosomes.[3534] More recently, it has been found that the bacteria can recruit and retain TACO (tryptophane aspartate-containing coat protein) in the mycobacterial phagosome, preventing cargo delivery to lysosomes.[3535] It has also been proposed that the polyanionic nature of the cell wall of *M. tuberculosis*, containing sulfatides (anionic trehalose glycolipids[3536]) and sulfalipids,[3536,3541] could allow it to modify lysosomal membranes to inhibit phagosome-lysosome fusion in macrophages,[3536-3541] although this mechanism has been disputed.[3542] The microbe also may have cytolytic pore-forming ability,[3543] may inhibit complement-receptor Ca^{++} signaling,[3544] and may display selective inhibition of fusion only with proton-ATPase-containing lysosomal vesicles.[3545] *Salmonella* exhibits phagolysosomal fusion inhibition while also acquiring lysosomal membrane glycoproteins (lgp) to redirect fusion to lgp-rich compartments different from the classical mature lysosome.[3546] Cord factor,[3547] the adjuvant dimethyldioctadecylammonium bromide,[3548] the drug suramin,[3549] and an unknown component of *E. coli* cytoplasmic membrane[3550] are additional phagolysosomal fusion inhibiting substances.

Legionella pneumophila[3551-3553] possesses a cytolytic activity that may allow the insertion of pores into the phagocytic membrane upon contact.[3543] This apparently facilitates delivery of bacterial-derived effector molecules to the host cell cytoplasm that are capable of inhibiting phagolysosomal fusion. *Legionella*-containing phagosomes may also intercept and fuse with early secretory vesicles and recruit proteins that were originally destined for the endoplasmic reticulum, setting up a privileged membrane compartment resistant to fusion with lysosomes and permitting the development of an organelle for bacterial multiplication.[6029] *Afipia*,[3554] *Bordetella*,[3555] *Brucella*,[3556-3559] *Chlamydia*,[3560] *Ehrlichia* (Cytoecetes),[3561] *Glugea* spores,[3562] influenza[3563] and parainfluenza[3564] viruses, *Listeria*,[3565] *Neisseria*,[3566] *Nocardia*,[3567] *Pseudomonas*,[3568] and *Toxoplasma*[3569] also display total or partial inhibition of phagolysosomal fusion. Symbiont-derived lipopolysaccharides are involved in the prevention of lysosome-symbiosome fusion in amoebas harboring bacterial endosymbionts.[3570] Further identification and isolation of the mechanisms utilized by these organisms will be necessary to assess their potential usefulness in nanorobot design.

15.4.3.6.8 Inhibit Phagocyte Metabolism

Medical nanorobots might find it useful to slow or temporarily inhibit phagocyte metabolism to improve the likelihood of avoidance or escape. The simplest method is to selectively absorb oxygen or glucose intracellularly (ideally after avoiding or escaping the phagolysosome), thus asphyxiating or starving the phagocyte. This assumes these substances are not sequestered in an intracellular microzone (Section 15.5.7.5) or membrane-enclosed compartment close to the metabolic machinery that is consuming them, and that these substances can be absorbed by the intracellular nanorobots faster than the maximum transport rate into the cell (Section 10.4.2.1). Alternatively, a coordinated population of extracellular nanorobots could temporarily and reversibly hypoxify or hypoglucosify the local environment as a macrophage approaches. Hypoxia inhibits macrophage migration,[3571] probably due to metabolic changes in the cell.

Another method is to deny energy to the cell by selectively absorbing intracellular ATP using molecular sorting rotors on the nanorobot exterior (ideally after avoiding or escaping the phagolysosome). Again, this assumes the ATP is not sequestered in

an intracellular microzone (Section 15.5.7.5) or membrane-enclosed compartment that is diffusion-inaccessible to the nanorobot, and that the ATP can be absorbed by the intracellular nanorobots faster than the maximum production rate of the intracellular mitochondrial population (Section 8.5.3.10). In nature, the adenylate cyclase bacterial exotoxins such as anthrax toxin edema factor[3368] and pertussis toxin[3369] act to depress phagocytic activity in a similar manner. For instance, *Bordatella pertussis* releases an extracellular adenylate cyclase which, when taken up by phagocytic cells, sabotages intracellular metabolism by converting internal ATP to cAMP, effectively de-energizing the cells.[3369] *Yersinia* similarly disarms macrophages using a hybrid YopT-adenylate cyclase.[3572] Depletion of extramitochondrial intracellular ATP pools converts apoptosis to necrosis in human T cells subjected to two classic apoptotic triggers.[5934]

Dansylcadaverine, amantadine, and rimantadine have actions on phospholipid metabolism[3355] and reduce the production of membrane lipids such as phosphatidylcholine that are necessary for engulfment. Numerous phagocyte phospholipid and cholesterol synthesis inhibitors are known.[3436] Intracellular free oxygen, such as might be released by medical nanorobots from onboard tanks containing pressurized gases,[3573] regulates enzymatic activity via enzyme activation or deactivation by S-thiolation controlled by local oxygen tension.[3574] Intracellular oxygen also impairs arachidonic acid metabolism[3575] and phagocytic function[3576-3579] in lung macrophages, and can have intracellular toxicity.[3581,3582] Inhibition of natural antioxidants increases cellular susceptibility to oxygen toxicity;[3580,3581] at the organismal level, O_2 exposures exceeding 2.5 atm can cause seizures in animals.[3581]

15.4.3.6.9 Phagocytocide

If no other means are available, in rare circumstances it may be necessary for a medical nanorobot to kill a phagocyte that is ingesting it. This is not a desirable procedure unless the total systemic nanorobot dose is extremely light, since it would be easy for even a modest number of active nanorobots to quickly deplete a significant fraction of the body's professional phagocytes, substantially impairing the reticuloendothelial system and possibly contributing to inflammatory and autoimmune disease.[5769] Furthermore, a nanorobot that permanently poisons a phagocyte is a potentially harmful device that may not pass governmental regulatory muster. Many of the techniques of cytocide and virucide summarized in Section 10.4 may be applicable to phagocytes. However, it is important to recall that an anergic or apoptotic outcome is cleaner and thus is preferable to a necrotic outcome — if cell death has become inevitable — for the reasons described in Section 10.4.1.

Before internalization, nanorobots may kill phagocytes mechanically (Section 10.4.2) or chemically (e.g., $GdCl_3$,[3583] beryllium phosphate,[3584] or dichloromethylene diphosphonate[3585]). Antigen overstimulation of T cells, a phenomenon known as high-dose suppression, can also induce T-cell death.[2543] Various substances produced by pathogens that cause damage to phagocytes have been called aggressins.[3302,3586-3590] Most aggressins are extracellular enzymes or toxins that kill phagocytes, and include:

1. streptolysin O (an oxygen-labile thiol-activated cytolysin) from *Streptococcus pyogenes* (ovoid cocci 0.6-1 micron in diameter[3309]) that binds to cholesterol in the membranes of mammalian cells and organelles[3591] with various cytotoxic effects;[3592,3593]
2. leukocidal toxins including γ-hemolysins and leukocidin[3594-3597] from Gram-positive pyogenic cocci such as *Staphylococcus aureus*[3594-3597] and *Staphylococcus intermedius*,[3597] and cell-bound leukocidin from *Pseudomonas aeruginosa*;[3598]
3. exotoxin A, a bacterial extracellular protein of *Pseudomonas aeruginosa* that inhibits protein synthesis by ~50% and kills macrophages in ~1 hour at ~10 ng/ml;[3599-3601] and
4. various substances secreted by *Enterococci* with cytolytic toxicity for phagocytic cells.[3301,3602]

After internalization, nanorobots may kill phagocytes chemically, for example, by toxifying the cell via intracellular acidosis[3603-3608] from CO_2 gas release from onboard pressure tanks[3573] with sufficient speed and quantity to overcome the bicarbonate buffer system. Like lymphocytes, erythrocytes, and platelets[3609] (but unlike brain[3606-3608] and muscle[3605] cells), alveolar macrophages are permeable[3604] to H^+/HCO_3^-. Measured mean cytosolic pH is 7.1 in rat renal epithelial cells,[3610] 7.09-7.19 in rat cardiac myocytes,[3611] 7.18-7.21 in rat fibroblasts,[3611] 7.21 in normal human platelets[3612] 7.33 in human erythrocytes,[3613] and 7.39 in human lymphocytes.[3614] Lethal intracellular CO_2 acidosis in nonpermeable cells is approximately 5.8-6.2,[3606] so CO_2-induced lethality requires a decrease in intracellular pH of at most 1.6, corresponding to the injection of 5.2 million CO_2 molecules (~0.1% of respirocyte[3573] storage capacity) into a $(20 \text{ micron})^3$ cell comprised 70% of water. Of course, artificial CO_2 intracellular acidosis elicits a restorative alkalinization response[3603] including extracellular transport,[3604] thus likely necessitating a somewhat higher intracellular lethal dose to be administered by nanorobots, in actual practice.

Nanorobots also may induce phagocyte death much like the intracellular parasites of macrophages such as *Mycobacterium*, *Brucella*, and *Listeria* — for instance, via lymphokine-activated killer-mediated cytolysis of monocytes chronically infected with mycobacteria.[3615] A more direct example is offered by the malarial (*Plasmodium*) sporozoites.[3616-3618] These enter the fixed phagocytes of the liver (Kupffer cells) enclosed in a vacuole that resists phagolysosomal fusion (Section 15.4.3.6.7). But before forming a parasitophorous vacuole, the sporozoites can travel completely through the body of the fixed phagocyte and exit the Kupffer cell on the other side.[3618] Then they invade the hepatocytes (other liver cells) that lie adjacent to the Kupffer cell. The sporozoites accomplish this by releasing into the phagocyte cytosol a considerable amount of circumsporozoite (CS) protein, a ribotoxic agent that inhibits phagocytic protein synthesis and selectively kills the Kupffer cells through which the sporozoites pass.[3618]

It is believed that all eukaryotic cells, including phagocytes, incorporate an evolutionarily conserved self-destruct mechanism called programmed cell death or apoptosis (Section 10.4.1.1). This is an intracellular cascade of genetically predetermined biochemical steps in which the cell disassembles itself in an orderly manner, in 30-60 minutes.[3619] Phagocyte apoptosis may be triggered by various means. For example, B lymphocytes and T lymphocytes undergo apoptosis in response to anti-IgM antibodies and dexamethasone (a glucocorticoid), respectively.[3620] Exposure to 4.25% solution of glucose-lactate-based peritoneal dialysates elicits accelerated apoptosis in cultured phagocytes (monocytes and neutrophils).[3621] Phorbol 12-myristate 13-acetate (PMA) induces morphological degeneration and cell death in 3-6 hours in porcine PMNs in vitro.[3622] Apoptosis-inducing CD95L ligand expression has already been mentioned in connection with immune privilege (Section 15.2.3.5). *Shigella flexneri* produces apoptosis in cultured macrophages via IpaB protein secretion — IpaB binds to interleukin-β-converting enzyme (ICE), a cysteine protease that can initiate apoptosis when expressed in cells.[3623] In vivo, *Shigella flexneri* induces extensive apoptosis of macrophages, B cells, and T cells located under M cells in the intestinal walls.[3623] Yop proteins from

Yersinia species signal macrophages to undergo rapid apoptosis.[3624-3627] S*almonella typhimurium* also induces apoptosis in macrophages,[3389,3628] as does *Listeria* during listeriosis in infected hepatocytes,[3629] both in vivo and in vitro, mediated by listeriolysin O.[3630]

It should be possible to design explicit biological-derived autodestruct mechanisms into biorobots (Chapter 19) that are analogous to apoptosis. However, disposability engineering for diamondoid nanorobots which allows for biocompatible planned biodegradability — nanorobot apoptosis — will be difficult to accomplish (Section 9.3.5.2) and would probably present higher risks due to reduced process control during intermediate stages of self-disassembly.

15.4.3.6.10 Systemic Phagocytic Blockade

Finally, there is the possibility of systemic phagocytic blockade.[1391,3631-3645] It is well known that a large quantity of carbon particles present inside an alveolar macrophage will decrease its lysosomal enzyme concentrations and depress its phagocytic function.[880] At large enough whole-body particle loads, all professional phagocytic activity ceases. The phagocytic cells of the RES would be "full" of ingested medical nanorobots (Sections 15.4.3.1 and 15.6.3.4) and the RES is said to be blockaded, with the result that all subsequently arriving nanorobots will be ignored by a population of phagocytes overwhelmed beyond their functional capacitance. Acute blockade typically persists for 1-4 hours for metabolizable particles,[2863,3646] but may last 24-48 hours if nontoxic indigestible particles such as carbon[2863] or diamondoid nanorobots are used. RES blockade is sometimes employed clinically to improve graft survival in transplant recipients.[3643,3645] Impaired particle clearance due to RES blockade by parvovirus particles has been observed in minks,[3647] and the excessive use of hair spray has reportedly induced partial RES blockade.[3639] Blockade can also be chemically induced, as for example using $GdCl_3$ at ~0.005 gm/kg in rats,[3383] or with cortisone.[3648]

What volume of medical nanorobots might be needed to induce complete human RES blockade? There is some relevant experimental evidence from animal models:

1. A 0.0025 cm^3/kg test dose of radioiodinated colloidal albumin constituted an "appreciable phagocyte load" for human Kupffer cells but did not produce blockade[2845]
2. 20 mg of colloidal carbon[872,3644] produced complete RES blockade in rats (0.05 cm^3/kg), though another similar experiment[875] found no blockade at a dose of 320 mg/kg (~0.16 cm^3/kg). (Average rat weight is typically ~200 gm.)
3. Particle loads of 1 mg of dextran sulfate[3649,3650] (~0.03 cm^3/kg body weight), or 5-10 mg of carbon[3641,3645] or carrageenan[3638] (0.10-0.20 cm^3/kg), or 2 x 10^9 sheep erythrocyte cells[3650] (~3 cm^3/kg), have produced RES blockade in mice.
4. 1 gm/kg of carbon black injected IV in mice[873] produced complete macrophage blockade (0.5 cm^3/kg).

Assuming 3.8 x 10^6/cm^3 granulocytes (volume ~700 $micron^3$) and 0.4 x 10^6/cm^3 monocytes (volume ~1500 $micron^3$) in the blood, and 200 x 10^9 RES phagocytes[2863] (volume ~1500 $micron^3$[3651]) in the tissues, then the total human phagocyte volume is ~300 cm^3. If the maximum particle storage capacity of each cell is ~10% (Section 15.6.3.4), then the maximum phagocytic capacity of the system — the maximum possible requirement for blockade — is ~30 cm^3 of medical nanorobots, or ~0.4 cm^3/kg, which is very roughly consistent with the rodent data, above. Since only ~2 cm^3 of micron-sized particles may be harmlessly sequestered in lymph nodes and spleen (Section 15.4.3.4), safe blockade of the human RES with inert particles might not be feasible.* However, temporary blockade using biodegradable particles would enable a subsequent dose of medical nanorobots to operate for a time within the human body without risk of RES sequestration.

Continuous systemic blockade is also undesirable because it can leave the body phagocytically defenseless against foreign particle accumulations and pathogenic invasions, can increase the lethality of certain infections,[2863] and may contribute to the pathogenesis of inflammatory and autoimmune diseases.[5769] Normal adult human blood contains ~4 million neutrophils/cm^3 (Appendix B). If the number of active neutrophils falls below ~0.5 million/cm^3, the risk of infections increases markedly.[361] A sudden systemic cessation of phagocytic activity may produce symptoms similar to acute neutropenia and lymphocytopenia, with impaired immune defenses and susceptibility to a wide range of opportunistic infections such as aspergillosis, cytomegalovirus, mucormycosis and nocardiosis.[361] These symptoms should abate as the blockading particle mass is gradually cleared from the RES by the death of blockaded phagocytes, whose inert trapped particles are rephagocytized or permanently granulomatized, and the phagocytes are slowly replaced from storage pools (over many hours) or by accelerated granulopoiesis[3640] in bone marrow (over many days). However, the spleen's ability to recycle aging red cells and platelets, and to filter particulate debris, may be compromised. There could be permanent lymph node swelling, chronic hepatosplenomegaly,[3638] or even significant organ necrosis. Later, the widely dispersed sequestered particle load would have to be retrieved by injecting additional scavenger nanorobots (Chapter 19), compounding the problem. Experimentally-induced blockade of rat RES using carbon colloid also produces (1) marked reductions in terminal arteriolar lumen sizes, (2) curtailment of capillary inflow and outflow, (3) hyperreactivity to the constrictor (noradrenaline) and hyporeactivity to the dilator (acetylcholine), (4) arteriolar spasms, and (5) pronounced uptake of carbon particles in the endothelial cells with different degrees of endothelial cell swelling, often bulging into the microvessel lumens.[872] Intentional nonspecific blockade using inert particles probably should be avoided in most medical nanorobot mission designs.

15.4.3.6.11 Artificial Biological Phagocytes

If antibodies and related biological receptor molecules can recognize diamondoid materials (Section 15.2.3.3), then it should be possible to bioengineer slightly altered genes for human phagocytes so as to produce a new phagocytic phenotype that cannot recognize, or is not activated by, or is actively repelled by, particles comprised of these diamondoid materials. Nanorobotic materials, if recognized by the modified phagocytes, could mechanically or chemically activate a chimeric or artificially designed cytosolic signal pathway cascade previously installed as a transgene or genomic cassette[5602-5606] in the artificial phagocytic genotype.[5607] (Installation of >1000 bp cassettes has already been demonstrated in human fibroblasts.[5608]) This cascade would elicit chemorepellent-like behaviors

** Waste heat generated by blockade is not an issue. With <10^{12} white cells in the human body (Section 8.5.1) whose power consumption may increase by 20-100 pW/cell when activated[2853] (Table 6.8), the entire human phagocytic system would generate <100 watts of excess thermal power during the blockade process, thus by itself producing no measurable increase in body temperature (Section 6.5.2).*

by the phagocytic cell, or would actively inhibit actin-based phagosome-formation or other crucial multi-pathway events in the particle internalization process. For example, the ability of mouse neutrophils to phagocytose bacteria falls by half when the natural phagocytes are genetically engineered with a single-factor (CCAAT/enhancer binding protein) deficiency.[3652]

In view of the relative abundance of techniques for phagocyte avoidance and escape as outlined above, such genetic modifications to human cells should prove to be unnecessary in most cases. However, R. Bradbury points out that the likelihood of robust gene therapy and whole genome engineering techniques will make the ability to tune the response of the human immune system a much more common medical procedure long before robust engineering of nanorobots is available. Total replacement of the immune system is already a well practiced medical therapy (e.g., total body irradiation[5943] and myeloablative chemotherapy[5944] for leukemia, total lymphoid irradiation for lupus nephritis[5945] or prevention of graft-host disease[5946]). It seems likely that the next step of replacement or augmentation of the immune system with enhanced biological components[5947,5948] is a highly probable path for biotechnological (pre-nanorobotic) nanomedicine.

Note that artificial biological phagocytes are to be distinguished from artificial mechanical phagocytes[2762] (i.e., nonbiological nanorobots such as microbivores[2762]).

15.4.4 Biocompatibility of Nanorobot Fragments in vivo

The partial or complete disintegration of diamondoid medical nanorobots in vivo should be an exceedingly rare event (Chapter 17). Nevertheless, if and when this occurs, nanorobots that have lost physical integrity should be recognized as foreign matter and be engulfed by free macrophages or resident phagocytes such as Kupffer cells. The uncoated, rough exposed surfaces of these diamondoid devices should invite prompt opsonization (blood protein tagging) and removal from blood or tissue via geometrical (Section 15.4.2) or phagocytic (Section 15.4.3) processes.

Large nanorobot fragments consisting of sharp indigestible shards might destroy the phagocytosing cell, causing it to rupture and discharge its cytoplasmic contents. This could lead in turn to acute local inflammation (Section 15.2.4) and the probable release of chemotactic agents attracting mesenchymal cells to the site, which would then differentiate into fibroblasts, resulting in entombment of the shards in the adjacent tissue by a permanent fibrous spherical granulomatous capsule (Section 15.4.3.5). Studies show that jagged mechanically-produced PMMA wear particles elicit increased inflammatory responses compared to smooth round latex particles.[646] Attachment to phagocytic cells may be enhanced by the rough surface of mechanically-produced particles,[3653] the increased surface area of rough particles,[646] or by other factors.[646] Less jagged nanorobot fragments might ultimately be sequestered in the lymph nodes or other lymphatic organs, or may also suffer granulomatous entombment in place. Nanorobot fragments resulting from dental grinding (Section 9.5.1, Chapter 28) may be swallowed and eliminated from the body via the alimentary canal. Alternatively, these fragments may become embedded in the oral mucosa, subsequently either being encased in a permanent granuloma or being extruded from the mucosal epithelium (e.g., marsupialization) back into the oral fluids, then swallowed and excreted (unless reabsorbed in the gut; Section 15.4.3.3.2).

A medical nanorobot, like any machine, is most likely to rupture at its weakest links. Noncovalent (e.g., van der Waals) bonds will break before covalent bonds, so nanorobots that are subjected to catastrophic physical forces initially are most likely to fragment into relatively less reactive nanoparts and nanoassemblies, rather than into more highly reactive semirandom molecular fragments of such components. A few representative diamondoid nanoparts have already been designed (Section 2.4.1) by K.E. Drexler, R.C. Merkle, and R.A. Freitas Jr. These nanoparts are essentially very large molecules incorporating multiatom structures held together by a combination of internal covalent and noncovalent bonds (including steric hindrance), having, for example, the following basic chemical formulas:

$C_{20}\,H_{24}\,Si_2$ and $C_{20}\,H_{24}\,Ge_2$ for the dimer placement mechanosynthesis tool tip;[36,5683]

$C_{1433}\,N_{536}\,H_{403}\,O_{134}\,Si_{44}\,S_{34}\,F_{12}$ for the fine motion controller;[3654]

$C_{1826}\,H_{1806}\,Si_{1645}\,O_{367}\,N_{224}\,S_{220}\,P_{77}$ for the neon gas pump;[3655]

$C_{2461}\,Si_{2792}\,H_{864}\,N_{628}\,P_{452}\,O_{367}\,S_{356}$ for the differential gear;[3656]

$C_{1472}\,H_{1000}$ for the hydrocarbon bearing;[3657] and

$C_{4708}\,H_{2020}$ for the hydrocarbon universal joint.[3658]

Such nanocomponents clearly are not pure diamond structures — the mean atomic weight per atom for the above designs is 7.0-18.8 daltons/atom of structure, with an average of ~12 daltons/atom. Sapphire (aluminum oxide) based nanorobot components are also likely. In 2002 few such nanocomponents had been precisely defined at the molecular structural level, so their biochemical and biological reactivity is largely unknown. Will they be opsonizable and phagocytosable? Large free nanoparts with irregular exterior contours and surface charge distributions are probably immunogenic (Sections 15.2.3.3 and 15.3.7) and thus will likely become visible to the immune system and to the RES. It is already known that nanometer-size pieces of amorphous carbon and pure diamond can undergo photooxidation in the presence of light, oxygen (air) and water,[3659] and sapphire can suffer slow chemical dissolution under certain conditions (Section 15.3.5.6). Designed to be built and operated in vacuo[10] and often containing relatively energetic strained-shell structures (Section 2.4.1), individual nanoparts could be chemically reactive in vivo with water, oxygen, ions and free radicals, proteins, or other biological substances that are abundantly available. Detached protein-based presentation semaphores might also be immunogenic (Section 15.2.3.3). Stably functionalized adamantanes, the smallest possible chunks of diamond that can exist, appear reasonably biocompatible and are generally excreted unchanged in the urine (Section 15.3.1.4(8)).

Will free nanoparts be cytotoxic, pyrogenic, or systemically toxic? A large solid pure hydrocarbon-like molecule with a lengthy stretch of exposed hydrogens might be nontoxic, as is the case with large chunks of long-chain linear hydrocarbons such as paraffin wax.[3660] However, some short-chain linear paraffin hydrocarbons (C_nH_{2n+2}) such as propane are considered "poisonous"[3661] with an official NFPA Health Hazard Rating of 1 or "slightly toxic" (scale 0-4).[3662] Hydrogen-terminated diamond and diamond-like coatings appear relatively nontoxic and inert (Section 15.3.1), as do sapphire-like particles (Section 15.3.5.5). Nanoparts with exposed sulfur or nitrogen atoms could be more reactive in vivo. In vitro studies of ultrafine particles with living cells show an increased ability to produce free radicals which then cause cellular damage,[6199-6201] manifested as genotoxicity[6200] or altered rates of apoptosis.[6200-6203] As

noted by Howard,[6188] the upper size limit for the lung toxicity of ultrafine particles is not fully known but is believed to lie between 65-200 nm.[6190] Endocytic vesicles in alveolar membranes may be 40-100 nm in size and are thought to be involved in protein macromolecule and occasionally virus transport into cells.[6189] Medical nanorobots or passive inert nanoparticles larger than 100-200 nm should present relatively low endocytic transport risk, although smaller particles, free nanoparts, or devices might pose some incremental risk.

It is possible that stray nanoparts may prove relatively more inflammatory than whole nanorobots, all else equal. One experiment[769] found that 14-nm carbon black particles (about the size of individual nanoparts; Section 2.4.1) produced a much greater alveolar neutrophil inflammation reaction than was elicited by larger 260-nm carbon black particles (closer to the size of whole medical nanorobots). This is especially important at the very low doses of free nanorobot parts anticipated in vivo where particle area dominates the inflammation response, as distinct from the relatively unlikely higher overload-inducing doses where total particle mass or volume of the instilled particles dominates without any influence of total surface area.[769] Several in vivo studies have found elevated inflammation in animal lungs exposed to ultrafine (<100 nm) particle aerosols.[6190-6196] For example, Donaldson[6194] notes that "ultrafine particles made of low-solubility, low-toxicity materials are more inflammogenic in the rat lung than fine respirable particles made from the same material. The property that drives the greater inflammogenicity of ultrafines is unknown but very likely relates to particle surface area and involves oxidative stress. Ultrafine particles can also impair the ability of macrophages to phagocytose and clear other particles, and this may be pro-inflammogenic." Seaton et al[6197] have proposed that the chronic inhalation of nanoparticles can provoke alveolar inflammation that can damage the lining of the blood vessels, leading to arterial disease, though there is some evidence[6198] that nanoparticle-induced lung inflammation and peripheral vascular thrombogenesis can be partially decoupled. Oberdorster[6216] reported that exposing rats to air containing 20-nanometer-diameter PTFE (Teflon) nanoparticles for 15 minutes leads to death for most of the animals within 4 hours, whereas animals exposed to air with much larger 130-nm particles suffered no ill effects. Histology studies showed that macrophage cells that normally clear out foreign material had trouble ridding tissue of the smaller particles.

What about the biodistribution of stray nanoparts? Kreyling et al[6177] examined the distribution of nanopart-sized 15-nm and 80-nm particles of chemically inert radiolabeled iridium particles in rats. Inhaled particles (including particles deposited in the alveolar region) were cleared predominantly via airways into the gastrointestinal tract and feces, with only <1% of nanoparticles translocated into secondary organs such as liver, spleen, heart, and brain after systemic uptake from the lungs and the translocated fraction of 15-nm particles about ten times larger than for the 80-nm particles. Iridium nanoparticles injected intravenously were "rapidly and quantitatively accumulated in the liver and spleen and retained there," and nanoparticles inserted gastrointestinally by gavage were not absorbed through gut walls. The study concluded that "only a rather small fraction of [the inert nanoparticles] has access from peripheral lungs to systemic circulation and extrapulmonary organs." A similar study of 20-29 nm carbon particles by the same researchers[6178] found significant translocation only from lung to liver after 1 day post-exposure, but it was unclear whether translocation had occurred via the circulation or the GI tract. Oberdorster[6216] reportedly also found that rat-inhaled carbon-13 and manganese nanoparticles reached the olfactory bulbs and then migrated throughout the brain.[6212]

R. Bradbury notes that the three most common unguided active chemical reactions that occur in biological tissues are oxidation/free-radical damage, nitrosylation (e.g., NO attacks tyrosine and perhaps other amino acids), and glycosylation. The potential for stray nanorobot parts or their randomly-structured fragments to catalyze or enhance the rates of these reactions should be studied, and the resistance of undefended nanorobot surfaces to attacks by these reaction molecules should also be investigated.

In the case of fragmented biorobots (Section 1.3.2.1, Chapter 19), the biocompatibility of cell parts could be of special interest.[3663-3666] For example, Glaumann and Trump[3664] injected loose mitochondria and microsome organelles intravenously into rats, and found that half of the injected dose was recovered in the liver, with smaller amounts found in the lungs, kidneys, spleen, and heart. Serum clearance half-life was 5-15 minutes for microsomes and 30-60 minutes for mitochondria.[3663,3664] Glaumann and others have also examined the uptake of injected liver cell plasma membranes,[5060] erythrocyte ghost cell membranes,[2847] lysosomes,[2848] microsomes,[2851] mitochondria,[3666,5062] ribosomes,[2851] and other subcellular organelles[5061] by Kupffer cells; of mitochondria[3665] by human glial cells; of sperm tails by oocytes;[5066] of collagen,[5078-5083] fibronectin[5083] and melanosomes[5084] by fibroblasts; and of amyloid fibrils,[5063] DNA/RNA (Section 15.3.6.1), ECM,[5064] myelin debris,[5065] and red cell ghost membranes[5049,5380-5384] by various phagocytic cells. Actin (released from dying or lysed cells) can circulate at μM concentrations in peripheral blood and may modulate plasmin-dependent biological responses.[5067] Free α-actin is present in the blood of patients with angina pectoris and acute myocardial infarction or ischemia up to 0.112 mg/ml.[5068] Bloodborne actin is scavenged or sequestered by Vitamin D binding protein[5069-5071] and gelsolin,[5071,5072] with a serum clearance half-life for free actin of 30 minutes at the liver.[5071] Granulocytic fragments have been observed in blood during sepsis.[5387] Finally, an inhaled vaccine consisting mostly of free bacterial ribosomes has been tested as a treatment for respiratory infections,[5073-5076] producing significantly increased serum concentrations of immunoglobulins.[5077]

Nanosecretagoguery — e.g., triggered enzyme release by nanorobots or free nanoparts — is another ever-present concern. Under some circumstances phagocytes can release enzymes directly into the extracellular fluid in response to particles with certain physicochemical characteristics. For example, incubation of particulate activators of the alternative complement pathway such as zymosan or glucan (polyglucose) particles with monocyte monolayers in vitro causes the monocytes to release 9-18% of their internal stores of lysosomal enzyme, N-acetylglucosaminidase, directly into the culture medium.[3667-3669] Similar releases are observed in human monocytes exposed to latex beads at Nct ~ 5-10%[3667,3668] and asbestos,[3668] and occasionally in eosinophils and neutrophils.[3670] Interestingly, monocyte enzyme release due to inert latex beads (the closest analog to medical nanorobots) is almost completely inhibited by ~8 μg/ml of the fungal metabolite cytochalasin B.[3667] Nanorobot fragments that inadvertently mimicked the relevant molecular structures of glucan or other stimulatory particles might trigger similar unwelcome accidental releases in vivo — several adamantane derivatives are secretagogues for insulin release by mouse islets in vitro,[5570] and proteins (analogous to secretagogic nanoparts) capable of serving more than one function (e.g., both ion channel and enzyme[3671]) are known.

CHAPTER 15.5

Nanorobot Mechanocompatibility

Unlike pharmaceutical agents whose interactions with biology are largely chemical in nature, medical nanorobots will interact both chemically and mechanically (Chapter 15.1) with human tissues and cells. Similarly, traditional biomedical device implants (Section 15.2.1) produce both chemical and bulk mechanical[6049] effects, but nanoorgans and nanoaggregates include active nanoscale features and moving parts that can apply spatially heterogeneous mechanical forces at the microscopic and molecular scale. Thus any discussion of biocompatibility in nanomedicine must necessarily include an analysis of the mechanical biocompatibility,[5728] or mechanocompatibility, of nanorobotic systems as they interact with the tissues and cells of the human body.

Section 15.5.1 describes the mechanical interactions of nanorobotic systems with human skin and other epithelial tissues. This is followed by a discussion of mechanical tissue penetration and leakage as a result of perforation (Section 15.5.2), and mechanical interactions with vascular systems (Section 15.5.3), with extracellular matrix and tissue cells (Section 15.5.4), and with nontissue cells such as erythrocytes, platelets, and leukocytes (Section 15.5.5). Electrocompatibility is briefly mentioned (Section 15.5.6), followed by a more detailed review of cytomembrane and intracellular mechanocompatibility (Section 15.5.7). The discussion concludes with a brief consideration of nanorobot-nanorobot mechanocompatibility (Section 15.5.8).

15.5.1 Mechanical Interaction with Human Integument

Various potentially undesirable interactions between medical nanorobots and the human integument have been discussed elsewhere and will not be repeated in detail here. These interactions include excessive nociceptor stimulation during outmessaging (Section 7.4.6.1), excessive acoustic and optical energy densities at auditory and ocular surfaces due to communications among airborne nanorobots (Section 7.4.8); tickling sensations that might be attributable to skin-traversing nanorobots (Section 9.5.2(F)); tracheal damage from inhaled nanorobots (Section 9.5.3.6); physical damage to mucous membranes, the auditory canal, and ocular surfaces by the impact of aerial nanorobots (Section 9.5.3.6); and the possible triggering of sneezing (Section 15.2.6.2) or nausea and emesis (Section 15.2.6.3) by nanorobots traversing the relevant epithelia. In rare cases, excess heat generated by nanodevices located on or near the skin might induce sensations of pain, as in erythromelalgia.[5447] None of these risks appears particularly serious if proper nanomedical designs and operational protocols are observed.

Additional related concerns to be addressed in this Section include pruritus (Section 15.5.1.1); epidermalgia and allodynia (Section 15.5.1.2); epidermal pressure ulcers (Section 15.5.1.3); as well as peristaltogenesis and mucosacompatibility of medical nanorobots (Section 15.5.1.4).

15.5.1.1 Pruritus

Pruritus (itching) is an unpleasant cutaneous sensation[3672-3675] that usually (but not always[5596]) evokes the urge to scratch. These poorly-localized primary sensory impulses are carried on unmyelinated C fibers through the spinothalamic tract to the thalamus and on to the sensory cortex.[3674,3676,5595] Scratching appears to interrupt the rhythm of afferent impulses to the spinal column and relieves the sensation of itching.[3676] Chemical mediators such as histamine and peptidases such as papain[5594] (a plant enzyme) produce itching when injected, known as alloknesis,[3677] while several mediators (e.g., bradykinin, neurotensin, secretin, substance P) stimulate the release of histamine from histamine-containing cells.[3674] Kinins may be pruritic, but prostaglandins are only weak pruritogens.[3672] Subdermal bile acids are found in cases of pruritus associated with obstructive biliary disease.[3676] Some cases of generalized pruritus can be attributed to dry skin. But there are many other causes including parasites (e.g., scabies, pediculosiss), physical obstruction of ducts (e.g., miliaria), and physical or chemical irritation of the skin (e.g., fiberglass dermatitis, contact dermatitis).[3674] Histamine release can be elicited by activation of complement (Section 15.2.3.2); by immunoglobulin IgE (Section 15.2.3.3) which mediates some allergic responses (Section 15.2.6.1); or by nauseogenic stimuli (Section 15.2.6.3). This in turn produces itching, probably mediated by subdermal "itch units" consisting of unmyelinated nerve fibers.[3678]

Can the passage of nanorobots across the epidermis cause itching, either chemically or mechanically? Nanorobots should be designed with chemically nonpruritic external surfaces, and the mechanical forces produced by individual 1- to 100-micron nanorobots traversing human skin at <1 m/sec appear to be insensible (Section 9.5.2). However, >1000 large legged nanorobots simultaneously traversing the receptive field of a single dermal tactile receptor (10-100 mm^2; Table 7.3) at >45 cm/sec might just be detectable at some highly sensitive locations such as tongue and fingertip (Section 9.5.2(F)). This implies a minimum threshold dermal-sensible number density of $>10^3$-10^4 nanorobots/cm^2, which is ~10-100% coverage of the skin. For comparison, the scabies mite *Sarcoptes scabiei*, ~100-300 microns in diameter, is perhaps the smallest legged mite that causes itching.[5385] But this itching is caused by a local Type IV delayed hypersensitivity (allergic) reaction (Section 15.2.6.1) and not by mechanical irritation.[5386] Abundant dust mites of similar size live uneventfully on human epidermis and hair follicles, producing allergenic itching only rarely[3679] and without producing mechanical itch — though the superficial dust mites are not an ideal comparison because they don't burrow as deeply as scabies mites (or as deeply as nanorobots might).

Pruritus from immotile medical nanorobots cannot be completely ruled out because nanorobot-size pruritic fiberglass strands

measuring 7-24 microns in diameter are known to produce a mechanical abrasive dermatitis[196,197,201,3680-3685] whose severity increases with applied pressure.[3686] However, the author's informal experiments with 0.25- to 250-micron diamond grit particles on his own skin (Section 15.1.1) suggest that diamondoid nanorobots with generally smooth surfaces should elicit few if any mechanical itching sensations. Obviously, more formal studies with quantifiable results are needed for confirmation.

15.5.1.2 Epidermalgia and Allodynia

Will epidermal penetration by nanorobots produce a sensation of pain (epidermalgia) in the human patient? Modern hypodermic needles have outside diameters of >200 microns (33 gauge)[3687] and can barely be felt penetrating the skin. Most of the sensation generated by fine needle stick can probably be attributed to subdermal needle cantilevering motions rather than skin penetration per se. (The smallest solid acupuncture needles are ~120-180 microns in diameter[3688] and there is generally little or no sensation of pain upon insertion of the needle* which sometimes produces analgesia.[3689]) Hypodermic injections can also produce a sensation of fluid flowing into the veins, probably due to: (1) a thermal and viscosity mismatch between injecta and venous blood, (2) a slight vein expansion from the local rise in fluid pressure, (3) fluid shear forces (e.g., in dialysis needles[3690]), and (4) in some cases a direct chemical response.[3691]

Nanorobots which are 1-10 microns in diameter present far smaller dermal penetration footprints than a hypodermic needle and thus should produce a stimulus even farther below the threshold of sensibility than a needle. They should induce no detectable cantilevering motions because tissue-transiting nanorobot convoys (Section 15.5.2.3) need not be flexurally rigid. As with tickle (Section 9.5.2) and itch (Section 15.5.1.1) sensations, individual nanorobots appear unlikely to exert sufficient forces to elicit sensations of stretch from Ruffini endings.[3694] Equally unlikely are pressure sensations from other mechanoreceptive afferents in the skin[3695] even if the nerve is directly contacted, itself an improbable occurrence given the typical number density of <1 afferents/mm^2 in the skin (Table 7.3). Flow sensations also should be minimized because nanorobots may be self-injecting without carrier fluid or without motion of carrier fluid (Chapter 16) thus minimizing vein expansion. Nanorobots can also self-heat to blood temperature during injection, and should be chemically inert. Nanocatheters and nanocannula (Chapter 19) larger than ~100 microns in diameter and major nanosurgical interventions (Chapter 12) may require analgesic auxiliaries to entirely suppress epidermalgia during the procedure.

Allodynia — including nanorobot-induced cutaneous tactile allodynia,[3696,3697] mechanical allodynia,[3698] mechanical hyperalgesia[3699] or mechanical hyperesthesia[3700] — might be possible in unusual circumstances when a normally painless stimulus such as hair deflection is perceived as painful. (An extreme example is reflex sympathetic dystrophy[5597] or RSD.) In one experiment,[3701] median threshold of A fiber nociceptors to monofilament stimulation was in the range 207-1639 kPa (mean 744 kPa) and 130-764 kPa (mean 411 kPa) for the C fibers, thus requiring allodyniagenic pressures >1 atm. Hair follicle nerves have a receptive field of ~0.01 mm^2 (Table 7.3), hence >1 mN nanorobotic forces may need to be applied near the base of the hair shaft to induce allodynia. Under normal circumstances not involving crinal aerobots (Chapter 28), this seems unlikely. The threshold for first sensation during esophageal wall distension is ~2900 N/m^2, with chest pain ensuing at a threshold distension pressure of ~6100 N/m^2.[3702] Colorectal mechanical allodynia is induced in rats at 1300-5300 N/m^2.[3703]

15.5.1.3 Epithelial Pressure Ulcers

Pressure ulcers (e.g., decubitus ulcers or bedsores) are normally caused by a prolonged mechanical pressure against epidermal tissues (e.g., in persons bedridden for prolonged time periods), typically at sites over bony or cartilaginous prominences including sacrum, hips, elbows, heels and ankles. The combination of pressure, shearing forces, friction and moisture[3704,3705] leads to tissue death due to a lack of adequate blood supply. If untreated, the ulcer progresses from a simple erosion to complete involvement of the dermal deep layers, eventually spreading to the underlying muscle and bone tissue.[2004] In at least one rare case,[3706] mechanical frictional stimulation of the skin apparently precipitated systemic cutaneous necrosis and calciphylaxis, a state of induced tissue sensitivity characterized by calcification of tissues.

Nanomedical applications which envision prolonged periods of dermal contact with tight-fitting articles of nanorobotic apparel (Chapter 28), haptic or VR controllers (Chapter 12), exoprostheses (Chapter 30), or defensive armor (Chapter 31) must incorporate active components on the skin-contacting interior surface that can forestall the development of pressure ulcers. Molecular sorting rotors can remove water,[3707,3708] waste gases, secreted salts and other organic materials from the skin-device interface volume. A sensor-guided metamorphic interior surface can allow the garment to dynamically mirror epidermal tissue micromovements and perhaps actively undulate to mechanically encourage blood flow in the underlying tissues.[3709,3710] A thin layer of slightly pressurized dry nitrogen gas could be maintained in the interface volume, greatly reducing shearing forces and friction.[3711] For example, fluid mattresses can greatly reduce pressure ulcers in long-duration surgeries[3712]. Pressure-relieving surfaces have been investigated for surgical patients,[3713,3714] wheelchair users,[3715-3718] and for other circumstances.[3719-3721] The interior surface should employ materials having roughly the same mechanical properties as the enclosed tissue,[3207-3210] and the applied interfacial pressures should be reduced to below 1 psi[3716] or ~ 50 mmHg. Mechanical pinch-induced pain[5449] should also be avoided.

Stercoral ulcers[3722-3724] are caused by the necrosis of intestinal epithelium due to the pressure of impacted feces. Macroscale colonic nanorobot aggregates (Chapter 26) must avoid applying such harmful luminal pressures during lengthy missions.

15.5.1.4 Mechanical Peristaltogenesis and Mucosacompatibility

Will colonic nanorobots trigger diarrhea? The mechanical movements of medical nanorobots should not stimulate adverse biological responses during the traversal of mucosal membranes. For example, mucosal surfaces in the stomach and small intestine contain emetogenic mechanoreceptors,[2433] and the mechanical stimulation of esophageal[3725] or intestinal[3726] mechanosensors can elicit peristalsis. But shear forces generated during luminal wall locomotion can be held low enough to avoid nausea and emesis (Section 15.2.6.3). Colonic peristalsis may be initiated by the passage of roughage through the colon[3727-3730] or by mechanical brush strokes applied directly to the mucosal tissue,[3731] but the shear forces

** Acupuncture needles have a doweled end, not a cutting end like most hypodermic needles, thus may be less likely to cause tissue damage, vascular puncture, or bruising when inserted.[3692] The needling sensation (*de qi*) is thought to be caused by muscle fibers being caught and twisted on the needle tip.[3693]*

generated by nanorobot mechanical activities may be held below the threshold required to stimulate diarrhea. This threshold has not yet been precisely measured in humans, but it is known that the peristaltic threshold for marmoset ileum is <1000 N/m^2,[3733] about 2700 N/m^2 for canine gut wall[3734] and for feline small bowel,[3735] and that the distension pressure threshold to induce peristalsis in human esophagus is 1500-1900 N/m^2.* [3702] (The mechanical stimulation threshold to activate peristalsis in chicken ureters ranges from 770-9330 N/m^2.[3732]) Interestingly, mechanical sensory impulses (e.g., air or ~0.3 cm^3 water injection) from the pharynx actually inhibit esophageal peristalsis.[3736]

Although unlikely to trigger peristalsis, nanorobot mechanical activities may slightly increase mucus secretions from mucosal surfaces. For example, mechanical stimulation of the feline gastric mucosa doubles the rate of submucosal gland secretions.[3742] In rat, adherent mucus is 5-500 microns thick over the gastroduodenal mucosa.[3743] Particles instilled in the lungs, including inert dusts,[3744] cause increased numbers and activity of alveolar macrophages and an increased mucus flow rate.[3745-3747] Rapidly adapting receptors throughout the respiratory tract from the nose to the bronchi respond to mechanical stimuli, producing additional airway mucus secretion along with cough and bronchoconstriction.[3748] Particles[3749] or tubes[3750] placed in the nose cause increase nasal mucus flow and mechanical sinusitis. Mechanical stimulation of the nose, nasopharynx and larynx increases tracheal mucus output in the cat.[3751] Mucociliary cilia beat most strongly in the vicinity of a particle due to direct tactile stimulation.[3752]

15.5.2 Histopenetration and Perforation

Some medical nanorobots must be able to cross the epithelial barriers of skin and gut (Section 15.5.2.1), penetrate the vascular endothelium (Section 15.5.2.2), and migrate through tissues (Section 15.5.2.3) without introducing microbial flora and without causing edema, bruising, or other injury related to mechanical trauma. Various bacteria, neutrophils, fibroblasts and macrophages often make such journeys, usually without incident. It is also important to avoid tissue injury that might result in the sensitization of nociceptors, exposing the patient to the possible development of hyperalgesia.[5450]

15.5.2.1 Transepithelial Penetration

Past studies[6173] have shown that the percutaneous penetration of passive microspheres is a function of particle diameter. In more recent studies, Tinkle et al[6174] studied the penetration of size-selected fluorospheres (dextran beads) into postmortem human skin using laser confocal microscopy. They found that beads as large as 0.5-1 micron in diameter can penetrate the stratum corneum and reach the epidermis, and occasionally even the dermis (possibly deep enough for lymphatic system uptake), if the skin is flexed, as at the wrist; >50% of samples showed this activity after 1 hour of flexing. Lademann et al[6175] found that ~0.1 micron titanium dioxide particles used in sunscreen lotions penetrated into the hair follicles of the skin, with <1% of the applied particle concentration found in any given follicle. But in the interfollicular areas the deepest layers of the stratum corneum (and the viable skin tissues below) were devoid of penetrating particles even after repeated applications; microparticles were found only in the areas of the pilosebaceous orifices.

The careless penetration of nanorobots through human skin (Section 9.5.2) could potentially create microscopic perforations through which microbes (e.g., as in cellulitis) and undesirable environmental substances could enter the body and cause disease. (T.G. Wilson notes that with gingival inflammation, which almost everyone has, the epithelium around the tooth becomes quite porous and bacterial entry into the connective tissues and bloodstream is common.) Other pathological conditions associated with numerous and frequent epithelial penetrations include the development of deeply pigmented or discolored skin associated with an excess of skin penetrations by body lice (pediculosiss corporis, aka. vagabond's disease or vagrant's disease)[3755] and the granulomatous "stylosome" (stalk-mouth) that rises up from the skin in an attempt to wall off burrowing chiggers.[3755,3756] These results may be avoided by employing exterior lipophilic coatings on the nanorobot (Section 15.2.2.2) to encourage close nanorobot-tissue contact during transit, followed by active breach-sealing procedures (Section 9.4.5.6) once histopenetration is complete.

However, it appears unlikely that lymphatic or other fluids could exude from the body through unsealed epidermal transit holes created by medical nanorobots. The time-averaged interstitial pressure in subcutaneous tissue is 0.8-5 mmHg,[3753,3754] with mean value ~1.4 mmHg (Section 8.2.1.3). Even taking the highest pressure and assuming no tissue self-sealing, internal fluids can overcome surface tension at the fluid-air interface and begin to ooze from pores only if those pores are larger than ~60-600 microns in diameter (Section 9.2.4). Most medical nanorobots and their transit holes should be much smaller than this, and any microholes in soft tissue should rapidly plug or reseal. R. Smigrodzki agrees that "the size of the nanorobots is so small that a channel produced by the robot actively traversing the skin should spontaneously seal within a very short time, unless extreme stretch forces are applied."

Similar considerations may apply to the transepithelial penetration of nanorobots through stomach, intestinal, or bladder walls lined with cells having tight occluding junctions. Hemorrhage and perforation are two common complications of gastric and duodenal ulcers. Underlying tissues may then suffer chemical irritation by gastric acids and digestive enzymes. Gastric or duodenal perforations develop in 5% of ulcer patients. Such perforations result in chemical peritonitis and could also lead to bacterial peritonitis that causes sudden, severe generalized abdominal pain. Gas intrusion causes the presence of free intraperitoneal air (usually not itself pathological) in 75% of all cases.[2421] However, in the resting stomach a viscous protective layer of bicarbonate-rich mucus adheres closely to the surface of the underlying gastric epithelium. Gastric contents cannot pass into the tissues along unsealed nanorobot transit holes through the gastric epithelium as long as the thick alkaline mucus layer is maintained intact. It has already been noted that nanorobot-sized particles up to ~10-15 microns in diameter normally pass out of the small intestine into lymphatic tissues (i.e., Peyer's patches) without incident (Section 15.4.3.3.2). Nanorobotic perforation of the wall of the bacteria-rich colon could potentially introduce gut flora into the bloodstream or surrounding tissues — although R. Smigrodzki notes that gut microbes commonly reach the bloodstream even during straining at stool, so the very small number that might be introduced during nanorobot transit should not be problematic. Lipophilic coatings and breach-sealing protocols could again be employed here, as in dermal histopenetration.

** Human esophageal peristaltic pressure is normally 8100-10,200 N/m^2 depending upon position[3737] with >4000 N/m^2 needed to properly propel a swallowed bolus,[3738] and esophageal sphincter pressure is 1790 N/m^2.[3739] Spontaneous jejunal contractions have been measured as 4700 N/m^2.[3740] Colonic wall tension is typically ~5000 N/m^2 but can rise as high as 10^6 N/m^2 in ileus patients, higher than the maximum contraction capacity of the large intestine's muscle system (~5 x 10^5 N/m^2).[3741] Mechanical destructive forces of the gastrointestinal tract are sufficient to crush test pills having crushing strength of 1.2-1.89 N when swallowed by humans, or 3.2 N in dogs.[5017]*

Bowel necrosis and intestinal infarction are unlikely if no blood vessels are broken or occluded.

The risk of mechanical damage due to epithelial laceration by aerial nanorobots has already been described in Section 9.5.3.6. Vision loss from corneal abrasions is due to changes in many layers of the cornea. According to Sano et al,[3757] abrasions severe enough to mechanically remove cells from the corneal epithelium would also cause massive enlargement of mitochondria in the underlying endothelium and intracellular migrations of fibrillogranular material, thus potentially causing progressive vision loss.

15.5.2.2 Transendothelial Penetration, Bruising and Edema

Transendothelial penetration may involve either the injection of medical nanorobots into the luminal space of a blood or lymphatic vessel via an injection carrier, or alternatively the migration of nanorobots under their own power out of a blood or lymphatic vessel into the tissues or out of the tissues into a blood or lymphatic vessel.

Injections of nanorobots directly into blood vessels (Chapter 16) should produce minor localized disturbances to just a small number of vascular endothelial cells. The metamorphic hypodermic injection carrier can maintain a tight seal throughout the injection process. Rather than relying on natural endothelial lesion repair mechanisms that may take many weeks to complete in the case of a traditional large-gauge hypodermic needle,[3758,3759] the vascular breach due to a nanomedical hypodermic carrier is cellularly resealed immediately post-injection. Fluid leakage, bruising and edema should be negligible.

Incautious or reckless migration by medical nanorobots from a blood vessel lumen through vascular walls into the tissues, called transmigration, extravasation or diapedesis (Section 9.4.4.1), could produce unwanted pathologies ranging from minor bruising or ecchymosis (usually not causing serious pain[4740,4741]), to localized hematomas, to (in the most extreme case imaginable) massive hemorrhages comparable in severity to the hemorrhagic fevers[3760] caused by filoviruses such as *Ebola* and *Marburg*[3761] or (analogously) to cases of full thickness dermal necrosis following extravasation of chemotherapy[5693] or other[5694] agents. These outcomes should be avoidable with good design, including membrane sealing protocols during intercellular passage (Section 9.4.4.3) and attention to avoidance of unintentional mechanical cytocide (Section 10.4.2).

Reverse diapedesis[3762,3763] or intravasation,[3764] from tissues to vascular compartment, also may be undertaken by medical nanorobots analogously to living cells.[3762-3765] Under normal circumstances, nanorobot diapedesis including endothelial gap widening, nanorobot extravasation or intravasation, and gap resealing, should be accomplished in some tens of seconds (Section 9.4.4.1). If the gap between parted endothelial cell junctions and the exterior surfaces of the transiting nanorobot is held to 1 micron or less, then platelets, red cells,* and white cells cannot escape from the vascular compartment during diapedesis. This virtually eliminates any possibility of bruising or hemorrhage and greatly limits the potential for thrombogenesis, inflammation or pain at the site of histopenetration. Transdermal injections of nanorobots (Chapter 16) channeled directly into tissue compartments using sensor-tipped metamorphic needles can actively avoid all vascular penetrations, again virtually eliminating any possibility of the local bruising that was common with 20th century hypodermic rigid needles.

Typically more than 70% of the water of the blood is exchanged with extravascular water every minute (~35 cm^3/sec whole-body) — the walls of smaller capillaries are veritable sieves with respect to water (Section 8.2.1.2) — and about 20 liters/day (~0.2 cm^3/sec whole-body) of free water leave the circulation via ultrafiltration through leaky capillaries. Of this amount, 18 liters/day are reabsorbed after passing through the lymphatic capillaries and back into the venous loops, leaving ~2 liters/day to pass onward through the lymphatic system (Section 8.2.1.3). If the mean endothelial-nanorobot gap during the entire transit event is equivalent to a pipe of radius 0.1 micron, length 10 microns, and assuming a histoarterial pressure differential of ~0.1 atm (76 mmHg) for plasma fluid of viscosity 0.001 kg/m-sec (Table 9.4), then from Eqn. 9.25 the Poiseuille plasma fluid flow through each diapedetic gap is at most ~40 $micron^3$/sec. In the worst-case scenario, the simultaneous parallel transit of 10^{12} nanorobots past the ~10^{12} endothelial cells of the human vascular tree (Section 8.2.1.2) releases an additional ~40 cm^3/sec — or roughly the normal extravascular water exchange rate — during the nanorobot fleet transit which may last only some tens of seconds. Total systemic fluid leakage volume during this scenario is 0.5-1 liter (1-2% of total body water, 9-18% blood volume or blood pressure reduction). This is far less than the hourly lymphoplasmatic circulation, and blood hematocrit temporarily rises from 44% to 50-55% in human males, all of which seems tolerable in healthy patients. (A packed cell volume >~55% is the recommended clinical threshold requiring therapeutic bloodletting during apparent polycythemia.[3766]) However, the tolerability will depend largely on the fluid status of the patient (e.g., hypovolemic or euvolemic) and on the patient's cardiovascular status (e.g., how well the heart can compensate for a decrease in blood pressure and volume). In each case, it will be important to assess the patient's health status and evaluate the medical risks, however small, of a nanorobotic procedure — as nothing is totally without risk.

Nanorobot-induced vascular leakage could be pathognomically similar to: (1) fluid retention syndrome[3767] or idiopathic edema, which can produce symptoms of bloating, fatigue and generalized weakness, headaches, blurring of vision, abdominal pains and diarrhea, and (possibly psychosomatic) signs of fibromyalgia;[3767] (2) contracted plasma volume syndromes (relative polycythemias);[3768] (3) vascular leak syndrome[3769] during immunotherapy, with more serious effects; or (4) other systemic causes.[5894] However, patients with high-altitude sickness experience changes in total body water** ranging from 4.7%[3770] to 18%[3771] with an elevated hematocrit >62%.[3771] Edematous patients with chronic severe anemia have body water 14% above normal.[3772] Untreated patients with chronic limb edema,[3773] severe clinical edematous congestive heart failure,[3774] or edematous obstructive pulmonary disease[3775] may have body water 13%, 16% or 21% above normal, respectively. By comparison, a worst-case nanorobot-induced 1-2% change in total body water distribution that persists for perhaps some tens of minutes seems unlikely to prove troublesome. Syncope due to the 9-18% reduced blood pressure (hypotension) also appears unlikely. In one hyperbaric experiment,[3776] a transient ~50% circulatory depression in which arterial pressure fell from 120/80 mmHg down to 60/53 mmHg in just 20 seconds did not cause the healthy young adult subject to lose consciousness or significant mental capacity, and C. Wiley notes that ER or OR patients with systolic pressures in the 70s are often conscious. Another experiment[3777] on children

** During erythrocyte diapedesis, red cells can sometimes pass through endothelial wall openings as narrow as 0.5 microns.[2755]*

*** These shifts, though compensatory for decreased atmospheric pressure and decreased oxygen availability and not due to vascular leakage, may suggest potentially useful thresholds for leakage tolerance.*

exhibiting unexplained syncope found an average blood pressure decline of -45/23 mmHg (-40%/30%) after moving from supine to upright posture, with a 27.7 sec recovery time compared to 16.5 sec for normal children. Yet another study[3778] of postprandial hypotension in elderly subjects found a mean reduction of –30 mmHg (-25%) following an oral glucose tolerance test, with only one of the five subjects reporting a brief episode of light-headedness. Again, it is worth noting that many of the patients receiving nanorobotic procedures may not be healthy young adults, so extrapolation of the data to other populations should be done with caution; it is essential to identify the health status of the patient prior to performing a nanorobotic procedure.

Fortunately, most therapeutic applications may allow local vascular transit rates 1-2 orders of magnitude lower than the worst-case scenario described above, or may involve significantly smaller nanorobot populations in transit. The overall conclusion is that fluid leakage through temporary vascular breaches induced by extravasating or intravasating medical nanorobots can be made acceptable and largely nonedematous, nonhemorrhagenic, and insensible to the patient. It is important to note the risk of passage of some bacteria and viruses between blood and tissue compartments during nanorobot histopenetration. Such risks, although realistically unavoidable whenever tissue barriers are breached, appear to be much reduced when such methods are compared with conventional hypodermic needles.

Elevated interstitial colloid osmotic pressure — most severely, due to blockage of the lymphatics which prevents the normal return of proteins to the circulation — can also cause high interstitial fluid pressure and edema.[5893] Proteins that would normally leak through capillary walls gradually accumulate in the tissue spaces until the interstitial colloid osmotic pressure approaches the plasma colloid osmotic pressure, whereupon the capillaries lose their normal osmotic advantage of holding fluid in the circulation so that fluid now accumulates abundantly in the tissues.[5893] Guyton[5893] notes: "Lymphatic blockage commonly occurs in the South Sea Island disease called filariasis, in which filariae (a type of nematode worm) become entrapped in the lymph nodes and cause so much growth of fibrous tissue that lymph flow through the nodes becomes totally or almost totally blocked. As a result, certain areas of the body, such as a leg or an arm, swell so greatly that the swelling is called 'elephantiasis.' A single leg with this condition can weigh as much as the entire remainder of the body, all because of the extra fluid in the tissue spaces." Care must be taken to avoid analogous lymphatic blockages by large numbers of medical nanorobots passing through, temporarily parked in, or geometrically trapped in prelymphatic pores (Figure 8.5, Section 8.2.1.3) in large tissue regions, or in the lymph nodes — that is, nanorobot-induced lymphedema.[5895-5899] Inflammation (Section 15.2.4) or granulomas (Section 15.4.3.5) of the lymphatic channels due to the presence or passage of medical nanorobots, if not avoided by good device and mission design, could also result in nanorobot-induced lymphangitis with edema[5900-5902] and fibrosis,[5903] with exacerbation of certain infections.[5904]

15.5.2.3 Nanorobot Convoy Formation

All else equal, mechanical damage during histopenetration by medical nanorobots is proportional to the volume of disturbed tissue. The tissue volume required to be displaced by a given population of passing nanorobots is minimized if transit tunnel volumes are reused by successive nanorobots — that is, if nanorobots histopenetrate in linear convoys. More quantitatively, if a population of N_{bot} cube-shaped nanorobots each of edge d moves at velocity v_{bot} through a cubic tissue block of volume L^3 using c_{tunnel} separate histopenetration tunnels each of length L and cross-sectional area d^2, then the tissue holing fraction is $f_{hole} = c_{tunnel}\ d^2 / L^2$, the length of each convoy is $L_{convoy} = d\ N_{bot}/c_{tunnel}$, and the transit time for the fleet is $t_{transit} = (L + (d\ N_{bot} / c_{tunnel})) / v_{bot}$.

For $N_{bot} = 10^9$ nanorobots, L = 1 cm, d = 1 micron, and v_{bot} = 100 microns/sec (Section 9.4.4.2), then randomized single-nanorobot histopenetration ($c_{tunnel} \sim N_{bot}$) gives f_{hole} = 1000% and the block of tissue is entirely holed ten times by the passing nanorobot fleet, a massively intrusive event. However, if f_{hole} = 1% is regarded as an acceptable and fully biocompatible maximum degree of tissue intrusion (Section 15.6.3), then $c_{tunnel} = 10^6$, giving $t_{transit}$ = 110 sec and L_{convoy} = 1 mm. (See also Section 15.3.6.5.)

15.5.3 Vascular Mechanocompatibility

Medical nanorobots may be resident in the vascular compartments of the human body for extended periods of time. Such devices may take the form of individual nanorobots or nanorobotic aggregates arranged in 1-, 2- or 3-dimensional arrays (Chapter 14), and may be free-floating, vasculomobile (endothelial surface locomotion), or anchored. Nanorobots in all their forms must be as mechanically biocompatible with the vascular walls (Section 15.5.3.1) as are stents (Section 15.5.3.2), must not produce mechanical vasculopathies whether obstructive (Section 15.5.3.3) or destructive (Section 15.5.3.4), and must not provoke deleterious changes in vascular permeability (Section 15.5.3.5).

15.5.3.1 Modulation of Endothelial Phenotype and Function

The luminal surfaces of all blood and lymph vessels consist of a thin monolayer (the endothelium) comprised of flat, polygonal squamous endothelial cells (EC) which is a part of the intima (endothelium plus basement membrane and elastic lamina), covering a much thicker layer (the media) which in turn is comprised of vascular smooth muscle cells (SMC). Both layers are subject (and respond) to tangential fluid shear stresses (Section 15.5.3.1.1) across the endothelial cell surface. These stresses are attributable to: (1) the bulk flow of blood,[3782-3785] (2) normal hydrostatic pressure stress acting radially on the vessel wall due to the propagation of the pressure wave, and (3) cyclic stretch or strain (Section 15.5.3.1.2) due to blood vessel circumferential expansion in vivo.[3785-3787] As a result, these two vascular layers might also be sensitive to similar mechanical stresses that may be applied by stationary or cytoambulatory intravascular nanorobots. Increases in vessel wall rigidity could cause diastolic and systolic pressures to progressively diverge, with subsequent increased risk for a vascular event, such as a stroke. M. Sprintz notes that another risk of nanorobots penetrating and residing in the vascular integument is a potential weakening of the vessel wall. This weakening could increase the probability of aneurysm formation or direct rupture of the vascular endothelium, a possibility that should be investigated further and minimized in mission design.

15.5.3.1.1 Fluid Shear Stress

Endothelial cells (EC) are randomly oriented in areas of low shear stress but elongated and aligned in the direction of fluid flow in regions of high shear stress. In vitro endothelial cells previously acclimatized to physiological fluid shear stresses respond to artificial changes in local fluid shear stress only very slowly, and in three stages.[3797] In the first stage, EC initially respond to the imposition of stress within 3 hours by enhancing their attachments to the substrate and to neighboring cells. The cells elongate and have more stress fibers, thicker intercellular junctions, and more apical microfilaments. In the second stage, after 6 hours the EC show constrained

motility as they realign, losing their dense peripheral bands and relocating more of their microtubule organizing centers and nuclei to the upstream region of the cell. In the third stage, after 12 hours the EC become elongated cells oriented in the new apparent direction of fluid flow. Stress fibers are thicker and longer, the height and thickness of intercellular junctions are higher, and the number and height of apical microfilaments are increased. This produces a new cytoskeletal organization that alters how the forces produced by fluid flow act on the cell and how the forces are transmitted to the cell interior and substrate.[3797]

Physiological fluid mechanical stimuli (e.g., fluid shear stresses*) are important modulators of regional endothelial phenotype and function.[3798-3802] For example, endothelium exposed to fluid shear stress undergoes cell shape change, alignment, and microfilament network remodeling in the direction of flow (though nanorobots could block this remodeling, as illustrated crudely via microtubule disruption using nocodazole).[3803] Interestingly, the application of a steady laminar shear stress (a physiological stimulus) upregulates the human prostaglandin transporter (hPGT) gene at the level of transcriptional activation, whereas a comparable level of turbulent shear stress (a nonphysiological stimulus) or low stress (such as a vascular surface coated with sessile nanorobots) does not.[3802] The precise molecular mechanisms that mediate shear stress response were unknown in 2002, although the cell-cell adhesion site is a likely location of flow sensing and PECAM-1, a cell adhesion molecule found at that site, has been suggested[5768] as one possible mechanoresponsive mechanism. Fourfold-elevated hemodynamic wall shear stress also produces elevated neointimal SMC apoptosis in baboon aortoiliac grafts,[5949] and an increase in blood flow and velocity in canine vein grafts produced elevated apoptosis within the adventitia and media of the vein during the first week following grafting.[5952]

Endothelial cells thus respond to sustained physiological fluid shear stresses** from 0.02-100 N/m^2, spanning the range of normal arterial wall fluid shear stresses of 1.0-2.6 N/m^2 from the aorta through the capillaries[3813,3814] and 0.14-0.63 N/m^2 for the venous circulation.[3814,3815] By contrast, legged vasculomobile medical nanorobots may apply shear stresses during luminal anchorage or cytoambulation at velocities up to 1 cm/sec of at least 40-200 N/m^2 or higher (Section 9.4.3.5). (Self-expanding aortic stents forcibly pulled from the vessel require an extraction force of ~400 N/m^2 assuming a 10-cm length, rising to ~1200-3600 N/m^2 for stents anchored with hooks and barbs.[3816] Varying the radial force applied by stents against the vascular wall has little impact on the required extraction force.) Such shear forces, if imposed unidirectionally by large numbers of closely-packed co-ambulating nanorobots for time periods of >10^3 sec, may induce significant changes in shape, orientation, and physiological function in the underlying endothelial cell population. If instead these forces are applied in randomized directions by opportunistic individual nanorobots cytoambulating across the local endothelium for very short durations, then mechanically-induced modulation of endothelial phenotype and function would be greatly diminished or possibly eliminated.

A nanorobot aggregate that shields vascular cells from fluid shear for an extended time may induce those cells to revert to their flow-unstressed phenotype or to undergo apoptosis. Analogously, endothelial cells cultured in the absence of shear stress rapidly lose many of their differentiated features and become insufficiently adherent to artificial surfaces to resist physiological shear stress.[3817] In one study,[3818] after blood shear was artificially reduced near a wound lesion for 24 hours the local endothelial cells became less elongated, contained fewer central microfilament bundles, and exhibited a slower repair process. Endothelial cell apoptosis was observed for a week after a decrease in carotid arterial flow by closure of an arteriovenous fistula in rabbits.[5951] In another study with rabbits, vein grafts removed from the higher-shear arterial circulation and reimplanted in the lower-shear venous circulation of the same animal showed regression of intimal hyperplasia and medial rethickening in 14 days, apparently due to induction of smooth muscle cell apoptosis by a reduction in pressure or flow forces.[3819] Stent implantation in the canine portal vein also has induced a prolonged apoptotic response in intimal and medial smooth muscle cells.[5950]

15.5.3.1.2 Stretch Forces

Endothelial cells can respond to persistent static overstretching in many ways, up to and including apoptosis. For instance, hypertension caused by hydrostatic edema can induce apoptosis in capillary EC.[3820]

Vascular wall cells also respond to lateral stretch forces due to cyclical blood vessel expansion in vivo. For example, in one experiment[3854] bovine aortic endothelial cells were seeded to confluence

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** For laminar fluid flow in cylindrical tubes of radius R and length L through a pressure differential of ΔP, the fluid shear stress[3814] is RΔP/2L.*

*** A few of the many quantitative experimental observations include:*

1. *shear stresses from 0.02-1.70 N/m² produce flow-induced membrane K⁺ currents;[3798]*
2. *cultured subconfluent bovine aortic endothelial cells subjected to uniform fluid shear stress of 0.1-0.5 N/m² proliferate at the similar rates and achieve similar saturation density as static cultures, but confluent monolayers exposed to 0.5-1.0 N/m² laminar shear stress undergo a time-dependent change in cell shape from polygonal to ellipsoidal, becoming uniformly oriented with flow;[5960]*
3. *physiological shear stresses of 0.35-11.7 N/m² stimulate mitogen-activated protein kinase in a 5-min peak response time;[3804]*
4. *0.04-6 N/m² shear stresses increase inositol trisphosphate levels in human endothelial cells, with a 10-30 sec peak response time;[3805,3806]*
5. *shear stresses from 0.5-1.8 N/m² regulate (in frequency and amplitude) oscillating K⁺ currents known as spontaneous transient outward currents or STOC which are observed both in isolated bovine aortic endothelial cells and in intact endothelium; activation of STOC depends on the existence of a Ca⁺⁺ influx and is blocked by 50 μM of Gd⁺⁺⁺ or is significantly reduced by 20 μM of ryanodine;[3807]*
6. *shear stress of 1.2 N/m² induces transcription factor activation over response times ranging from 0.3-2 hours;[3779]*
7. *shear stresses of 1.0-2.5 N/m² induce increased ATP release from endothelial cells;[5715]*
8. *arterial shear stresses of 1.5-2.5 N/m² induce endothelial fibrinolytic protein secretion[3800] (though a venous shear stress of 0.4 N/m² does not);*
9. *shear stress of 2 N/m² induces TGF-β1 transcription and production in a ~60 sec initial response time, with a sustaining increase in expression after 2 hours;[3808]*
10. *a shear stress of 2 N/m² suppresses ET-1 mRNA on confluent bovine aortic endothelial cell monolayers;[3809] these effects of shear may be completely blocked (thus allowing ET-1 to be expressed) using 875 nM of herbimycin to inhibit tyrosine kinases or 10 μM of quin 2-AM to chelate intracellular Ca⁺⁺, partially inhibited using 3mM of tetraethylammonium (TEA), or attenuated by elevated extracellular K⁺ at 70 mM or completely inhibited by K⁺ at 135 mM;[3809]*
11. *shear stress of 3 N/m² induces Ca⁺⁺ membrane currents in a 30 sec peak response time;[3810]*
12. *shear stress of 6 N/m² applied for 12 hours causes endothelial cells to align with their longitudinal axes parallel to flow;[3795]*
13. *membrane hyperpolarization occurs as a function of local shear stress up to 12.0 N/m², with an exponential approach to steady state in ~1 minute; the process is fully reversed once the artificial fluid flow stress is removed;[3799]*
14. *critical shear stress of 42 N/m² is the disruptive threshold for endothelial cells, inducing cell mobility;[3811] and*
15. *shearing stresses of 5-100 N/m² occur at the contact interface when a leukocyte is adhering to or rolling on the endothelium of a venule.[3812]*

on a flexible membrane to which cyclic strain was then applied at 1 Hz (0.5 sec strain, 0.5 sec relaxation) for 0-60 min. After 15 minutes of this cyclic stretching, there was an increase in adenylyl cyclase (AC), cAMP, and protein kinase A (PKA) activity of 1.5-2.2 times control levels at 10% average strain, as compared to unstretched cells, but there was no activity increase at 6% strain. Evidently, cyclic strain activates the AC signal transduction pathway in endothelial cells by exceeding a strain threshold, thus stimulating the expression of genes containing cAMP-responsive promoter elements. Stretch-activated cation channels in bovine aortic EC are inhibited by $GdCl_3$ at 10 μM.[3809] Human umbilical EC subjected to a 3-sec stretch pulse show an intracellular rapid-increase Ca^{++} spike, followed by a (ryanodine-inhibitable) slower prolonged influx, due to biphasic Ca^{++} entry into the cell through stretch-activated channels. Mn^{++} also permeates mechanosensitive channels (but not Ca^{++} channels) and enters the intracellular space immediately after an application of mechanical stretch.[3787] Cyclic strains of 10% at 1 Hz induce intracellular increases in Ca^{++},[3823] diacylglycerol,[3821,3822] inositol trisphosphate[3821-3823] and protein kinase C (PKC)[3821] in peak response times of 10-35 sec, often sustained for up to ~500 sec. These strains also induce transcription factor activation over response times ranging from 0.25-24 hours.[3779-3782] Several endothelial cytokines are elicited by cyclic mechanical stretch,[3824] and cyclic mechanical strain modulates tissue factor activity differently in endothelial cells originating from different tissues.[3825] The physical and mission designs of nanorobotic organs containing moving components or of vasculomobile nanorobot aggregates must take these differences properly into account.

Similarly, bovine aortic smooth muscle cells (SMC) seeded on a silastic membrane and subjected to cyclic strains up to 24% enhanced SMC proliferation at any strain level,[3826] although SMC under high strain (7-24%) showed more proliferation than SMC at low strain (0-7%) in this experiment. High-strained SMC aligned themselves perpendicular to the strain gradient, whereas low-strained SMC remained aligned randomly. PKA activity and CRE (cAMP response element) binding protein levels increased for highly strained cells, compared to low-strained cells.[3826] Other experiments have found that:

1. small mechanical strains of 1-4% at 1 Hz applied to human vascular smooth muscle cells can inhibit intracellular PDGF- or TNFα-induced synthesis of matrix metalloproteinase (MMP)-1;[3855]
2. saphenous vein SMC distention by 0.5 atm pressure subsequently elevates cell apoptosis;[3827]
3. cyclic mechanical strain at normal physiological levels decreases the DNA synthesis of vascular smooth muscle cells, holding SMC proliferation to a low level;[3828]
4. 1 Hz, 10% cyclic strain on SMC activate tyrosine phosphorylation and PKC, PKA, and cAMP pathways over response times from 10 sec to 30 min;[3826,3829] and
5. vascular SMC exhibited stretch-induced apoptosis when subjected to cyclic 20% elongation stretching at 0.5 Hz for 6 hours.[3862]

Hipper and Isenberg[3828] suggest that abnormally low strains can also induce vascular SMC proliferation. If true, then medical nanorobot aggregates which shield the vasculature from normal cyclical strains might elicit excess growth of vascular smooth muscle cells, which growth is normally held in check by the rhythmic stretching from the arterial pulse. On the other hand, intravascular nanorobot aggregates that apply cyclic mechanical strains exceeding a few percent might encourage increased SMC proliferation and activate mechanosensitive and stretch-activated channels in EC, along with cellular realignment and subsequent SMC apoptosis at the highest strain levels. These factors must be taken into consideration during nanorobot mission design so that mechanisms can be incorporated to prevent or to attenuate such effects.

In 2002 it was unknown whether high frequency (>KHz) cyclic mechanical strains likely to be employed by vasculomobile medical nanorobots (Section 9.4.3.5) would have biological effects similar to or different from those described above for low-frequency cyclic strains — excepting certain specialized mechanoreceptor cells such as the cochlear stereocilia,[3830] other hair cells,[3831-3833] and somatosensory neurons[3834-3836] — since most mechanical cell stimulation experiments have been conducted at low frequencies.* Unrecognized effects that might be triggered by high-frequency cyclic strains cannot be ruled out. However, given the relative safety of procedures involving intravascular ultrasound[3837-3846] with its low complication rate (e.g., only 1.1%, including spasms, vessel dissection and guidewire entrapment[3840]) using frequencies as high as 10-20 MHz,[3837-3839] it seems improbable that KHz or MHz acoustic waves of the intensities that might be employed by medical nanorobots for communication (Section 7.2.2) or power supply (Section 6.4.1) will damage the endothelial vascular walls. Interestingly, relatively high-intensity intravascular ultrasound has been used to dissolve occlusive platelet-rich thrombi safely and effectively in myocardial infarctions[3842] and in restenosed stents.[3845]

In the case of intrusive vasculoid-class devices[4609] (Chapter 30), it is likely that the appliance will need to control smooth muscle cell proliferation,[4610-4617] in the simplest case releasing specific cytokines into the vasculoid-endothelial space. Such factors may include known SMC proliferation promoters[4618,4619] such as thrombin (esp. alpha-thrombin), PDGF's (esp. PDGF-AA), FGF (esp. basic FGF), HBEGF (heparin binding epidermal growth factor), TGFβ (transforming growth factor-beta) at low concentrations, angiotensin II, thrombospondin-1 (stretch/tension), and known SMC proliferation inhibitors[4620-4626] such as heparin sulfate, TGFβ (transforming growth factor-beta) at high concentrations, nitric oxide, prostaglandins, calcium antagonists, agonists that activate guanylate and adenylate cyclases, inhibitors of angiotensin-converting enzyme, interferon gamma, 18-beta-estradiol, sodium salicylate, and the topoisomerase I inhibitor topotecan. (Note that these promoters and inhibitors can have multiple effects on other cells, so these effects must be considered prior to use.) Adult arterial walls contain both differentiated and immature SMCs.[4627] Reviewer R. Bradbury notes that further research may be needed regarding how SMCs handle conflict resolution between simultaneous "divide" and "don't divide" signals they may be receiving. Given the large number of signals that SMCs currently respond to, it seems highly likely that the vasculoid can "manage" them.

15.5.3.2 Vascular Response to Stenting

Mechanical biocompatibility must also be demonstrated by intravascular nanorobots that are intended to remain in long-term contact with blood vessel walls. A good medical analog is the vascular stent. A stent is a flexible metal coil or open-mesh tube that is surgically inserted into a narrowed artery, then expanded and pressed into the vascular wall at up to 10-20 atm pressure. The stent

** Specifically, between 0.05-5 Hz (Section 9.4.3.2.1) and more recently at: 0.01 Hz,[3847] 0.03 Hz,[5085] 0.05 Hz,[3848,3864] 0.1 Hz,[3847,3852] 0.15 Hz,[5085] 0.2 Hz,[3849] 0.3 Hz,[3850-3853,5085,5086] 0.4 Hz,[3860] 0.5 Hz,[3828,3861-3864,4767,5087] 1 Hz,[3853-3859,5088-5094,5331] 2 Hz,[5095] 3 Hz,[3853] 4 Hz,[3865] 5 Hz,[3866,5094] 6 Hz,[3860] 10/20/50 Hz,[3865,5094] and DC-100 Hz.[3867]*

ensures long-term local vascular patency by providing a scaffold to hold the artery open. Within 4 days, SMC begin to appear in the intima.[3868] After a few months the stent is completely encased in new endothelium, forming a neointima, although the media is usually compressed with smooth muscle cell atrophy in all stented regions. Stenosis is prevented in vessels 10 mm or greater in diameter but is not precluded in vessels smaller than 6 mm.[3869] Histologically, in-stent restenosis appears to derive almost exclusively from neointimal hyperplasia.[3870,3871] Hyperplasia appears more abundant following stent implantation than balloon angioplasty, and more abundant in stents of greater stent length and smaller vessel caliber, or after inadequate stent expansion.[3872] Restenosis occurs in 22-46% of all stents emplaced within 6-12 months[3873]), in some cases requiring the insertion of a second stent into the first.[3874] Restenosis varies according to the material used. In one experiment,[1372] the thickness of the neointimal layer formed over wire-mesh stents placed in canine aortas was 83.9 microns thick for gold, 103.6 microns for stainless steel, 115 microns for Teflon, 209.6 microns for silicone, and 228.6 microns for silver. A copper stent produced severe erosion of the vessel wall, marked thrombus formation, and aortic rupture.[1372]

Improved prospects are reported for diamond-coated stents (Section 15.3.1.3), and stent surface coatings and textures can affect platelet-leukocyte aggregation and platelet activation.[3875] But all these devices are far from ideally mechanocompatible with blood vessel walls. For example, stents placed endovascularly in dog aorta for 4-45 weeks and then examined histologically show medial atrophy, intimal hyperplasia (tissue ingrowth), and proliferation of the vasa vasorum (the microvasculature of the aorta) more prominently for covered stents than for bare stents, probably due to hypoxia in the aortic wall.[3876] Cellular proliferation is highest when the artery wall is most hypoxic.[3877] Medical nanorobot aggregates that entirely cover the vascular endothelium can precisely regulate wall oxygenation by controlled oxygenation of the underlying tissue, using oxygen sourced directly from the blood.

Nanorobotic stents also should be able to inhibit stenosis due to vascular smooth muscle proliferation, migration, and neointima formation, without inducing apoptosis — e.g., possibly by releasing the topoisomerase I SMC-proliferation inhibitor topotecan in a localized 20-min exposure,[3878] or by using other similar drugs.[4913] In 2002, a new generation of vascular stents employing a similar strategy was introduced in the U.S. after previous testing in Europe. These new stents were impregnated with antibiotics such as Rapamune (sirolimus or rapamycin)[4892-4897] or other stent-eluting agents such as paclitaxel (an antimitotic drug that inhibits vascular smooth muscle proliferation in vitro),[4897-4902] docetaxel (a microtubule polymerizing agent with antiproliferative properties)[4903] or taxane[4904] in some cases virtually eliminating restenosis. The protection against restenosis persists even after the stent eluate is exhausted. Other impregnating agents such as human recombinant hepatocyte growth factor (a potent endothelial cell mitogen)[4906] can attenuate neointimal proliferation via quick endothelialization, and thus might also be useful in stents to prevent restenosis. Beta-particle radiation-emitting stents[4907-4911] can reduce luminal restenosis but induce restenosis at the edges (the "candy wrapper" effect[4897]) and have other undesirable long-term complications.[4912]

Arterial stents can also trigger thrombosis by inducing platelet activation due to shear forces, contact to the biomaterial, and release of metal ions. These triggers are all significantly lessened in diamond-coated (DLC) stents, reducing thrombogenicity and neointimal hyperplasia.[4723,4725] Drug-coated stents (e.g., dexamethasone[4905,4913]) can reduce or eliminate inflammation as well.

15.5.3.3 Nanorobotic Obstructive Mechanical Vasculopathy

Nanorobots, whether passive or active, may become trapped in the microvasculature if any one of their physical dimensions nearly equals or exceeds the diameter of the smallest capillaries, about 4-7 microns (Sections 8.2.1.2 and 15.4.2), thus producing a simple geometric obstruction. Positionally stable nanodevice protrusions (Section 15.5.3.6) into the bloodstream — such as dedicated energy organs (Section 6.4.4) — must be carefully designed to avoid both geometric and overgrowth-related vascular obstruction.

Motile medical nanorobots that are present intravascularly in large concentrations must take care to avoid swimming into "traffic jams" and the formation of a localized embolus (Chapter 12) that could physically block free circulation through a particular vessel[3879] For example, catheter emboli[3880] are foreign bodies that must be removed from the vasculature.[3880] Similarly, nanocrit concentrations of passive nanorobots higher than 10% may lead to increased viscosity and plug flow of the blood (Sections 9.4.1.5 and 9.4.2.6) and a significant impairment of the systemic circulation. In contrast, the deformability of normal red cells allows them to be packed by centrifugation to nearly 100% cells (vs. only ~60% for hardened red cells[3881]). Leukocytes are much less deformable than erythrocytes, and even more so when neutrophils are activated and are aggregating during phagocytosis of locally dense concentrations of bacteria.[3882] White cells present in large numbers can cause leukostasis.[3883-3887] Leukostasis is a plugging of the microcirculation, especially after mechanical interventions producing surgical trauma[3888,3889] or unintentional chaotic activation of the complement system.[3890]

Vascular spaces may also become physically obstructed by new endothelium that accumulates on almost any surface placed in the circulation for a period of time. In 1963, Stump et al[3891] first observed that a 4.5 cm Dacron vascular implant was fully endothelialized after 7 days of implantation in a pig, and subsequently that a small square Dacron hub suspended in the center of a Dacron prosthesis and having no direct contact with the prosthetic wall became completely coated with endothelial cells after a 4-week canine implantation. Spontaneous endothelialization from the circulating blood has since been confirmed by others.[3892-3896] Unless specifically designed to avoid it, blood-contacting surfaces of large positionally-stable nanorobotic protrusions or aggregates may eventually become coated with endothelial cells. Such cells will have migrated either from the endothelium of adjacent arteries or from nearby capillaries, or will have arrived as bloodborne CD34+ endothelial precursor stem cells which can seed the nanorobotic surface and then differentiate into EC.[3896] Energy organs that emit electrical fields or directly release glucose into the bloodstream may attract both microbes and phagocytes to the site, as well as promoting "benign" neoplastic growth and endothelialization, further increasing the potential for vascular obstruction.

15.5.3.4 Nanorobotic Destructive Mechanical Vasculopathies

The physical configurations or activities of medical nanorobots and their aggregates could in some circumstances be destructive to vascular tissue.[3897] Owens and Clowes[3898] point out that the severity of arterial injury is important in determining the ultimate pathophysiologic response. They describe a classification system[3899] based on the immediate histologic effect of the injury:

Type I injuries involve no significant loss of the vessel's basic cellular architecture, although there may be a slight change in endothelial architecture and associated cellular adhesion. Examples include the fatty streak (an early atherosclerotic lesion), hemodynamic

factors and flow disturbances which produce, at most, only a modification of the established cellular architecture.

Type II injuries involve loss of the endothelial layer, perhaps inducing platelets to adhere and begin forming a thrombus at the area of loss, but the internal elastic lamina remains intact and there is little or no damage to the media. Examples include injuries incurred during simple arterial catheterization, endovascular procedures, vein graft preparation, or gentle filament-induced endothelial denudation of the carotid artery in a rat model.[3900]

Type III injuries involve transmural damage in which the endothelium is removed, the internal elastic lamina is often disrupted, and a significant portion of the medial cells are killed.[3900,3901] In these situations, platelets deposit and a thrombus forms at the site of endothelial loss. An inflammatory response (vasculitis) including intimal hyperplasia[3898] is initiated within the vessel wall. Examples include spontaneous vascular dissection and various forms of surgical repair or reconstruction such as balloon angioplasty, endarterectomy, and atherectomy.

Nanorobot device and mission designs should always seek to avoid causing Type II and Type III injuries, although in some special circumstances the potential even for Type III injuries may be inescapable. Destructive vasculopathies which might be caused by medical nanorobots may be classified as ulcerative (15.5.3.4.1), lacerative (15.5.3.4.2), or concussive (15.5.3.4.3).

15.5.3.4.1 Nanorobotic Ulcerative Vasculopathy

A macroscale nanorobot aggregate might cause luminal vascular ulceration by prolonged mechanical pressure against intimal tissues, similar to pressure necrosis or epithelial pressure ulcers (Section 15.5.1.3). The symptoms might appear similar to the inflammatory condition of necrotizing vasculitis, whose cause is unknown but is probably usually related to autoimmune factors.[5598] Prolonged pressure could induce apoptosis. For example, mechanical stretch induces apoptosis in mammalian cardiomyocytes[3902] and hypertension caused by hydrostatic edema can induce apoptosis in capillary endothelial cells.[3820] Another example of mechanical ulceration, though not, strictly speaking, within a vascular lumen, is IUD-induced metrorrhagia[3903] (nonmenstrual uterine bleeding), wherein the intrauterine device elicits a vascular reaction that is most pronounced in the endometrium adjacent to the device. This reaction includes increased vascularity and degeneration with defect formation, which may lead to interstitial hemorrhage due to vascular damage from mechanical stress transmitted by the IUD through the endometrium to its vascular network.[3903]

Except in unusual cases,[3904] indwelling catheters can rest snugly against the vascular walls without complication for long periods of time — common recommendations that indwelling lines should be changed every 2-7 days[5599] are motivated by the ever-increasing risk of bacterial infection over time, not by the risk of vascular ulceration. A biological-like interface would further reduce the chances for nanorobotic-related ulceration in longer-term medical missions involving permanent or semi-permanent implants. In one study, a stented aortic graft was placed endovascularly inside the native aorta of male sheep, and a histological examination 6 months later found good incorporation of the graft with no pressure necrosis, although there was a foreign body reaction around the graft and an organized blood clot was noted between the graft and the aortic wall.[3905] (C. Wiley notes these are now in fairly common use in humans for repairing abdominal aortic aneurysms.) A few possible cases of vascular ulceration are also known — e.g., a chronic indwelling catheter that led to erosion and rupture of the anterior wall of the right ventricle, producing a near-exsanguinating hemorrhage[3933] (far more serious than traditional cardiac tamponade).

Ideally, long-duration nanorobotic organs or nanoaggregates that must maintain close contact with endothelium should employ a mechanically compliant coating having properties similar to extracellular matrix. All such linkages should be not just immunocompatible but also mechanocompatible, possessing an elasticity or mechanical compliance[3906] equivalent to the underlying tissue to which attachment must be secured. Compliance design may include assessments of: (1) circumferential compliance (measurement of changes in vessel diameter over a complete cardiac cycle, including pressure-radius curves,[3907] dynamic compliance,[3908] and mechanical hysteresis effects);[3906] (2) longitudinal compliance (elasticity of selected lengths of the vascular system, including any localized stiffening);[3909] (3) tubular compliance (imparity of elasticity between a prosthetic conduit and the native artery, elastic energy reservoiring, and pulsatile energy losses due to interfacial impedance mismatches);[3910] and (4) anastomotic compliance (suture line anastomotic compliance mismatch and the para-anastomotic hypercompliance zone,[3911,3912] localized regions of excessive mechanical stress,[3913-3915] and cyclic stretch effects on replication of vascular SMC and extracellular matrix[3914,3917]). A mismatch in mechanical properties between relatively compliant arteries and less-compliant metallic stents[3918] and tissue grafts has been thought to influence patency[3913] and pseudointimal hyperplasia.[3914-3916] Larger more central arteries are more compliant than the distal small-caliber arteries.[3919] Wall shear stress from blood flow differs on either side of a curving vessel and the stress is out of phase with the pulsing circumferential stretch strain.[3920] Significant compliance mismatch between host artery and prosthetic graft may promote subintimal hyperplasia.[3911]

15.5.3.4.2 Nanorobotic Lacerative Vasculopathy

Individual free-floating intravascular nanorobots or vasculomobile individual devices or nanorobotic aggregates may occasionally scratch, scrape, or gouge the vascular luminal surface, causing partial or complete loss of local endothelium (Type II damage), resulting in a form of mechanical vasculitis or capillaritis. Since the typical dimensions of bloodborne nanorobots approximate the endothelial thickness (~0.2-2.0 microns[2752,5953-5955]), transmural Type III damage to the media is unlikely. Turnover studies of rat endothelium show that: (1) injured endothelium can recover an area one cell wide (~1000 micron^2) in ~3 hours,[4600] (2) the natural loss rate is ~0.1% of endothelial cell area per day (~1 micron^2/day),[4601] and (3) the steady-state vascular denudation area is ~0.125 micron^2/cell.[4602]

Smooth nanorobot hulls lacking sharp edges or protrusions (during travel), boundary layer effects, and low blood velocity throughout the nonarterial vasculature should ensure that major "sandblasting" type erosion[3921,3922] is unlikely to occur inside human blood vessels even at the highest nanocrits consistent with continuous flow. Free-floating nanorobots that collide with blood vessel walls (given the no-slip condition at the wall) produce minimal shear forces, on the order of <~0.1 N/m^2 (Section 9.4.2.2). This is less than the 1.0-2.6 N/m^2 shear forces normally encountered in arteries and capillaries due to normal blood flow and the 0.14-0.63 N/m^2 shear forces in veins, but may be sufficient to cause a small biological response from the vascular endothelium (Section 15.5.3.1.1). Applying the maximum bloodstream velocity of ~1 m/sec (Table 8.2) to the impact-scratch relation (Eqn. 9.96) given in Section 9.5.3.6, it is clear that particle-wall collisions should produce only harmless submicron nicks even in the most turbulent arteries.

Nevertheless, some caution is warranted because natural endothelial cell wounding of 1-18% of all cells, possibly erosionally-derived, has been observed in rat aorta.[3923] Erosion of cultured fibroblast monolayers (simulating the vascular endothelium) using MHz ultrasound at acoustic pressures of ~10^6 N/m^2 is enhanced by the presence of a microbubble (particulate) contrast agent.[3924] Injection of crystalloid cardioplegic solutions into canine hearts at pressures >110 mmHg and at peak flow rates >25 ml/sec also causes a higher incidence of mechanical-physical trauma to the vascular endothelium and the endocardium.[3925] In another unusual case, intravenous self-injection by a drug abuser of dissolved tablets containing microcrystalline cellulose as filler material produced numerous microcrystalline cellulose pulmonary emboli, intravascular foreign body granulomas, focal necrosis and edema of the pulmonary parenchyma, and fatal vascular destruction.[3926]

Endothelial abrasion alone may not stimulate neointimal thickening[4599] but inevitably must involve some endothelial cell loss[3927] and other biological responses. For example, mechanically scraping cultured endothelial cells causes growth factor to be released within 5 minutes, not abating for at least 24 hours thereafter, due to plasma membrane disruption.[3928] In cases of vascular dissection, a piece of the endothelium peels up (with the break often extending deeper, into the media), making an intimal flap that defines regions of true and false lumina.[3837] Sometimes this may induce an intramural hematoma in the aortic wall.[3837] Endothelial cells mechanically damaged with a razor blade activate extracellular-signal-regulated kinases within ~300 sec, releasing fibroblast growth factor (FGF-2) which in turn induces intimal hyperplasia.[3929] Nanorobots which detect FGF-2 are alerted that mechanical endothelial injury has taken place. By absorbing the cytokine using molecular sorting rotors, the hyperplasia signal could be suppressed by a team of nanorobots, if desired (Section 7.4.5.4). However, shear-induced endothelial denudation of healthy canine arterial endothelium appears not to occur at shear stresses up to at least 200 N/m^2.[3930] The role of erythrocyte collisions with vascular walls on the detachment rate of endothelial cells is just starting to be seriously investigated.[3931]

15.5.3.4.3 Nanorobotic Concussive Vasculopathy

If a patient experiences significant external crushing or concussive forces, resident medical nanorobots that are present in small numbers can simply slide out of the way, as described previously in connection with the risks of dental grinding (Section 9.5.1). In the case of macroscale intravascular nanoaggregates (as opposed to individual physically isolated nanorobots), however, there are several additional risks.

First, sudden external tissue compressions can significantly alter cellular function, especially in the brain.[5956] For example, tests of percussive energy transfer to cerebral endothelium found that endothelial cells subjected to 200-500 Hz pressure waves at ΔP = 1.2-10 atm led human cerebral microvascular endothelium (HCME) cells to immediately lose their normal capacity to suppress adherence of activated platelets, with ΔP < 6.5 atm defined as the sublethal range.[5957] Sublethal percussion trauma also causes HCME to produce inflammatory cytokines (TNF-alpha and IL-1beta)[5958] and alters the response of HCME to cytokine-induced ICAM-1 upregulation, although the normal response is restored by oxygen free radical scavengers.[5959]

Second, there is the possibility that a sudden mechanical external tissue compression could push macroscale nanorobotic aggregates through the soft tissues, causing deep tissue penetrations, perforations, or other serious mechanical trauma. Aggregates with a density exceeding that of biological tissues could, under high acceleration, produce effects on those tissues that would be not unlike pushing gelatin through a metal wire strainer. Possibly relevant but crude analogies in the medical literature include:

1. ulnar artery erosion, thromboemboli, digital ischemia and skin necrosis from a glass foreign body in a patient's hand;[3932]
2. tantalum coil stent damage that was induced or aggravated by intravascular ultrasound inside a coronary artery;[3841]
3. cardiac perforation by a subclavian catheter;[3934]
4. pulmonary artery catheter-induced right ventricular perforation during coronary artery bypass surgery;[3935]
5. an ICD patch that migrated and perforated the right ventricular cavity;[3936]
6. a stent that migrated to an oblique position across the aorta, producing a 7-cm pseudoaneurysm after 3 years;[3937]
7. catheter-induced pulmonary artery rupture (a well-recognized complication of invasive monitoring) that often leads to fatal hemorrhage;[3938-3940]
8. femoral artery catheterization trauma producing hematoma, pseudoaneurysms and arteriovenous fistulas of the femoral vessels;[3941]
9. iatrogenic subclavian artery injury due to central venous catheterization;[3942]
10. repeated and prolonged vein catheterization that led to subsequent stenosis (presumably due to luminal vascular mechanical damage)[3943]
11. high-pressure injection injury that induced inflammation and foreign body granulomatous reaction, progressing to necrosis;[3944]
12. mechanical tearing of arteries due to overstretching;[3945] and
13. (possibly) spontaneous coronary artery dissection (mechanical arterial wall failure).[3946]

Third, a sudden external tissue compression could force nanorobotic aggregates into physical contact with neighboring nanoaggregates, possibly causing major structural damage or fragmentation of the devices. This risk increases as the nanodevices become more densely packed, especially along the crushing axis. Nanoorgans (as well as looser nanorobotic aggregates) can be crushed if sufficient force or mechanical shock is applied, particularly if these aggregates are adjacent to bone or other relatively incompressible materials. Again, a few possibly relevant analogies from the medical literature include:

1. external compression of emplaced stents that produced premature stenosis;[3947]
2. a transabdominal Teflon stent that broke intraperitoneally during tuboplasty procedure;[3948]
3. a strongly-beating heart that sheared off a pericardial drainage catheter;[3949]
4. a Hickman catheter that ruptured and embolized during normal use;[3950]
5. an indwelling catheter that fractured and a distal remnant embolized to the right ventricular outflow tract and main pulmonary artery, nearly precipitating cardiopulmonary collapse;[3951]

6. a catheter embolism that was produced when a catheterized patient engaged in power training exercises, externally crushing the catheter, although no symptoms or complications accompanied this event;[3952]
7. spontaneous fracture of indwelling venous catheter, leading to vascular leakage;[3953] and
8. other instances of catheter fracture and embolism,[3954-3957] including one case that led to cardiac arrest.[3958]

15.5.3.5 Reduction of Vascular Permeability by Nanoaggregates

A nanorobotic aggregate covering a macroscale area of the capillary luminal surface[4609] most importantly could reduce the normal flow of plasma water[3963] and other substances that leave the circulation via ultrafiltration. The plasma water flow helps to remove waste products from the extracellular spaces around tissue cells. This function could be compromised by the shielding presence of the nanoaggregate unless the aggregate replaces this flow with water transported through or around the device, by various means (Section 4.2 in ref. 4609). Many vasoactive substances (Table 7.2) might need similar remedial transport, whether by discharge from preexisting onboard storage, by absorption and banking from the bloodstream (e.g., NO concentration typically ~3.4 ± 2.1 μM or ~10^{-7} gm/cm^3 in the blood of healthy nonpregnant women, measured indirectly as nitrite[5600]) with metered passthrough to the underlying vascular surface, or by other means.

Nanorobotic aggregates may also be required to exhibit pulsatile movements to replace the peristaltic movements which transport lymph, if these mechanical movements have become attenuated due to the presence of the nanoaggregate.

15.5.3.6 Non-Occluding Indwelling Vascular Obstructions

In some applications it may be deemed useful to extend foreign objects into the vascular lumen, as for example power tethers (Section 6.4.3.6) and energy teats from dedicated energy organs (Section 6.4.4), communications fiber networks (Section 7.3.3), temporary or permanent nanocannula (Chapter 19), stents (Section 15.5.3.2), and luminal surface coatings or nanoaggregates including vasculoid-class systems (see ref. 4609; Chapter 30). Nanoscale cables, wires, and other fiberlike protrusions into the bloodstream could induce red cell hemolysis (Section 15.5.5.1.1). By analogy, forcing living cells through a finely-holed rigid strainer destroys them, and red cells can be torn in half by fibrin strands as the cells traverse platelet-fibrin plugs in arterioles and capillaries.[4023,4064] Hemolytic anemia may result from mechanical shearing damage to erythrocytes by microangiopathic fibrin strands in peripheral microvessels.[4060-4064] Indwelling materials that detach or migrate can occlude vital vascular structures, causing significant morbidity and even death (Section 15.4.1).

It is possible that mechanical stress from improperly-engineered vascular-indwelling foreign objects could produce a nucleation site for inflammation, infection, or calcification, and could eventually result in the rupture[5212-5214] or growth[5215-5220] of arteriosclerotic plaque. However, vascular platelet/leukocyte adhesion and smooth muscle proliferation is readily inhibited.[5221] Also, the chronic presence of long strandlike *Dirofilaria* heartworms* lying lengthwise along the luminal walls of canine pulmonary arteries without immediate bloodflow-related pathological consequences (though there is considerable vascular damage[5222-5226]) suggests that it should be possible to design vascular indwelling nanosystems having near-permanent biocompatibility and mechanical stability, possibly involving actual[5226] or biosimulated re-endothelialization. Interestingly, endovascular coil occlusion of vascular aneurysms (in which a platinum wire coil is permanently emplaced inside an aneurysm sac) seems well tolerated clinically.[5685-5687]

15.5.4 Mechanocompatibility with Extracellular Matrix and Tissue Cells

Nanomedical systems interact with components of the extracellular matrix or ECM (Section 9.4.4.2) primarily in two circumstances. First, during histonatation (Section 9.4.4) nanorobots traversing the ECM will apply nondestructive forces to ECM fibers as a consequence of locomotion. Second, traversing tightly-packed cell-rich tissues or performing macroscale surgical procedures may require the dissection, and later the reconnection, of ECM fibrous components by nanomedical systems. This is important because simple detachment of tissue cells from all contacts with the ECM[3964] and the physical manipulation of cell shape[3965] have been shown to induce apoptosis (Section 10.4.1.1) experimentally, and mechanosensitive channels may also modulate cell migration.[3792] However, R. Smigrodzki notes that a rather extreme damage to the ECM would be needed to induce apoptosis — e.g., "probably mere traversing of tissue by nanorobots would not be sufficient to cause it." The mechanocompatibility of nanofibers and stationkeeping nanorobots embedded in human tissue was briefly discussed in Sections 6.4.3.6 and 7.3.3.

Our brief discussion considers first the force threshold for biological response from cells whose physical connections to the ECM are mechanically disrupted (Section 15.5.4.1), and the known diseases involving mechanical damage to the ECM that such disruption might mimic (Section 15.5.4.2). Finally, we consider the size and force threshold for perceptible sensation to the patient, during nanorobot histonatation (Section 15.5.4.3). Many other fascinating but highly specialized mechanocompatibility issues are ignored here, as for example the role of mechanical fluid flows (such as might be generated by micromechanical or nanomechanical devices) in the generation of left-right asymmetry during the development of vertebrate embryos.[6218]

15.5.4.1 Force Threshold for Biological Response

Mechanical stresses modulate cell function by either activating or tuning signal mechanotransduction pathways, via various connections between the internal cytoskeleton, the ECM, and traditional signal transducing molecules.[5332] Vibrations or tugging forces applied to the ECM are transmitted to focal adhesions, attachment points at the plasma membrane surfaces of nearby tissue cells. ECM-cytoskeletal couplings occur through transmembrane integrins having greater mechanical stiffness at high applied stress (>1 N/m^2) than similar couplings through transmembrane E-cadherins.[3966] At the tissue cell surface, gated transmembrane channels are activated by simply stretching the plasma membrane, or by tension or stress development in cytoskeletal elements associated with the cell membrane.[3967,3968] Mechanical strain deformation modulates the morphology, metabolism and activation of: chondrocytes in articular cartilage;[3790,3969] airway[3970] and vascular[3794] smooth muscle cells; primary astrocytes and glioma cells,[3971] neurons,[3789] and auditory sensory cells;[3972] endothelial cells;[3809] and even prostate cancer

** In vivo canine microfilariae are typically ~300 microns long and ~6 microns wide,[3959] but larvae have been grown to 100 microns x 25 microns in vitro[3960] and in vivo sloth* Dirofilaria *parasites have been reported as large as 214 mm in length and 360 microns in width.[3961]*

cells.[3973] Simple fluid nozzling or mechanical prodding elicits mechanosensitivity in rat myocytes[3858] and neurons.[3789,3974] Mechanical pulling force applied by micropipette to the integrin-containing dot-like focal adhesion complexes, ~1 micron in diameter, between cell and ECM leads to local assembly and elongation of these structures into streak-like focal contacts (3-10 microns long). Focal complexes thus serve as cellular mechanosensors exhibiting directional assembly in response to locally applied force.[3975] The response to mechanical strain can take place over a period of years[3976] or can occur as fast as minutes[3788,3858] or even seconds.[3971,3977]

Biochemical transduction of mechanical strain has been investigated quantitatively in bone cells during normal loading. Linear strains of <0.05% are nonstimulative; those between 0.05-0.15% maintain normal bone mass; strains >0.15% stimulate osteoblasts to increase bone mass;[3978-3980] and linear strains >1% induce osteoblasts to alter morphology, becoming fibroblast-like.[3981] For instance, chick osteoblasts subjected to 1.3% applied strain as a 0.25 Hz dynamic spatially uniform biaxial strain for 2 hours experienced elevated osteopontin expression, rising to a maximum 4-fold increase after 9 hours from the beginning of strain onset.[3982] Differentiated mechanosensitive mouse podocytes (glomerular cells) cultured on silicone membrane and subjected to a 0.5 Hz biaxial cyclic stress for up to 3 days at 5% linear strain experienced a reduction in cell body size, a thinning and elongation of cellular processes, and a reversible reorganization of the actin cytoskeleton, uniquely involving formation of radial stress fibers with the disappearance of transverse stress fibers.[3793] A 15% surface-to-surface strain imposed on articular cartilage ECM triggered a shrinkage of chondrocyte cell height (-14.7%) and volume (-11.4%) and a shrinkage of chondrocytes nucleus height (-8.8%) and volume (-9.8%) as well.[3983]

What is the force threshold for biological response by tissue cells to the mechanical disruption of cell-ECM contact? There is a range of forces* from 0.08-400 pN that produces a span of responses in different cells, given that mechanosensitivity is a near-ubiquitous property of cells.[3858] Some biological response may occur near the lower end of this range of forces. For instance, when laser tweezers applied a force of 7 pN to individual bone- and cartilage-derived cells in vitro, an immediate increase in intracellular Ca^{++} ions was observed in human-derived osteoblasts, and force applied to different regions of a cell produced a variable response.[3993] (The response is inhibited by the calcium channel blocker nifedipine.[3993]) In rat femur-derived osteoblasts, the Ca^{++} elevation in response to a similar load was lower, and was entirely absent in primary chondrocytes and the osteocytic cell line.[3993] Osteoblasts also express certain proteins when subjected to fluid shear stress of ~1.2 pN/micron^2 (inhibited by intracellular calcium chelator or by the calcium de-storage agent thapsigargin).[3994] Mechanical shear stress sufficient to generate acute release of prostaglandin E2 (PGE2) in isolated chicken osteocytes (bone mechanosensory cells that translate mechanical signals into biochemical bone metabolism-regulating stimuli necessary for the adaptive process) was induced by 10 minutes of 5 Hz pulsating fluid flow at 0.7 pN/micron^2.[3995] Again, several inhibitors are reported.[3995] Optical tweezer manipulation of neutrophils with ~pN forces does not damage the plasma membrane but instead stimulates a mechanically-inducible, membrane channel-mediated influx of extracellular Ca^{++} into the cell.[3791]

Nevertheless, somewhat higher forces from nanorobotic histonatation (Section 9.4.4) and cytopenetration (Section 9.4.5) might be tolerated without reaction by the ECM because such higher forces are frequently applied by individual motile cells traversing human tissues. For example, the adhesion strength for the protozoan A*moeba proteus* has been measured as ~100-1000 nN,[3996] giving a transient adhesion force of 100-1000 pN/micron^2 over a focal contact area of ~1000 micron^2.[3997] The tension force exerted by a single fibroblast during locomotion has been measured as ~165 nN,[3998] or ~1000 pN/micron^2 (1000 N/m^2). Cell-cell adhesion of T cells and target cells is ~1500 pN/micron^2,[3999] and live cells may apply ~5500 pN/micron^2 constant stress at focal adhesions to ECM.[3977] The foregoing would suggest conservative thresholds for biological response from human tissue cells subjected to nanorobotic mechanical operations of perhaps ~10 pN absolute force, ~1-100 pN/micron^2 shear stress, or ~0.1% linear strain on cellular membrane. If these response thresholds unavoidably must be exceeded, many inhibitors of cellular mechanosensitivity are known[3787-3794] but these must be delivered at μM-mM concentrations to the immediate vicinity of the cell in order to be effective.

Recent experiments with *Lymnaea* neurons[4000] found both the expected result that the probability of mechanosensitive channels being open is proportional to membrane tension, and also the unexpected result that many channels appear insensitive to mechanical stimuli in situ. Failure to elicit mechanocurrents from in situ cells having abundant channels suggests that channels may normally be protected from mechanical stimuli in situ, and that only traumatized cell membrane (i.e., traumatized cortical cytoskeleton) may be unable to prevent transmission of mechanical stimuli to plasma membrane channels, a theory the authors call "mechanoprotection" or "capricious mechanosensitivity". (It is already known that cultured chondrocytes must be externally loaded at >0.5 MPa to prevent disassembly of the vimentin components of their cytoskeleton.[4001]) If these results are confirmed for human tissue cells, then in situ tissue cells would be suppressed from reacting to nanorobots

** We can get a sense of the magnitudes involved by reviewing some of the forces required to mechanically separate, or to extract, integral proteins or ECM-attachment molecules from the cellular plasma membrane. For example:*

1. *0.08-0.35 pN/bond to separate CD2 molecules (expressed on Jurkat cell surface) from two isoforms of transmembrane or glycophosphatidyl LFA-3 (lymphocyte function-associated antigen 3) that are already incorporated into lipid bilayers;[3984,4647]*
2. *2.1 pN to separate platelet cell surface-activated GpIIb-IIIa integrin from an attached fibrinogen molecule, compared to 0.57 pN for nonactivated integrin;[3984]*
3. *4 pN/bond to separate a human T cell and its target cell doublet, with 400 bonds/micron^2;[3984,3990,3999]*
4. *2.8-11 pN/bond to separate murine fibroblast cells bearing ICAM-1 (intercellular adhesion molecule 1) and murine T cells expressing LFA-1 (lymphocyte function-associated antigen 1);[3984,4648]*
5. *6-10 pN to separate each connexin-32 hepatic cell gap junction unit;[3985]*
6. *10-20 pN to extract glycophorin A from RBC membrane;[3986]*
7. *25-45 pN for L-selectin (CD62L) extraction from neutrophil membrane in 1-2 sec;[3987]*
8. *35-85 pN for CD45 extraction from neutrophil membrane in 1-11 sec;[3987]*
9. *~60 pN to extract PSGL-1 selectin from platelet membrane;[3988]*
10. *65 pN to rupture bond between lectin and RBC membrane-bound glycolipids;[3989]*
11. *60-130 pN to extract β2-integrins (CD18) from neutrophil membrane in 1-4 sec;[3987]*
12. *~100 pN to extract integral glycoprotein from cell lipid bilayer (RBC membrane);[3990]*
13. *165 pN to rupture P-selectin bond with leukocyte-membrane-bound P-selectin glycoprotein ligand-1;[3991] and*
14. *40-400 pN to separate a pair of cell adhesion proteoglycan molecules on marine sponge cell surfaces.[3992]*

whose passage produces only nondestructive mechanical strains at their surfaces. Additional research is clearly required.

Similarly, Zhang and Hamill[5662] found that mechanical stimulation of *Xenopus* oocytes by inflation, aspiration, or local indentation (even to the point of membrane damage) fails to activate mechanosensitive ion channels, which they attribute to changes in membrane geometry (e.g., buffer membrane drawn from surface microvilli ~1.4 μm in length, 0.12 μm in diameter, and numbering 6-7/μm^2 on the surface[5663]). The discrepancy between patch and whole cell mechanosensitivity (i.e., "mechanoprotection") arises because animal cells have an excess membrane area (compared to the minimum necessary to cover their volume if enclosed as a sphere) that tends to buffer changes in bilayer tension caused by mechanical stimulation. Notes Owen Hamill [personal communication, 2002]: "For the specific case of a nanorobot, a problem could arise if the robot applied a local increase in tension in the bilayer beyond its elastic limit and thereby ruptured the patch. I would presume that nanorobots would be less able to apply global changes in cell tension. Local changes could occur, for example, if the robot legs in sticking to exposed area of the bilayer (after the external matrix had been removed) stretched a patch of bilayer similar to that what occurs when suction is applied to a patch clamp pipette."

15.5.4.2 Mechanical Damage to Extracellular Matrix Proteins

Uncorrected ECM damage caused by medical nanorobots might resemble any of several human disease conditions that are associated with disruptions in the ECM. For example, muscular dystrophy may be caused by disorganization of links between the intracellular cytoskeleton and the ECM through the plasmalemmal interface.[4002,4003] However, R. Smigrodzki notes that dystrophy usually involves very widespread damage (some of it actually killing the cells), so for this kind of damage to occur, "you would probably need a very high, prolonged level of nanorobot activity." Nanorobot-induced ECM damage might symptomatically resemble cystic fibrosis (which also involves ECM degradation[4004]), though CF is a genetic disorder associated with defective chloride ion channel protein, not mechanical damage per se. Alternatively, nanorobots could disrupt cell-cell connections, causing symptoms analogous to certain desmosomal genetic disorders[4005] or to tumor cell disruptions of normal tissue architecture.[4006] A wide range of connective tissue disorders and mechanical tissue abnormalities are known,[4007,4008] including spontaneous arterial dissections,[4009] perforating disorders of skin,[4010] and genetic disorders of the ECM[4011] (though these genetic coding errors are not due to mechanical damage by an external agency). Hair follicle growth may be compromised following the disruption of epithelial-mesenchymal interactions.[4012] Even a weakened ECM in atherosclerotic plaques can cause fibrous cap rupture in the high stress (>10^5 N/m^2) vascular shoulder regions.[4013] All of these forms of mechanical damage to ECM should be avoidable by good design — specific force and duration thresholds for ECM damage should be investigated experimentally.

Fibrosis as a consequence of injury is characterized by accumulation of excess collagen and other extracellular matrix components, resulting in the disruption of normal tissue architecture and function.[4608] Without careful design, the emplacement of artificial fiber materials in the extracellular spaces by motile fiber-laying nanorobots could induce analogous destruction of normal tissue architecture.

15.5.4.3 Size and Force Threshold for Perceptible Histonatation

Individual nanorobots smaller than ~100 microns in largest dimension are unlikely to cause perceptible sensations during histonatation if physical disturbance of neural cells is avoided and if the passage through tissue does not produce an enlarged or displaced peridermal tissue volume (e.g., via direct mechanical distension or indirectly from edema) sufficient to (1) activate dermal pressure or vibration sensors, stretch receptors, or dermal nociceptors each of which may lie 500-3000 microns from their nearest neighbor (Table 7.3); or (2) to activate vascular stretch sensors or barosensors. Pain has been reported[2086] possibly caused by numerous small insoluble crystals in the renal tubules, a crude nanorobot analog. But motile biological cells such as neutrophils (random motility coefficient 1.6-13.3 x 10^{-13} m^2/sec),[4014] T cells,[4015] dendritic cells,[4016] fibroblasts (tissue transits at 15-55 microns/hour),[4017] hematopoietic progenitor cells,[4018] human mast cells,[4019] brain macrophages,[4020] and tissue macrophages[4021] (up to 80 microns in diameter) regularly ply human tissues completely imperceptibly and without pain, though at modest speeds, typically 0.01-0.7 micron/sec (Section 9.4.4.2).

Inertial and viscous shear forces generated by a single nanorobot of size L ~ 100 μm moving at velocity v ~ 100 micron/sec through a medium of density ρ ~ 1000 kg/m^3 and viscosity η ~ 10^{-3} kg/m-sec is $P_{inertial} = F_{inertial} / L^2 \sim \rho v^2 \sim 0.00001$ N/m^2 and $P_{viscous} = F_{viscous} / L^2 \sim \eta v / L \sim 0.001$ N/m^2, respectively (Section 9.4.2.1). Both figures are well below the ~2900 N/m^2 threshold for first sensation during esophageal wall distension,[3702] or the esthesiometer-measured[4022] minimum epidermal stimulus threshold of ~2000 N/m^2, or even the shear stress activation thresholds for living cells of ~1 N/m^2 (Section 15.5.3.1.1 and 15.5.4.1). However, simultaneous passage of more than a thousand 100-micron nanorobots through the receptive field of an individual skin sensor (~1-1000 mm^3, assuming 1 mm depth; Table 7.3) could elicit some biological response, and the passage of >10^6 of these large nanorobots through the same tissue volume could become perceptible to the patient. Viscous pressure scales inversely with L, so for 1-micron nanorobots the threshold perceptible number density may be as high as 0.1-100 million nanorobots/mm^3, but these figures are little better than crude estimates. Direct experiments will be required to resolve the question.

15.5.5 Mechanocompatibility with Nontissue Cells

The mechanical compatibility of medical nanorobots with nontissue cells, the most numerous cells in the human body, is also of great importance. It has already been estimated (Section 9.4.2.6) that the maximum nanorobotic-induced cell damage rate consistent with human health is ~0.3 damaged cells/nanorobot-day for RBCs, ~0.2 damaged cells/nanorobot-day for platelets, and ~0.03-0.2 damaged cells/nanorobot-day for WBCs — assuming a 1-terabot bloodstream dose of medical nanorobots each measuring 2 microns in diameter. This Section briefly describes several possible mechanical interactions between nanorobots and each of the three largest classes of nontissue cells — red blood cells, RBCs, or erythrocytes (Section 15.5.5.1), platelets (Section 15.5.5.2), and white blood cells, WBCs, or leukocytes (Section 15.5.5.3). Our discussion of nanorobot mechanical interactions with glycocalyx and intracellular components common to most or all human cells is deferred to Section 15.5.7.

15.5.5.1 Mechanical Interactions with Erythrocytes

Possible pathological mechanical interactions uniquely between medical nanorobots and erythrocytes may include nanorobotic-induced hemolysis (Section 15.5.5.1.1), unintentional modulation of red cell membrane fluctuations (Section 15.5.5.1.2), and the disruption of normal erythrocyte aggregation (Section 15.5.5.1.3).

15.5.5.1.1 Nanorobotic Hemolysis

Intravascular hemolysis[4023] occurs when red cells encounter excessive mechanical forces[4024,4025] in the bloodstream, causing the cells to become damaged or destroyed. The hallmark of this type of hemolysis is the fragmented red cell, an irregularly contracted cell called a schistocyte. Schistocytes are seen in all fragmentation syndromes (except those in athletes) and can take the shape of helmets, triangles, burrs, crescents, or microspherocytes. These objects are formed after the shearing of red cells by mechanical trauma, whereupon the torn membranes reseal around whatever hemoglobin remains. Schistocytes are relatively rigid. They cannot tolerate the rigors of the circulation and are soon destroyed. If the amount of hemoglobin released from disintegrating red cells into the plasma exceeds the ability of blood mucoprotein (e.g., haptoglobin) to combine with it (thus allowing removal by the liver), then the excess hemoglobin is lost through the kidneys and appears in the urine, a condition known as hemoglobinuria.

Red cell fragmentation disorders normally arise in three clinical settings: (1) conditions of rapid, turbulent blood flow in the heart or major arteries (e.g., artificial heart valves,[4026,4027,5020] stenotic vessels,[4028,4029] aortic coarctation, arteriovenous fistula); (2) athletic activities involving impact or long-lasting exertion (e.g., march hemoglobinuria, swimmer's hemolysis); and (3) many acquired small blood vessel disorders (e.g., diverse microangiopathies such as hemolytic-uremic syndrome, eclampsia, or vasculitis), which tend to involve variable degrees of thrombosis or disseminated intravascular coagulation,[4023] or various erythropathies. The fragmentation syndrome of thrombotic thrombocytopenic purpura apparently results from the shearing of red cells as they traverse platelet-fibrin plugs in arterioles and capillaries, especially near renal glomeruli — red cells can be torn in half by fibrin strands.[4023,4064] Hemolysis can also occur following the intravenous injection of hypotonic solutions or distilled water. In this case, the red cells swell, become globular, and ultimately burst; all injected solutions must be isotonic with the blood. Finally, at least one case of schistocytic hemolytic anemia has been reported[5393] in a fetus due to a varix (twist) in the intra-abdominal umbilical vein.

Impact hemolysis or "march hemoglobinuria"[4030-4055] is classically seen in marathon runners but has also been described in persons involved in the martial arts,[4051-4055] basketball,[4049] aerobic dancing,[4023] or playing the drums.[4048-4050] Mild intravascular hemolysis also occurs during long swim races.[4056,4057] Although nonmechanical factors may contribute, it is generally believed that most of the damage is caused by mechanical tearing. A human runner of weight ~10^3 N whose footfall force is spread over a ~100 cm^2 area exerts a momentary tissue overpressure of ~10^5 N/m^2. This is well in excess of the red cell fragmentation shear stress limit of 150-250 N/m^2.[4058,4059] Shear forces from free-floating nanorobots are of order <0.1 N/m^2 (Section 9.4.2.2) and vasculomobile or stentlike nanoaggregates could exert forces of order ~10^2-10^3 N/m^2 (Section 9.4.3.5 and Chapter 14), presenting only a minor comparative risk of direct mechanical hemolysis. Conventional stent balloon-installation forces (Section 15.5.3.2) or episodic nanorobotic concussive vasculopathies (Section 15.5.3.4.3) might momentarily apply forces exceeding ~10^6 N/m^2, presenting at least a brief potential risk of hemolysis in these rare circumstances. Exposure of human hands to 120 Hz 250-micron vibrations produces ischemic "vibration white finger," with increased plasma hemoglobin concentration and viscosity.[5409]

Nanoscale or submicroscale cables, wires, or other fiberlike protrusions into the bloodstream (Section 6.4.3.6 and 7.3.3) could directly cause red cell hemolysis. Forcing living cells through a finely-holed rigid strainer destroys them. Red cells can be torn in half by fibrin strands as the cells traverse platelet-fibrin plugs in arterioles and capillaries.[4023,4064] Hemolytic anemia may be a consequence of mechanical shearing damage to erythrocytes by microangiopathic fibrin strands in peripheral microvessels.[4060-4064] The number of schistocytes (re-formed red cell fragments) naturally present in the blood appears to be correlated with the extent of vascular fibrin deposition.[4061] Moderate schistocytosis is common after organ transplantation, with no clinical significance.[4067] Quantified as the number of fragmented red cells per 1000 red cells, expressed as a percentage, normal human blood may contain 0.1-1% schistocytes in mild schistocytosis.[4065-4067] A schistocyte count up to 2% is considered moderate but abnormal;[4065-4067] >2% is considered clinically serious;[4067] up to 6% may be found within 2 hours of a major surgical procedure;[4065] and up to 10% may be seen after intraoperative blood transfusion,[4065] or up to 35% in patients undergoing splenectomy.[4065] Nanorobotic hemolysis of up to ~1%/day of all red cells — the natural rate — or about 0.25 destroyed red cells per nanorobot-day for a 1 terabot dosage (Section 9.4.2.6) can probably be tolerated by the human body. Anemia due to mechanical hemolysis can be ameliorated in some cases by administering erythropoietin.* [5395] Materials-induced hemolysis is near-zero for diamond,[643,660,4726] graphite,[643] and alumina[643] powders, although free aluminum ion may be hemolytic.[1079] Bulk Teflon can be very mechanically hemolytic[1347,1348] and colloidal silica may also be hemolytic.[4068] Intravascular stents do not appear to cause microangiopathic hemolysis or thrombotic microangiopathy,[5389] and replacement of heart valves with contemporary mechanical prostheses has been associated only with subclinical (mild) intravascular hemolysis.[5390,5391]

Careless perforation of red cell plasma membrane by cytopenetrating nanorobots (Section 9.4.5) could result in nanomechanical hemolysis crudely analogous to the hemolysis accompanying certain membrane-perforating parasitic infections such as babesiosis.[4069] Utilization of proper cytopenetration techniques (Section 9.4.5) and the avoidance of extremely rapid manipulator movements (sufficient to rupture RBC plasma membrane) should reduce or eliminate this risk. In some cases, applied forces as small as 10-60 pN may be sufficient[4070] (Section 9.4.3.2.1) to cause red cell membrane fragmentation. The passage of red cells through catheters at various clinically relevant flow rates can cause significant hemolysis.[4071,4072] Each trip through a 14-gauge blood dialysis needle at 91 ml/min and a 2.2 m/sec peak velocity damages 0.001% (near the center) to 0.1% (near the needle wall) of the red cells.[3690] Erythrocyte trauma is increased at elevated static pressures, especially in high-shear conditions.[5394] Larger red cells are more susceptible to mechanical hemolysis than smaller red cells.[5396] The additional hemolytic effects of surface hardness and surface texture (e.g., collision against a sanded wall) are being investigated but may be relevant only for flow velocities exceeding 3 m/sec and surface rugosity exceeding ~1 micron.[4073] Patients with spherocytic hereditary elliptocytosis[5398-5403] — a normally benign condition in which the red cells are oval or elliptically shaped, occurring in 1 of 2000 births[2004] — or pyropoikilocytosis may be at slightly higher risk of mechanical red cell fragmentation because of the greater fragility of these abnormal red cell membranes.[4074,5403,5404]

** In contemporary medical practice, such erythropoietin treatment would be too expensive unless the patient is on dialysis or has a bone marrow disorder. Instead, the treatments of choice are transfusion in life-threatening situations, oral iron supplements otherwise. In an era of advanced molecular manufacturing, human hormones such as erythropoietin should be easily synthesized at a cost of pennies per dose or less (Section 2.4.2, Chapter 19).*

Drugs can reduce the severity of intravascular hemolysis, e.g., by increasing red cell membrane elasticity and compliance.[5397]

15.5.5.1.2 Erythrocyte Surface Fluctuations and Elasticity

Low frequency submicron fluctuations of the cell membrane, known as cell membrane fluctuations or CMF,[4075] have been shown to be characteristic for different cell types[4076-4082] and to occur in the 0.3-30 Hz frequency range.[4075] For erythrocytes,[4085] these fluctuations typically exhibit displacement amplitudes of 160 nm for deoxygenated red cells and 290-400 nm for oxygenated red cells[4082-4084] (236 nm in diabetic patients[4084]) as observed over 0.25-micron^2 membrane surface patches.[4082,4086] These fluctuations apparently provide a dynamic control of bending deformability of the membrane-skeleton complex[4086] and assist red cells in performing their function of oxygen delivery[4087] by improving their efficiency in passing through capillaries narrower than the cellular diameter.[4084]

Nanorobots might incidentally alter red cell membrane mechanical properties by their presence or activities at the cell surface, as in cytocarriage (Section 9.4.7), or might purposely alter those properties by locally extracting, releasing or injecting specific chemical species. For example, nanorobots could elevate the amplitude of red cell bending fluctuations by the local release of human atrial natriuretic peptide.[4087] Adrenaline (epinephrine) and isoprenaline[4086] increase maximum fluctuation amplitude by +45%, although adrenaline stimulates only the low-frequency component at 0.3-3 Hz, reaching maximum effect after 20-30 minutes and fully dissipating after 60 minutes.[4086] Increasing extracellular solvent macroviscosity by adding macromolecules such as dextrans, polyethylene glycol, or carboxymethylcellulose diminishes cell membrane fluctuations.[4075] Wheat germ agglutinin diminishes fluctuations tenfold, and fluctuations are totally suppressed by a 0.01% solution of glutaraldehyde, which also decreases RBC adhesivity to glass by twofold.[4088] Increasing the cholesterol content of the RBC phospholipid bilayer causes large reductions in internal fluidity of membrane and a change in its preferred direction of bending without changing the gross mechanical rigidity. On the other hand, an increase in intracellular (cytosolic) concentration of polyamines (especially spermine) adds to the cohesion of the membrane cytoskeleton and increases the mechanical rigidity of the membrane.[4089] Amphipathic drugs also modify the mechanical properties of the cell plasma membrane.[4090] The tension required to smooth out the thermal undulations or Brownian motions of the outer membrane of artificial phospholipid vesicles 10-20 microns in diameter (~typical cell size) has been determined experimentally as 0.01-0.1 x 10^{-3} N/m[4091] (Section 9.4.3.2.1).

15.5.5.1.3 Disruption of Erythrocyte Aggregation

At low shear rates, red cells aggregate into rouleaux (i.e., the stack-of-coins configuration) and migrate inward, forming a network of linear and branched chain aggregates in the core of the vascular tube (Section 9.4.1.3). Individual rouleaux may incorporate 10-20 red cells, or more, creating by far the largest cellular elements normally present in the blood. At the highest shear rates, the rouleaux break up entirely into single red cells, and the red cells then distribute themselves more uniformly in the radial direction (Section 9.4.1.3). Red cell disaggregation is essentially complete when the shear stress of the cell suspension is raised above 0.2 N/m^2.[4092]

Could medical nanorobots similarly disaggregate erythrocyte rouleaux? Collisions between free-floating nanorobots and rouleaux should produce shear stresses <0.1 N/m^2 (Section 9.4.2.2). The energy required to disaggregate individual red cells has been estimated as ~10^4 ergs/cm^2 (~10 pJ/micron^2)[4093] or a force of ~70 pN (Section 15.5.6.1). A specialized nanomanipulator driven by a ~10 pW power source plausibly could purposely pry apart two aggregated red cells with a mutual contact area of ~10 micron^2 in a time on the order of ~10 sec. But random disaggregation is unlikely to occur during simple elastic impacts between free-floating nanorobots and red cell rouleaux because the kinetic energy of a ~1-micron^3 diamondoid nanorobot even traveling at 1 m/sec is only ~0.001 pJ.

During tube flow, rouleaux migrate inward forming a network of aggregates in the core of the tube surrounded by a peripheral cell-depleted layer consisting of single cells, occasional small rouleaux, white cells, platelets, and, potentially, nanorobots. This results in a two-phase flow of a relatively higher shear rate peripheral zone surrounding a lower shear rate, high cell concentration, central zone.[4094] Even at a maximum 10% Nct blood concentration, nanorobots represent at most 20% of total red cell mass, so collisional dispersion of the high-shear peripheral zone should be modest and effective diffusion rates should remain high. Moreover, free-floating medical nanorobots should exhibit no axial preference[4094] and should be maximally marginated towards the vessel walls even under high-shear conditions (Section 9.4.1.3). This, along with their biochemically inactive diamondoid surfaces, suggests that the mere presence of medical nanorobots in the blood should not interfere with adhesive processes involved in axial rouleaux formation far from vessel walls, where shear rates are lower.

15.5.5.2 Mechanical Interactions with Platelets

Platelets (aka. thrombocytes) are more fragile than red cells and can break more easily in a wound, physically bursting open and spilling out their contents into the local tissue (i.e., degranulation). The material within triggers a complex chain of biochemical events involving numerous proteins that results in soluble fibrinogen being converted into insoluble fibrin, which condenses out in the form of a fibrous scaffolding upon which a clot can be built (Section 15.2.5). The primary danger of unintended thrombocytolysis normally lies at the arterial wall, which may be layered with rough-textured cholesterol and lipid plaques, and where shear forces are highest. Fortunately, hundreds of platelets may break nearby without triggering a local thrombogenic event (Section 15.2.5). The human body normally has ~2.1 trillion platelets in circulation or pooled (Section 8.5.1), each with a ~10 day lifespan,[4095] so the natural platelet destruction (and production) rate is ~2.4 x 10^6 sec^{-1}, almost as many as for red blood cells.

Possible pathological mechanical interactions uniquely between medical nanorobots and platelets may include nanorobotic mechanical thrombocytolysis (Section 15.5.5.2.1) and the disruption of platelet aggregation (Section 15.5.5.2.2). Nanorobots might also interfere with phagocytosis by platelets,[775,868,875,881-883,885] or with the motility of platelets[1969,4096-4099] (e.g., 0.1-0.5 micron/sec across HEMA surfaces[1969]), two relatively minor functions of the platelet which will not be discussed further here.

15.5.5.2.1 Nanorobotic Thrombocytolysis

Collisions between platelets and medical nanorobots in the bloodstream will take place at similar velocities and frequencies as collisions that normally take place between platelets and other natural blood elements. Hence nanorobots should not significantly increase the risk of mechanical thrombocytolysis and subsequent thrombosis. For example, each ~2-micron diameter platelet[4100] present in human blood that contains a 10% Nct of 2-micron diameter nanorobots may experience ~2 collisions/sec with neighboring nanorobots at a mean collision velocity of ~2 mm/sec but may also

experience ~0.5 collisions/sec at ~2 mm/sec with other platelets, ~110 collisions/sec at ~3 mm/sec with nearby red cells, and ~100 collisions/sec at 0.5-5 mm/sec with capillary walls (Section 9.4.2.2). Such high nanorobot dosages induce the highest collision rates because red cells disproportionally occupy blood vessel axial regions[4100] (forcing platelets and nanorobots together preferentially toward the periphery; Section 9.4.1.3) and because erythrocyte flip-flop motions[4094] impart additional radial energy to platelets and nanorobots.

Even with the extra collisional energy, the maximum shear stress per collision is only <0.1 N/m^2 (Section 9.4.2.2). This is far less than: (1) the time-averaged shear stress of 1.5-2.0 N/m^2[24101,4103] (range 0.5-5.6 N/m^2[24094]) for blood circulation in normal vessels, (2) the threshold limit of 6-9 N/m^2 for shear stress-induced platelet aggregation,[4102-4107] (3) the >14 N/m^2 shear stress required for large platelet aggregate (>10-micron diameter) formation,[4109] and (4) up to 10-40 N/m^2 reached when small arteries and arterioles are partially occluded as by atherosclerosis or vascular spasm.[4105-4108] So thrombocytolysis by free-floating nanorobots in the bloodstream seems extremely unlikely.

15.5.5.2.2 Disruption of Platelet Aggregation

Platelet aggregation is necessary for clotting to occur. Detailed studies of two-body collision hydrodynamics and platelet activation[4110] suggest that platelet aggregation takes place at a rate of ~192.5 fibrinogen bonds/micron^2-sec, with ~50,000 GPIIb/IIIa fibrinogen cross-bridging receptors per platelet plasma membrane[4110] and ~46,000 plasminogen binding sites per platelet (the platelet surface serves as a site of assembly for plasminogen and tissue plasminogen activator and facilitates plasminogen activation).[4111]

Could the presence of medical nanorobots in human blood inadvertently — or purposely — interfere with this process? The force required to separate two platelets that have adhered via platelet membrane receptors cross-linked (i.e., covalent bonds) by fibrinogen was tested experimentally with receptor coated latex microspheres.[4112] Doublets were subjected to hydrodynamic shear stress of 0.6-2.9 N/m^2 and doublet breakup occurred as follows: 15.6-17.0% broke up within the force range (70-150 pN) to (230-310 pN), and all of these breakups occurred within the first 10 rotations of the doublet. The rest (~83%) of the doublets did not de-aggregate, up to ~310 pN. Another experiment[3988] found that the adhesion between a neutrophil and an activated platelet is broken in 130-630 millisec as the shear rate is decreased to 100 sec^{-1} (F_{bond} = 86 pN) from 250 sec^{-1} (F_{bond} = 172 pN).

These results suggest that forces of many hundreds of pN must be applied in order to mechanically separate a covalently attached platelet-platelet pair. Such forces are within the abilities of an individual nanorobot designed for the purpose but are unlikely to occur casually during in sanguo operations of the typical manipulator-equipped nanorobot. Of course, nanoaggregates should have no difficulty applying the requisite forces if that is their intended function: the elastic moduli of human platelets measured with AFM range from 1-50 kPa in the frequency range of 1-50 Hz.[4113]

15.5.5.3 Mechanical Interactions with Leukocytes

Nanorobots must also be mechanically compatible with white blood cells (WBCs) or leukocytes, a group of blood cells that includes both granulocytes (neutrophils, basophils and eosinophils) and agranulocytes (monocytes and lymphocytes). Many interactions between nanorobots and neutrophils or other phagocytes have already been described at length in Section 15.4.3. Possible mechanically pathological interactions uniquely involving medical nanorobots and leukocytes may include nanorobotic mechanical leukocytolysis (Section 15.5.5.3.1), unintentional modulation of white cell membrane fluctuations (Section 15.5.5.3.2), interference with leukocyte margination and migration (Section 15.5.5.3.3) and interference with leukocyte aggregation (Section 15.5.5.3.4). The possibility that nanorobots or their errant parts could trigger an unwanted enzyme release from human phagocytes (nanosecretagoguery) is briefly discussed in Section 15.4.4.

15.5.5.3.1 Nanorobotic Leukocytolysis

Nanorobotic leukocytolysis — the mechanical fragmentation of white cells by individual nanorobots or by nanoaggregates — is a less serious concern than hemolysis and thrombocytolysis because there is only 1 white cell in normal human blood for every 740 red cells and 36 platelets. Nevertheless, mechanical white cell fragmentation has been seen in at least one patient who was using single-lumen subclavian hemodialysis catheters.[4071] A leukemic patient[4114] who underwent therapeutic mechanical leukapheresis suffered white cell fragmentation with complications including renal failure and disseminated intravascular coagulation (DIC) (Chapter 17). In another case,[4115] the blood of a patient with extreme leukocytosis was found to have large numbers of platelet-sized particles, originally counted as platelets, but which post-mortem immunological analysis revealed to be leukocyte cell fragments at a particle concentration ~24 times the normal white cell count. In yet another study,[4063] blood smears from half of all patients with septic shock or DIC showed leukocytic fragments, always associated with fragmented erythrocytes, all of which cases (of leukocytolysis) later proved fatal. The appearance of leukocytic fragments in such cases is believed to be related to mechanical shearing through microangiopathic fibrin strands which may also cause erythrocyte fragmentation,[4063] though in DIC death is the result of the concomitant thrombus formation and hemorrhaging.

The responses of white cells to mechanical stress are well known. For example, the sudden imposition of ~0.04 N/m^2 fluid shear stress induces adherent leukocytes to retract their pseudopods, a process involving the breakdown of F-actin and which eventually causes the cell to round and detach from a glass surface.[4116] Raising the peak fluid stress to 0.07 N/m^2 does not increase the rate of pseudopod retraction.[4116] Pseudopod retraction serves a useful biological purpose: to minimize leukocyte entrapment in capillaries. Interestingly, these effects of shear stress may be overridden by integrin-mediated membrane adhesion.[4117] That is, the ability of shear stress to inhibit pseudopod formation may be counteracted by stimulatory agents.

A threshold shear stress above 0.04 N/m^2 is required to support rolling of leukocytes on selectin-coated surfaces[4118] (Section 9.4.3.6). In one experiment,[4119] shear forces on leukocytes rolling on adhesion-molecule-coated surfaces ranged from 0.2-1.5 N/m^2 for VCAM-1 and up to 3-4 N/m^2 for selectins. In another experiment[4120] involving leukocytes rolling on endothelium, the equilibrium force that would balance fluid shear stresses on the leukocyte and the attachment forces at its site of contact with the endothelium spanned 0.11-7.61 nN for wall shear stresses ranging from 0.2-2.5 N/m^2 in venules 23-49 microns in diameter in cat mesentery. Another experiment[4121] found that adherent human PMNs (polymorphonuclear leukocytes such as neutrophils) are virtually all detached from human umbilical vein endothelial monolayers at a shear stress of ~1 N/m^2. However, leukocytes remain rolling at up to 65 microns/sec and attached to endothelium via ~200 selectin binding sites/micron^2 at shear stresses up to at least 3.2 N/m^2 — a neutrophil 8.5 microns in diameter has ~240 microvilli/cell with

~260 L-selectin molecules per microvillus and crawls using up to 9 microvillus tether "feet" during rolling.[4122] The nature of the attachment surface is critical. For instance, half of all adhered human fibroblasts will detach from an FEP-Teflon surface at a fluid shear stress of 2 N/m^2 but more than half of similar cells that are adhered to a glass surface will require 35 N/m^2 to detach, after "rounding" (i.e., assuming a spheroidal shape).[4123]

As for cell lysis, critical shear stress levels have been defined[4124] for the viability, morphology, size, and lysis of adherent mammalian cells between 1-2.5 N/m^2. For example, neutrophils adherent to cardiovascular device material subjected to shear stress above 0.6 N/m^2 for 1 hour undergo complete apoptosis, displaying irreversible cytoplasmic and nuclear condensation while maintaining intact membranes.[4125] Leukocyte suspensions exposed to higher shear stress are subject to cell swelling as well as lysis[4059] and, in T lymphocytes, a depression of the proliferative response.[4126] In other studies, neutrophils exposed in vitro to shear stress of 7.5-15 N/m^2 for 10 minutes will release enzymes both from azurophilic and specific granules.[4127] The number of ruptured leukocytes rises significantly at these levels of mechanical trauma. At 15 N/m^2, the remaining intact cells display morphological changes including clublike cytoplasmic protrusions, spherical shape, and a circumferential distribution of cytoplasmic granules.[4127] Degranulation of cytoplasmic alkaline phosphatase granules begins to appear.[4059] The frequency of disrupted leukocytes increases with shear stress above 15 N/m^2.[4059] Human neutrophils undergo homotypic aggregation in the physiological range of fluid shear stress of 1.2-3 N/m^2, along with an increase in intracellular Ca^{++} concentration,[4128] but aggregates of disrupted cells disappear after exposure to 45 N/m^2 for 10 minutes.[4059] At still higher shear stresses of 60 N/m^2, cell destruction is marked.[4127] Intact PMNs contain fewer cytoplasmic granules, a large number of vacuoles, and condensed nuclear chomatin.[4127] A 10-minute shear stress of 60 N/m^2 destroys 25% of human leukocytes.[4059] On the other hand, non-shear hydrostatic pressures of 10-50 N/m^2 have no measurable influence on the shear stress response of leukocytes.[4116] During micropipette aspiration leukocytes neither retract nor project pseudopods in response to purely hydrostatic pressures of 100 N/m^2 or above.[4116] Interestingly, the bursting strength of whole mammalian hybridoma cells has been measured[4129] by squashing them between two parallel plates. The required bursting force is ~2000 nN (~6400 N/m^2) for 10-micron diameter cells and ~4500 nN (~3600 N/m^2) for 20-micron cells. From this data, we conclude that mechanical interactions between leukocytes and nanorobots or nanorobotic organs imposing shear forces exceeding ~1 N/m^2 for more than an hour may induce white cell apoptosis, or rupture at 10-50 N/m^2 — an important limitation in medical nanorobot mission design.

Shear forces arising from collisions between bloodborne leukocytes and individual free-floating nanorobots are at most <0.1 N/m^2 (Section 9.4.2.2), but may be far less for encounters involving co-vasculomobility or histonatation where the speed of interaction is substantially lower. While it is possible that individual medical nanorobots may unintentionally induce pseudopod retraction or other minor physiological changes in white cells, this possibility may be greatly reduced, given an appropriate device configuration and mission design.

15.5.5.3.2 Leukocyte Surface Fluctuations and Elasticity

As with erythrocytes (Section 15.5.5.1.2), low frequency submicron cell membrane fluctuations (CMF) have also been observed in lymphocytes, monocytes, and even nonleukocytes such as fibroblasts at frequencies between 0.2-30 Hz,[4079-4082] although the vertical amplitude of these fluctuations is typically only 20-30 nm over 0.25-$micron^2$ areas, far smaller than the RBC membrane fluctuations of 160-400 nm. However, murine B lymphocytes showed transverse displacements of 131 nm in 0.2-$micron^2$ microdomains at 0.3-15 Hz.[4079] Colchicine at 1 μM concentration reduced these membrane fluctuations down to 88 nm, whereas dihydrocytochalasin B at 2 μM increased the membrane displacement amplitude up to 184 nm.[4079] Medical nanorobots using leukocytes as cytovehicles (Section 9.4.7) — whether by external attachment or from a cytosolic residence — must take care to avoid impairing leukocytic plasma membrane fluctuations, whose biological function appears to be, at least in part, to assist the cell in achieving efficient diapedesis.

Leukocytes are also much less deformable than erythrocytes,[5411-5414] especially when activated, hence WBCs may better resist cell deformation by passing nanorobots (Section 15.5.5.3.1). Venous blood from patients with ischemic "vibration white finger" caused by occupational exposure to ~120 Hz mechanical vibrations contains a subpopulation of hard and poorly deformable granulocytes.[5410] However, acute hand-transmitted vibration has no in vitro effect on leukocyte rheology.[5410]

15.5.5.3.3 Leukocyte Margination and Migration

When aggregated in low shear conditions, red cells preferentially take up axial flow which induces margination of platelets and leukocytes (Section 9.4.1.3), increasing endothelial adhesion and other cell-wall vascular interactions for these non-RBC elements.[4130] Medical nanorobots seem unlikely to disturb this aggregation and axial migration of red cells, or the resulting peripheral migration of white cells, platelets, and smaller blood components including bloodborne nanorobots (Section 15.5.5.1.3). This is important because without white cell margination, natural phagocytic defense mechanisms could be greatly impaired.

Given that free-flowing nanorobots will likely be marginated toward the vascular walls (Section 9.4.1.3) along with platelets and white cells at low shear rates, could nanorobots interfere with the wall-related functions of those cells? For example, nanorobots may share the plasmatic layer or plasmatic zone (Sections 9.4.1.4 and 9.4.2.6; aka. Poiseuille's space) closest to the vessel walls with leukocytes and platelets. Collisions there will involve shear stresses of at most <0.1 N/m^2 (Section 9.4.2.2), hence should not significantly affect leukocyte morphology or function. At the highest shear rates in the vasculature, red cell aggregates break up and the erythrocytes distribute more uniformly, with white cell concentration becoming highest along the tube axis (Section 9.4.1.3). Nanorobots the size of platelets or smaller remain marginated to the periphery. Under these flow conditions the white cells and nanorobots should interact only infrequently. There is some evidence for margination of chylomicrons,[4131-4133] the only major particle population in human blood having smaller dimensions than medical nanorobots and hence theoretically capable of at least partially displacing free-floating nanorobots from the periphery.

Vasculomobile nanorobots also may collide with slow-moving leukocytes that are rolling along the local endothelium. The microvillus "feet" upon which a leukocyte rolls across endothelium are present on the white cell surface at a number density of ~1.1/$micron^2$.[4122] The equilibrium length of a microvillus ranges from 0.35 microns (untethered, at equilibrium) to 1.75 microns (tethered, at full stretch), and the step sizes range from 1.25 microns (extrapolated to zero rolling velocity) to 2-5 microns for continuous-contact locomotion.[4122] Thus it is likely that a rolling leukocyte could simply step over an isolated unmoving endothelium-anchored low-aspect-ratio nanorobot of lateral diameter ~1-2 microns.

More commonly, vasculomobile nanorobot ambulation velocities may be as high as 10,000 microns/sec (Section 9.4.3.5) compared to a maximum of 10-80 microns/sec for a rolling leukocyte.[4122] The locomotive force envisioned for vasculomobile nanorobots using legged ambulation is on the order of ~200 pN (Section 9.4.3.5). Distributed over a 1-10 micron^2 nanorobot-leukocyte contact area, this force induces a shear stress of 20-200 N/m^2, probably sufficient to dislodge a rolling white cell. Vasculomobile nanorobot control systems thus must include specific leukocyte (and platelet) encounter protocols. These operational protocols would provide that the forces or speeds generated by nanorobots are to be greatly reduced in the vicinity of a rolling white cell, or else the nanorobot is detoured either around or over the larger but much slower-moving motile blood cell. Crawling over the leukocytic obstacle may be a good option for isolated nanorobots or narrow nanoaggregates that can maintain low levels of applied shear stress during the transit, thus avoiding any unwanted activation of leukocyte morphological or functional changes. Achieving this objective when large numbers of nanorobots are in transit for extended periods of time across the same leukocyte may prove challenging. The mean number of marginated leukocytes in venous blood vessels in rat and mouse spleens has been observed to range from 0.1-4.5 WBCs per 1000 micron^2 of wall surface (a mean center-to-center separation of 15-100 microns), with rolling speeds from 11-20 microns/sec.[2869] Adherence times of leukocytes to vessel walls are log-normally distributed, with median values 30 sec, 130 sec, and 560 sec for lymphocytes, PMNs, and macrophages, respectively.[2869]

Nanorobot diapedesis should require only milliseconds for gap passage, plus possibly several seconds for gap management (Section 9.4.4.1). Leukocytes have been observed to migrate through the venous wall as fast as 1-2 minutes[2869] or as slow as 3-10 minutes[4134,4135] — roughly 100 times slower than medical nanorobots. Even a major convoy (Section 15.5.2.3) involving ~10^9 medical nanorobots can complete its extravasation in the shortest possible time required for a single WBC transit. As long as such passages are infrequent, they should not interfere with or impair normal leukocytic activities.*

15.5.5.3.4 Disruption of Leukocyte Aggregation

Human leukocytes are known to aggregate: (1) during phagocytosis of bacteria[3882,4138] (though somewhat less so during viral infections[4139]); (2) during passage through vascular stents of various designs and surface textures;[3875] (3) following surgery;[3889] or (4) in other situations such as cerebral ischemia and myocardial infarction.[4140,4141] Leukocyte aggregation is also involved in the generation of vascular damage during various inflammatory conditions.[4142] However, this aggregation is reversible in vitro and often presents no clinical evidence for leukoembolization,[4143] so any possible disaggregative influences from medical nanorobots — whether incidental or purposeful — are unlikely to prove pathological. The comparable aggregability of both white and red cells during acute myocardial infarction[4141] and the coaggregation of leukocytes and erythrocytes during infection[4144] and inflammation[4145] suggests that these two cell types may share common adhesive proteins. Since the mere presence of medical nanorobots is unlikely to significantly interfere with normal red cell aggregation (Section 15.5.5.1.3), this conclusion might be extended to white cells as well.

15.5.5.4 Viability of Confined, Pressurized, or Desiccated Cells

The effects of prolonged mechanical pressure between nanorobotic surfaces and biological tissues has already been addressed (Section 15.5.3.4.1). But in some applications[4609] it will be necessary to tightly confine individual cells in partially or completely enclosed containers for transport, storage, diagnosis or repair.

Cells confined on lithographically produced 2-dimensional islands of similar surface area to the cell typically may attach and generate normal secretion products, whereas larger islands will promote cell spreading instead and still larger islands may promote cell growth or replication (Section 15.2.2.3). Cells placed on square pedestals of roughly their own size will take up a square shape (Section 15.2.2.3). Cells including platelets, fibroblasts, osteoblasts and macrophages deposited or grown on diamond surfaces maintain their integrity, showing normal cell adhesion and no evidence of cytotoxicity (Section 15.3.1.2). Endothelial cells cultured on pyrolytic carbon or LTIC show no change in cell adherence with well-spread (not rounded) cells on this surface (Section 15.3.3.2). As for Teflon: monocytes and macrophage adhere weakly to Teflon surfaces, showing no obvious structural or functional defects; leukocytes and lymphocytes are not activated by Teflon in vitro, though platelets may be (Section 15.3.4.2); and endothelial, epithelial, neural and bacterial cells attach poorly to Teflon (Section 15.3.4.2). Fibroblasts and epithelioid cells adhere well to sapphire and experience no cytotoxic or antiproliferative effects, and osteoblasts show normal biochemical and biological functions on sapphire (Section 15.3.5.4).

Will full 3D confinement — cell containerization — cause cells to become apoptotic, or accelerate cell mitosis or proliferation? It is well known that a loss of contact with ECM by tissue cells, mediated by transmembrane proteins,[4952] can induce apoptosis (Sections 10.4.1.1 and 15.5.4.2). Forcing cells to adopt an unnatural square shape by culturing them on square-shaped planar adhesive islands enhances the rate of apoptotic cell death, "as indicated by an accelerated permeabilization of the outer mitochondrial membrane, loss of the mitochondrial inner transmembrane potential, and an increased frequency of nuclear apoptosis".[4943] This outcome may be avoided by inserting inhibitors of apoptosis[4914] or IAPs (Section 10.4.1.1) into the containerized cell during the period of containerization, then withdrawing the IAPs from the cytoplasm using molecular sorting rotors, after cell decontainerization but prior to final release, or by other means (Section 15.5.7.6).

A wide range of evidence[4944-4951] supports the conclusion that mechanical stress can induce cellular hypertrophy, mitosis and proliferation of cells. Thus it may also be advisable to introduce mitotic inhibitors into the cell (Section 10.4.1.3) to suppress mitosis during containerization, if containerization is found to produce unacceptable mechanical stress on the cell. These inhibitors can later be withdrawn and the cell should then resume its normal functioning. During containerization the cellular mRNA translation machinery could be temporarily shut down almost completely (and there are also selective inhibitors of transcription[4919-4921]). For instance, a number of ribosomal inhibitors are known — e.g., aminoglycosides inhibit translation in bacteria by binding to the A site in the ribosome,[4915] and an anti-RNA antibody is an inhibitor of ribosome-associated GTP hydrolysis[4916] — and other fully reversible inhibitors of transcription are known, such as the eIF4E-binding proteins (4E-BPs) which interdict translation initiation by preventing

** Extravasating leukocytes[4136] preferentially migrate around endothelial tight junctions or zonula occludens by crossing at tricellular corners where the borders of three endothelial cells meet, rather than by passing through the tight junctions that lie between two endothelial cells, thus preserving the barrier properties of the endothelium and avoiding widespread disruption of endothelial tight junctions.[4137]*

recruitment of the translation machinery to mRNA.[4917] It should be possible to recognize and selectively extract (using molecular sorting rotors or adhesion antennae; Sections 9.3.2 and 10.4.2.5.2) specific mRNA strands or various intracellular messenger molecules that would otherwise transduce the mitotic signal. This should be possible because anti-mRNA can be targeted to inhibit a single species of mRNA molecule within cells[4918] and because nanorobots should be able to intercept and alter intracellular messages as described in Section 7.4.5.4. However, R. Bradbury notes that mRNA molecules may have very directed routes from the nucleus where they are generated to the ribosome locations where they are utilized and that it could take longer to "read" an mRNA molecule than to sample the surface of a simple protein messenger molecule, looking for a unique amino acid tag — and as a result, cell functioning might be slightly altered by the delays the sampling process introduces.

Although red cells in vivo are often confined to tightly-packed rouleaux (Section 9.4.1.2), the biological effects of van der Waals adhesion between cell plasma membranes and tightly confining diamondoid walls are presently unknown and should be investigated further. For example, the consequences of physically preventing surface fluctuations on the plasma membranes of red cells (Section 15.5.5.1.2) or white cells (15.5.5.3.2) have not yet been studied. In this example, it should be possible to ameliorate some negative effects by interposing thin compliance-matching coatings at the cell-nanorobotic wall interface, possibly combined with cytoplasmic biochemical amendments.

Cells can tolerate static pressures of 300-1000 atm without exhibiting altered physiology (Section 10.3.3, Table 10.3), but compression of cells to force them through holes or tubes, or from one tight compartment to another, must not apply shear forces sufficient to induce biological response (Section 15.5.4.1). For instance, >0.04 N/m^2 shear stress (16 pN over a (20 micron)^2 cell membrane area) can induce adherent leukocytes to retract their pseudopods, eventually rounding and detaching from a glass surface.[4116] The minimum force required to initiate signal transduction may be as low as ~10 pN (Section 9.4.3.2.1). If these values must be exceeded during cell transport, then the cell's responses must be actively disabled as described above or as described in Sections 7.4.5.4, 9.4.7.4, and 9.4.7.6, unless it is determined that the effects are reversible after the stress is removed.

While the partial dehydration of cells to reduce their volume in order to permit more convenient transport in vivo by specialized carrier nanorobots[4609] might possibly trigger a response from cellular stretch-activated channels (Section 15.5.3.1), Owen Hamill notes that this is unlikely because cell inflation rather than cell shrinkage is generally assumed to activate these channels. In the case of bone cells, these responses are stimulated at linear strains of just >0.15% (Section 9.4.3.2.1). For stretch-sensitive cell types, such responses must be actively disabled as described above. But many mammalian cells can provably survive the loss of 50% of their water.[4922] Fibroblasts (e.g., mouse L-929 cells) have survived from 45%[4923] to 65%[4924] decrease in total cell volume (the latter representing 85% water loss by volume[4925]) via dehydration, and erythrocytes have survived 73% volume reduction by dehydration.[4926] Other cells, particularly bacteria,[4927-4930] can tolerate significant shrinkages without loss of viability.* However, even desiccation of microbes leads to dramatic lipid phase changes wherein carbohydrates, proteins and nucleic acids initially suffer spontaneous, reversible low activation energy Maillard reactions forming products that more slowly re-arrange, cross-link, etc. to give non-native states.[4931] So while initial products may spontaneously reverse to native states when water is restored, later products only do so through energy consumption and enzymatic activity, e.g., repair.[4931]

According to G. Fahy,[4933] in the 1980s LifeCell Corp. devised a technique by which cells were "vitri-dried": cells were cooled so rapidly that ice either doesn't form or forms such small crystals that they don't damage the cells, after which space-quality vacuums were used to distill off the water at very low temperatures.[4934] After vitri-dried cells were stored at room temperature for a short time, they could be rehydrated and, allegedly, recovered life functions, but were not able to divide.[4934] Experiments by others in the 1990s found that human mesenchymal stem cells that are air-dried and stored under vacuum are still viable when rehydrated ~12 hours later.[4935] Vacuum greatly enhances the ability of cultured human cells to withstand desiccation. Cells dried slowly in such a way that cellular structures are maintained and stored under vacuum in darkness can withstand desiccation even in the absence of added carbohydrates or polyols.[4936] Anhydrobiotic organisms such as the tardigrades[4937] survive practically complete drying in the absence of freezing, a feat made possible by the presence of a sugar, trehalose, whose geometry can support membrane structure against collapse by substituting for water at the polar head groups of the lipids.[4930,4938] One research group reports that "introduction of the genes for trehalose biosynthesis allowed human cells in culture to be reversibly desiccated for up to 5 days";[4936] and that human primary fibroblasts expressing trehalose and containing no detectable water could be maintained in the dry state for up to five days.[4940] However, another group[4939] reports that trehalose does not improve desiccation tolerance in mouse cells. More research is required to resolve this issue.

15.5.6 Electrocompatibility

Medical nanorobots must be electrically biocompatible with living cells and tissues.[5844] Various issues in electrocompatibility have already been raised and deserve further study, including electrical field and neuroelectric sensing (Sections 4.7, 4.8.6, 4.8.7, 4.9.3.1, 4.9.3.3, and 4.9.5), biological effects of radiofrequency power (Section 6.4.2), macrophage-stimulative electrical fields (Section 6.4.3.6), circumvascular current-carrying wire coils (Section 6.4.4), stray-field bioelectric interactions (Section 6.5.5), environmental electromagnetic and electrical biofeedback signals (Section 7.2.3), electrical adhesive forces (Section 9.2.3), and various electrical-related risks of in vivo nanorobots (Chapter 17). The discussion here is necessarily brief and considers only a few of the many possible electrical interactions with cells (Section 15.5.6.1), along with the important issue of surface electrical thrombogenicity (Section 15.5.6.2). Tangential important issues such as possible changes in whole-body electrical conductivity due to massive diamondoid materials implants should be studied but are beyond the scope of this book.

15.5.6.1 Electrical Interactions with Cells

The gross effects of electrical interaction with cells are well known. For example, a macroscopic intravascular electrode with constant current intensity 1 mA induces thrombosis and injury of the vascular wall, ranging from minimal lesion of endothelium to almost

** The record-holder may be the El Tor microbial strain of Vibrio cholerae, which according to Rita R. Colwell of the University of Maryland Biotechnology Institute[4932] can shrink itself 150- to 300-fold when plunged suddenly into cold salt water (e.g., cold shock[5425]), becoming the size of a large virus without loss of viability.*

total necrosis of the vascular wall.[4146] Schaldach[4147] reports that current densities in excess of 1-100 picoamp/micron^2 alter the thermodynamic equilibrium and cause "changes in pH, P_{O2}, irreversible reactions, and perhaps cell damage." Obviously, nanorobots must avoid unintentional electrocution, electrocautery, or cytotoxic electroporation[4148] of the patient's healthy cells and tissues. But electroporation may be used to temporarily permeabilize cell membranes to permit the insertion of foreign genes,[4149] and lipid bilayer membrane demixing can be induced by applying tangential electric fields on the order of 4000 V/m.[4150] As noted in Section 9.4.7.4, electric fields can be used to drive leukocyte motion (Section 4.9.3.1). For example, a mild electric current induces lymphocytes to travel in the same direction as the current ("electrotaxis") at speeds up to ~0.3 microns/sec.[6170] Small electric gradients have been shown experimentally[6171] to stimulate leukocyte diapedesis (Section 4.9.3.1), though multiple nanorobots would probably be required to generate the necessary currents.

Biological stimulation can alter the electrical characteristics of cells. For instance, the stimulation of thymocytes and B lymphocytes with specific mitogens causes the cells to increase in diameter from 5.6 to 8.8 microns, with membrane capacitance increasing from 7.6 to 12.4-14.6 mF/m^2 and from 9.3 to 16-17 mF/m^2, respectively.[4151] T cell membrane conductivity also increases from 50 to 210 S/m^2.[4151] Various immune (and other) cell responses to externally-imposed oscillating electric/magnetic fields have been reported[4152-4157] although there are negative results as well.[4158-4160] In one experiment,[4819] osteoblasts cultured on the surfaces of a polylactic acid-carbon nanotube composite and exposed to electric stimulation (10 μamps at 10 Hz) for 6 hours/day exhibited an upregulation of mRNA expression for collagen type-I after 1 day, a 46% increase in cell proliferation after 2 days, and a 307% increase in the concentration of extracellular calcium after 21 days. Electric fields can be therapeutic in some cases.[4161,4162] Cellular galvanotaxis (electric field-induced cell migration) has been demonstrated in algae,[4163] bacteria,[4164] chondrocytes,[4165] endothelial cells,[4166] epidermal cells,[4167] epithelial cells,[4168,4170] fibroblasts,[4169-4171] granulocytes,[4169,4172] keratinocytes,[4173] myoblasts,[4174] neural crest cells,[4175] neurons,[4176] osteoblasts and osteoclasts,[4177] protozoa,[4178] and spermatozoa,[4179] and has been modeled mathematically.[4180] Field-emitting nanorobotic systems might induce similar effects. Finally, a major hurdle in developing electronic implants is the design of devices that can withstand long-term exposure to the body's warm, salty fluids without mechanical failure. The corrosion electrochemistries of potential nanorobot building materials are briefly discussed in Sections 15.3.1.5, 15.3.3.6, and 15.3.5.6.

Perhaps more subtle are the effects of cell-cell electrostatics which have been under investigation since the 1920s.[4181] As an example, the negative surface charge of red cells provides an electrostatic repulsive force tending to cause disaggregation.[4092,4182] It has been proposed that the ~15 nm gap frequently observed between the surfaces of aggregated red cells in rouleaux[4183] represents the position of the potential energy minimum where the forces of electrostatic repulsion between negatively charged red cells and the van der Waals attractive forces are equal.[1554] Taking H = 30 zJ, r_{red} = 3 microns and z_{sep} = 15 nm in Eqn. 9.7, the net attractive force between red cells aggregated in rouleaux is F_{vdW} ~ 70 pN. (This lies well within the range of mechanical forces potentially accessible to medical nanorobots; Section 9.3.) Cationic particles strongly bind to human erythrocytes.[6146] The streptococcal bacterial coat has negatively-charged termini, creating a mild electrostatic repulsion of phagocytes[4184,4185] (see below). The low Hamaker constants (Section 9.2.1) of cell plasma membranes gives rise to an appreciable mutual electrostatic repulsion between virtually all bloodborne cells.[4184] In general, at neutral pH there is a net negative charge for prokaryotic and eukaryotic cells and for DNA, although proteins may be either positive or negative.[4187] In an oscillating nonuniform electric field, Gram-positive bacteria experience positive dielectrophoresis because they appear more conductive than Gram-negative bacteria which experience negative dielectrophoresis, hence the two cell types are readily separated.[4186,4187] Red cell membranes carry electric charge and are readily deformed in a high-frequency oscillating electric field.[4188] Similar fields can induce cell vesicle budding or fission[4189] or cell fusion.[4190] These and other useful electrical forces and influences — which may include systemic mechanoelectric transduction (Section 4.9.3.3) and mechanoelectric feedback throughout all human tissues[4191] — may be exploited by medical nanorobots or by macroscale nanoaggregates.

Bacterial cell surfaces possess net negative electrostatic charge by virtue of ionized phosphoryl and carboxylate substituents on outer cell envelope macromolecules which are exposed to the extracellular environment.[4665] For example, Gram-negative bacteria have an outer layer of lipopolysaccharide (LPS) and protein which forms a highly charged surface that is stabilized by cation binding.[4666] Variations in the structure and chemical composition of the LPS have been shown to affect bacterial surface charge and the ability of bacteria to adhere to both glass and polystyrene surfaces.[4669] LPS can occur in two general forms, a hydrophobic (A form) and a charged hydrophilic (B form).* [4667-4669] Most protozoan[4670] and bacterial cells[4671-4674] are negatively charged to varying degrees, though there are a few rare instances of positively-charged bacteria such as *S. maltophilia*.[4672] Bacterial negative charge can be reduced by antibiotics,[4675,4676] and complete bacterial charge reversal, from negative to positive, has been observed in the presence of certain metals and high pH.[4677,4678] Note that the internal bacterial proton gradient does not affect the external charge.**

As mentioned earlier (Section 15.4.3.6.2), the phagocytosis of polystyrene beads (as measured by cellular oxygen consumption) appears strongly dependent on local surface potential and thus upon fixed surface charge.[3327] Surface charge heterogeneity across domains as small as 1-4 microns can greatly affect phagocytic ability.[3328] For instance, bacteria and epithelial cells, both of which possess a negative surface charge, should repel one another, but do not. Investigations[4674] by atomic force microscopy of the structures involved in the attachment of *Moraxella catarrhalis* bacteria (which have a net negative surface charge) and pharyngeal epithelial cells found that the cell surface microplicae have a positive charge of +30.1 mV whereas the depressions between the microplicae have a negative surface charge of -43.5 mV. Thus there are both positively and negatively charged domains on the surface of human pharyngeal epithelial cells, and *M. catarrhalis* evidently attaches to the positively charged domains.

** There is also a bacterial form which has no LPS coat — the "L form"[5980] — in which the bacterium exists, in essence, as a liposome (i.e., no protein/polysaccharide surrounding coat).*

*** A proton gradient builds up in the space between the outer face of the bacterial cell membrane and the innermost face of the bacterial cell wall outer coat, as a result of NADH-mediated translocation of H^+ from cytoplasm to the periplasmic space and the resulting accumulation of cytoplasmic OH^-. Once the charge gradient is large enough, the periplasmic protons enter back into the bacterial cytoplasm through channels in transmembrane ATP synthase enzyme complexes which drives the production of bacterial ATP from ADP. These charges do not escape through the bacterial outer coat.*

Bacteria adhere more readily to positively charged surfaces,[4679] and enzymes with a large global positive charge more easily penetrate bacteria cell walls.[4680] The effects of surface charge on adhesion[4681] and absorption[4682,4691] by phagocytes has been studied with variable results due to inconsistent experimental conditions. Some studies[4683-4686] indicate no effect of bacterial surface charge on phagocytosis, e.g., no significant difference in phagocytosis between cationic or anionic surfaces when compared at a zeta potential of the same absolute value.[2865] Other studies find increasing phagocytosis with increasing negative charge[4687,4688] or reduced phagocytosis with reduced negative charge.[4689] Still others[4690] show increased phagocytosis of microcapsules by a leukocyte only for targets of different charge from itself. The most recent results are that phagocytosis appears somewhat inhibited for negatively charged particles,[2336,2880,4691] and somewhat increased for less-negatively charged[4675] or for positively charged particles.[2880,4691,4692] Brodbeck et al[5507] found that phagocyte adherence is minimized for hydrophilic surfaces and for anionic surfaces containing negatively-charged groups, such as polymers made from organic acids. In another experiment,[2865] the least phagocytosis was observed for cellulose microspheres with non-ionic hydrophilic surfaces. But a reduction of phagocyte membrane negative surface charge has also been shown to decrease macrophage phagocytosis.[4693] These studies should be evaluated for quality and reliability, and further research may be required before we can make a definitive statement regarding the relationship between the surface charge of bacteria and phagocytosis.

The surface electrical characteristics of possible medical nanorobot building materials are only beginning to be explored. For instance, Donaldson[898] notes that the alumina (sapphire) surface is amphoteric. In a sufficiently acidic environment, the sapphire surface equilibrates with that environment by adsorbing hydrogen ions, acquiring a positive charge. In an alkaline environment, the sapphire surface acquires hydroxyls and a negative charge. At some intermediate pH near human physiologic (i.e., ~7.4), the sapphire surface is neither positively nor negatively charged — that is, it is isoelectric. The isoelectric point for pure alumina has been measured as a pH of 6.6 for anhydrous Al_2O_3,[1101] 9.2 for alumina submerged in water for a week,[1101] or 8.0 using an ISFET.[1102] Similarly, the electrical conductivity of DNA-based structures has been investigated (and controversial) for many years,[5770-5776] but until very recently[5777] could not readily be studied in a physiological environment.

The role of surface charge in the possible pathogenicity of microparticles[4192] and the influence of microparticle shape on electrocompatibility has only been lightly studied. For example, sharp edges and corners may produce higher local fields or create current density hotspots[4193] — the positively charged edges of kaolinite particles contribute slightly to particle cytotoxicity.[4194]

15.5.6.2 Surface Electrical Thrombogenicity

An early hypothesis held that surface charge was the primary physicochemical feature of blood-contact material surfaces in determining thromboresistance. Cell coats with negatively charged sialic acid termini on both the glycoproteins and gangliosides, and macromolecules in all known flowing biological fluids, carry a slightly negative charge, thus should be repelled by bloodborne nanodevice surfaces bearing a net negative charge, or negative electrochemical potential, reducing the risk of thrombosis.

However, it is now known that immersion of adherent particles in liquid virtually eliminates electrostatic image forces (Section 9.2.2), greatly reduces electrostatic contact potential forces (Section 9.2.2), and can reduce van der Waals forces (Sections 9.2.1 and 9.2.3) by at least a factor of six at organic-water interfaces.[4195] The early hypothesis is further weakened when the immersion fluid is not neutral or insulating, but rather consists of the high ionic strength, salty, highly conductive ("dead short") biofluids actually found in vivo. Careful experiments designed to measure surface potential and surface charge find that the choice of surface electrical properties of materials intended to be brought into contact with blood or other salty aqueous fluids has little influence on biological adhesion.[4196] Indeed, there is growing evidence that any state of surface electrification is associated with greater rather than lesser accumulations of biological debris on such surfaces. While there is an obvious accentuation of adhesive induction by net positive surfaces,[4196] negatively-charged surfaces may activate contact factors initiating the intrinsic coagulation pathway (Section 15.2.5). Hence a net neutral nanorobot surface may be preferable in order to minimize surface electrical thrombogenicity.

G.M. Fahy notes that an electric charge of oscillating polarity might discourage biological accumulations on nanorobot surfaces. A negative charge would repel most proteins; if this led to positive items clustering on the surface, an oscillating surface charge might get rid of those items before they become a problem.

Detailed calculations of nanorobot electrical characteristics[5096] should be a part of every complete design analysis.

15.5.7 Cytomembrane and Intracellular Mechanocompatibility

When penetrating and entering the living cell, nanorobot physical structures and activities must be mechanically compatible with the cellular glycocalyx (Section 15.5.7.1), the plasma and organelle membranes (Section 15.5.7.2), and all cytoskeletal systems (Section 15.5.7.3). Nanorobots must avoid causing intracellular cavitation, shock wave damage, or decompression nucleation (Section 15.5.7.4), disrupting intracellular microzones (Section 15.5.7.5), mechanically inducing intracellular proteolysis or apoptosis (Section 15.5.7.6), or mechanically disrupting chromosomes in the cell nucleus (Section 8.5.4.7).

15.5.7.1 Mechanical Interactions with Glycocalyx

Many disease processes are known that involve damage to the glycocalyx,[4197-4208] including some bacteria that phagocytose[4209] or otherwise destroy[4210-4213] the host cellular glycocalyx during an infection. Damage to the glycocalyx creates conditions that favor the binding of immune complexes, complement activation, and intravascular coagulation, with loss of gradients between blood and parenchyma.[4214] Desialylated glycocalyx of endothelium also allows an increased rate of endothelial cell detachment from arterial walls.[4215]

Nanorobots that rely upon absorption of local oxygen and glucose for their power supply (Section 6.3.4) or whose missions include extensive small-molecule exchanges with the environment (Chapter 19) may have ~10^4-10^5 molecular sorting rotors (Section 3.4.2) embedded in their exterior surfaces.[2762,3573] These spinning sorting rotors are unlikely to cause direct physical damage to formed blood elements for several reasons. First, rotors are atomically smooth and recessed into the housing, reducing physical contact with colliding surfaces and eliminating potential nucleation sites that may trigger blood clotting, gas embolus formation, or foaming. Second, only a small fraction of all available sorting rotors may be actively spinning at one time, further reducing the likelihood of physical trauma. Third, such limited physical contact, when it occurs, should be relatively benign. Maximum rotor rim velocity of 2.6 mm/sec is less than 1% of mean aortic blood velocity and lies only slightly above maximum capillary flow speed (Table 8.2).

Could the glycocalyx strands that are present at all tissue and nontissue cells surfaces get trimmed, even by a recessed sorting rotor? Nanorobot sorting rotor binding sites for small molecules (<20 atoms) involve pockets measuring <2.7 nm in diameter (see ref. 10, Section 13.2.1.a). These pockets are too small to physically accommodate the 10-20 nm thick plasma membrane or the main body of the glycocalyx projections that typically measure 5-8 nm thick and 100-200 nm long,[4216] and consist of glycoproteins comprised of 10,000 atoms or more. While an occasional sugar residue may get clipped, binding sites can be designed for maximum steric incompatibility with glycocalyx glycoproteins and proteoglycans, further minimizing the opportunities for trimming. Note that clipping a covalent C-C, C-O, or C-N bond probably requires a clipping energy >500 zJ/molecule (see ref. 10, Table 3.8), but sorting rotors designed to pump against pressures of ~30,000 atm can only apply ~100 zJ/molecule (i.e., per binding site). An accidentally-bound glycocalyx moiety seems more likely to jam the rotor than to be clipped off by the rotor. If this happens, the result may be a glycocalyx-tethered nanorobot, in which case a rotor-dejamming protocol* is needed to free the trapped nanorobot.

But what if glycoproteins can be clipped? Consider a population of N_{bot} spherical nanorobots of radius R_{bot}, the surface of each is covered with a fraction f_{rotor} of sorting rotors each of face area A_{rotor} with binding site aperture area A_{bind}, which are resident at nanocrit Nct in a blood compartment of volume V_{blood} in which each nanorobot experiences c_{bot} collisions/sec with glycocalytic biological surfaces of total area A_{glyx}, where $N_{bot} = 3$ Nct V_{blood} / ($4 \pi R_{bot}^3$) and the fraction of rotor surface that is binding site aperture is $k_{rotor} = n_{rotor} A_{bind} / A_{rotor}$, for rotors with n_{rotor} binding sites always exposed. The rate at which biological glycocalyx is encountered by the collective binding site aperture area of the entire fleet is $S_{bot} \sim \pi R_{bot}^2 c_{bot} N_{bot} k_{rotor} f_{rotor}$ (m^2/sec), so each glycoprotein strand is presented to a nanorobot binding site aperture once every A_{glyx}/S_{bot} seconds. If we assume that:

a. one in N_{enc} such encounters positions a glycoprotein strand moiety such that binding with it would be geometrically possible; and

b. ε_{rotor} is the relative affinity of the binding site for glycoprotein moieties (e.g., glucosyl, sialyl) properly presented to it as compared to desired targets such as O_2 molecules — that is, the rotor's specificity for glycocalyx — and

c. $t_{replace}$ is the natural replacement time for damaged glycoprotein strands in the glycocalyx;

then $\varepsilon_{rotor} <\sim \kappa_x A_{glyx} N_{enc} / (t_{replace} S_{bot})$, where κ_x is the maximum permissible fraction of damaged glycocalyx during the time $t_{replace}$. For this analysis, we take $V_{blood} = 5400$ cm^3, $R_{bot} = 1$ micron, $f_{rotor} = 1$, $c_{bot} \sim 100$ collisions/sec (Section 15.5.5.2.1), $A_{rotor} = 98$ nm^2 (Section 3.4.2), $A_{bind} = 0.033$ nm^2 for an oxygen molecule (the most common molecule likely to be sought by medical nanorobot exterior rotors), $N_{enc} \sim 10$, and $A_{glyx} \sim 4410$ m^2 (which is the sum of ~3850 m^2 for 28.5 trillion RBCs (Section 8.5.1), ~310 m^2 for the vascular endothelium (Table 8.1), ~210 m^2 for 0.7 trillion WBCs (Section 8.5.1), and ~40 m^2 for 2.1 trillion platelets (Section 8.5.1)). Since red cells are the most commonly impacted and do not self-repair, the worst-case replacement time is the mean RBC lifetime of ~120 days, or $t_{replace} \sim 10^7$ sec. Natural rates of glycocalyx damage are just starting to be precisely quantified,[4217,4218] so for the present analysis we assume that $\kappa_x \sim 0.01$ (1%) is an acceptable glycocalyx damage rate.

At Nct ~ 0.10 (10%), the largest plausible nanocrit (Section 9.4.2.6), the required relative rotor affinity for glycoprotein moieties vs. oxygen molecules is $\varepsilon_{rotor} <\sim 10^{-6}$. Drexler[10] notes that "analogies with antibodies suggest that an inward-transport rotor can deliver impurity fractions of 10^{-4} to 10^{-9}, depending on affinities, specificities, and the concentrations of the effectively competing ligands." Hence, it appears likely that rotor systems can be designed to achieve acceptable glycocalyx damage rates of $\kappa_x <\sim 1\%$ — if clipping damage is even possible at all. This conclusion is further reinforced when we consider: (1) that a more typical diagnostic or therapeutic medical nanorobot dose will be ~1 terabot (Nct ~ 0.01%), not ~1000 terabots (Nct ~10%) as assumed above; (2) that a more typical mission time may be only hours in duration (~10^4 sec), rather than the RBC lifetime (~10^7 sec) as assumed above, and may be comparable to or less than the time in which many tissue cells replace their glycocalyx or are retired, e.g., 10^3-10^6 sec**; and (3) that recessed access ports or protective cowlings near the binding sites might increase N_{enc} to 100 or better. All of these factors combine potentially to reduce the aforementioned worst-case damage rate by up to 7 orders of magnitude.

The glycocalyx cell coat is a secretion product incorporated into the plasma membrane that undergoes continuous renewal. Thus any trimmed glycocalyx glycoproteins from tissue cells would be rapidly replaced via biosynthesis in the ribosomes of the endoplasmic reticulum, followed by final assembly with the oligosaccharide moiety in the Golgi complex and subsequent export to the plasma membrane.[4225] Glycoprotein strands or stray sugar residues released into the extracellular medium as a consequence of such trimming are nonimmunogenic and would be quickly metabolized. However, it is possible that nearby parasites could absorb this released material onto their surface, affording themselves some camouflage protection (Sections 15.2.3.4 and 15.2.3.6) against host immune defenses.[4226]

15.5.7.2 Mechanical Cell Membrane Disruptions

Medical nanorobots that interact with living cells may cause mechanical damage to cellular lipid bilayer membranes — in particular the plasmalemmal, organelle and vesicular membranes. Membrane mechanocompatibility issues include natural cell membrane wounding (Section 15.5.7.2.1); cytopuncture and membrane resealing (Section 15.5.7.2.2); resident transmembrane nanodevice penetrators (Section 15.5.7.2.3); and organelle membrane breach by nanorobots (Section 15.5.7.2.4). Molecular dynamics simulations of lipid bilayer membranes have been underway for more than a decade.[4637-4644]

** One obvious backflushing procedure would use follower rods to affirmatively push unwanted ligands out of the binding pocket. Additionally, some molecular sorting rotor designs (see ref. 10, Section 13.2.1.d) assume a compliant mechanical coupling that permits the rotor to spin backward a short distance as if in free rotational diffusion, thus allowing improperly bound ligands to be freed.*

*** Schistosome parasites can shed some tegument-bound complexes in only ~1200 sec[503] to 3600 sec.[4219] Plasma membrane turnover rate is ~1800 sec for macrophage[2841] and ~5400 sec for fibroblast.[526] Cholesterol turnover rate in RBC membrane is ~7200 sec.[4220] Membrane phospholipid half-life averages ~10,000 sec.[353] Neutrophil lifespan in blood is ~11,000 sec.[234] Enterocyte glycocalyx is renewed in 14,000-22,000 sec, as vesicles with adhered bacteria are expelled into the lumen of small and large intestine.[4221] Some schistosome membrane antigen turnover may require from 68,000[4222] to 160,000-430,000 sec.[493] Typical protein turnover half-life is ~200,000 sec.[353,4223] Cell turnover time is ~86,000 sec in gastric body, ~200,000 sec for duodenal epithelium, ~240,000 sec for ileal epithelium, and ~400,000 sec for gastric fundus.[1841] Neutrophil lifespan in tissue is ~260,000 sec.[234] Glycocalyx turnover in rat uterine epithelial cells is ~430,000 sec.[4224] Platelet lifespan is ~860,000 sec.[4095]*

15.5.7.2.1 Natural Cell Membrane Wounding

Plasma membrane disruptions appear to be a common occurrence in cells residing in tissues such as gut and skin that are normally exposed to mechanical stress in vivo.[4227] Experimentally, animal locomotion transiently wounds the plasma membranes of various cells of skin, which allows otherwise impermeant tracer molecules to enter and be trapped in the cytoplasm. One study[4227] produced an estimate that the epidermis of digits from actively locomoting animals is composed of 10.5% wounded cells, vs. 3.7% wounded cells for quiescent animals. Wounded fibroblasts, glandular cells, and endothelial cells were also seen in mechanically stressed skin.[4227] Scrape wounding of epithelial cells activates repair-related gene expression inside the cell.[4228]

Exercise causes membrane damage in muscle cells (e.g., rat muscle fiber cells or myocytes[4229]) and red blood cells (Section 15.5.5.1.1), and dystrophic muscle cells are especially susceptible.[4230] The plasma membrane of cardiac myocytes can be wounded by vigorous cell contraction or by vascular pressure overloading (e.g., via aortic banding which produces abnormally high hemodynamic loads[4231]). The percentage of rat aortic endothelial cells found to be naturally wounded varies considerably between individual animals from 1.4-17.9% (mean 6.5%).[3923] Wounded endothelial cells are heterogeneously distributed, being found in distinct clusters either in the shape of streaks aligned with the long axis of the vessel or in the shape of partial or complete rims surrounding bifurcation openings such as the ostia of the intercostal arteries.[3923] However, physical exercise (running) and spontaneous hypertension may not produce an increased frequency of aortic endothelial cell membrane wounding.[3923]

Cells can also be mechanically damaged simply by rough handling. For example, passing cells back and forth through a standard syringe needle or similar narrow orifice causes transient membrane disruptions,[4232] and each trip through a 14-gauge blood dialysis needle at a 2.2 m/sec peak velocity damages 0.1% of red cells near the needle wall.[3690] Mechanical forces from tape stripping or needle puncture also transiently wounds the plasma membranes of various skin cells, though these cells can survive such wounding.[4227] Nanorobots located on membrane surfaces could be manipulated via external fields to flex[3971] or even to perforate those surfaces. In one proposal,[4233] MAb-complexed ferrofluid particles selectively bound to the surfaces of virus-infected cells would be rapidly vibrated using an external magnetic field, causing the bound particles to perforate the cell membranes of the infected cells or to damage their intracellular structures, leading to targeted cell lysis. However, neurons can survive patch clamp experiments which may involve suction and mechanical pinching of 30-100 micron^2 cell membrane areas for experiments lasting up to ~1 week in duration;[4234] note that cytoskeleton-free lipid bilayer tethers have been mechanically drawn from the plasma membrane of erythrocytes (~40 nm wide tethers),[5659] neurons (~200 nm wide),[5660] and neutrophils.[5661]

15.5.7.2.2 Cytopuncture and Membrane Resealing

The routine successful transplantation of cell nuclei by microbiologists using micropipettes demonstrates that cells can naturally recover from extreme membrane and cytoplasmic trauma. As noted in Section 9.4.5.6, it is not uncommon to observe rapid natural resealing of plasma membranes with little loss of intracellular contents.[4239,4240] In one experiment, tissue cell plasma membranes were punctured using 2- to 3-micron diameter micropipettes and a 300-millisec transit (wounding) time, and the torn plasma membrane spontaneously resealed in 10-30 sec with relatively little visible loss of injected dye.[4239] We can estimate (Section 9.4.5.5) that a cytopenetrating 1-micron nanorobot with a 10-millisec transit time may allow cytosolic leakage of only 0.006-0.03 micron^3, or ~0.0001-0.0004% of typical tissue cell volume, per nanorobot transit.

Interestingly, Maroto and Hamill[5642] point out that most animal cell types[5643] naturally release ATP (or UTP) into the extracellular medium, whereupon these external molecules, at μM concentrations,[5650] "act on ATP receptors that regulate diverse functions, including pain and touch sensation, smooth muscle contractility, synaptic transmission, platelet aggregation, epithelial fluid secretion, and endothelial release of vasorelaxants;[5649-5653] abnormalities in ATP release may contribute to specific human diseases, most notably cystic fibrosis.[5647,5654]" ATP release is often mechanosensitive and appears to arise through mechanical stimulation of brefeldin A sensitive membrane trafficking of ATP containing transport vesicles:[3973,5642-5649] a *Xenopus* oocyte releases ATP at a basal rate of ~1.3 ATP molecules/μm^2-sec, but even gentle mechanical stimulation can dramatically increase this to ~6700 ATP molecules/μm^2-sec (assuming 1.2-mm diameter oocytes).[5642] Care must be taken in medical nanorobot design and mission specification to avoid activities which may elicit elevated pathological ATP releases.

Microelectrodes traditionally used for intracellular injection had 0.5-micron diameter tips, beveled over a 1-2 micron length, and used very high fluid injection pressures of 0.3-1.5 atm.[4235] "Stab" microinjection at high pressure (0.1-0.2 atm) can be problematic in small cells (2-15 microns in diameter) because the nucleus-to-cytoplasm ratio is higher for these cells, hence the nucleus is more likely to be damaged during the stab. In one experiment,[4236] less than 5% of neutrophils survived the high-pressure stab intact, but a low-pressure (~0.01 atm) injection through a lipid bridge produced a ~100% survival rate. Optical fiber tips ~0.1 micron in diameter or "optodes" have been poked through a cellular plasma membrane to measure cytoplasmic pH and the concentrations of other intracellular analytes, making a penetration volume of just a few micron^3 in single cells and in single rat embryos, without ill effect on these cells.[4237,4238] Membrane resealing after electroporation has also been studied.[5981]

Exocytosis-based resealing[4240-4242] of a microneedle puncture through the fibroblast plasma membrane occurs in 5-10 sec,[4242] but a second puncture at the same site heals faster than the initial wound.[4241] At first wounding, the cell uses existing endocytotic compartment to add membrane necessary for resealing. But Ca^{++} entry at the first wound stimulates vesicle formation from the Golgi apparatus, resulting in more rapid resealing of the second membrane disruption.[4241] Plasma membrane disruptions are resealed by changes in the cellular cytoskeleton (partial disassembly)[4243] and by an active molecular mechanism thought to be composed of, in part, kinesin, CaM kinase, snap-25, and synaptobrevin.[4244] Transmission electron microscopy[4244] reveals that vesicles of a variety of sizes rapidly (in seconds) accumulate in large numbers within the cytoplasm surrounding the disruption site, and that microvilli-like surface projections overlie this region. Tufts of microvilli rapidly appear on wounded cells. A local exocytosis is induced, rather than global exocytosis, in response to wounding. One or more internal membrane compartments accumulate at the disruption site and fuse there with the plasma membrane, resulting in the local addition of membrane to the surface of the mechanically wounded cell.[4244] As an existence proof for membrane-patching medical nanorobots, specialized membrane-patching organelles are known in some species. For example, "reserve granule" or "yolk granule" fusion-competent cytoplasmic organelles in sea urchin eggs allow Ca^{++}-regulated fusion with a rapid ($t_{1/2}$ < 1 sec) response capable of erecting large (>1000 micron^2) continuous membrane boundaries.[4242] The cells of many species of fungi cells have a specialized peroxisomal plasma resealing

organelle called the Woronin body.[4245] In some circumstances, cells can re-seal themselves even after major dissections, and survive. For example, a rapidly vibrating (100 Hz) micropipette with a <1-micron tip diameter has been used to completely sever individual dendrites from single neurons without damaging cell viability.[4246]

15.5.7.2.3 Resident Transmembrane Penetrators

In some applications it will be desirable to establish a plasma membrane penetration for the duration of the nanomedical mission. Such applications may involve rods, cables or tubing that must pass from the extracellular to the cytoplasmic spaces through a fixed sheath, or artificial diamondoid sensors, pumps, or other mechanisms that must be installed in the plasma membrane wall and perform some useful function throughout the mission (e.g., external chemical sensors during cytocarriage; Section 9.4.7.5) without eliciting unwanted mechanosensitive biological responses.

The existence of natural transmembrane integral proteins (Figure 8.37) and artificial transmembrane ion channels,[5426-5436] synthetic pores and porins,[5437-5439] engineered antibiotic-based channel-forming peptides,[5440-5443] and artificial organic nanotubes[692,5444] implies that it should be possible to design, install and stabilize artificial transmembrane penetrator nanodevices. Such devices may anchor themselves in the membrane using an amphipathic coating similar to that employed by integral proteins — e.g., a hydrophilic (polar) coating above and below the plasma membrane, corresponding to the position of the polar lipid heads in the membrane, and a lipophilic (nonpolar) coating for the midmembrane region, corresponding to the position of the nonpolar lipid tails in the membrane. This gives the surface of each nanodevice the maximum membrane affinity when the device is properly positioned, and anchors it in place. Deployment of these anchoring coatings may be reversibly controlled by a nanorobot using an array of presentation semaphores (Sections 5.3.6 and 9.4.5.3). The hollow interior of a penetrating sheath should provide a low-friction interface with a fluid-tight seal (Section 10.3.4; and also Section 11.4.2 in Drexler[10]) so that forces from a cable, rod, or other object sliding through the sheath are not efficiently transmitted to the sheath and thence to the membrane and its attached cytoskeletal components. Hamill [personal communication, 2002] suggests that "nanorobots might be able to insert themselves into selective areas of the plasma membrane (e.g., of polarized cells) by hitchhiking in the trans-Golgi vesicles that are used to traffic/direct newly synthesized membrane proteins to specific regions of the cell surface."

Hamill and Martinac[5640,5641] have found that sub-nanometer changes in bilayer thickness can switch gramicidin A from a stretch-activated to stretch-inactivated channel. As they note, the presence of "a bilayer-controlled switch in signaling by a mechanotransducer channel emphasizes that the bilayer is much more than a neutral solvent [and] may actively modulate the specificity and fidelity of signaling by membrane proteins. This feature, in combination with protein-related factors (e.g., oligomerization state and cytoskeleton association) that determine not only protein recruitment into lipid microdomains but also the dynamic organization of the bilayer itself, indicates a dynamic reciprocity in lipid-protein interactions that is presumably necessary for the higher-order spatial and temporal control of signaling." The presence or movements of, or the forces applied by, a resident transmembrane penetrator could alter the thickness of adjacent bilayer, locally modifying the behavior of nearby mechanosensitive or mechanotransducing integral proteins. These modifications could significantly impact cell function — possibly including cell responses accompanying membrane resealing[5640] — if substantial numbers of artificial penetrators are resident (especially if closely grouped) on the plasma membrane of a single cell. Switch effects presumably may be minimized by avoiding both static and dynamic hydrophobic mismatch[5640,5641] between the hydrocarbon portion of the lipid bilayer (which may vary for different cell types) and the hydrophobic exterior surface of the penetrator.

Other complicating factors include the constant turnover of the plasma membrane (Section 8.5.3.2) and the likelihood that a cytoskeletally-unanchored penetrator might be dragged along with the usual lateral motions of membrane raft microdomains[4247,4248] and untethered integral proteins[4249] such as red cell aquaporins.[4250] Nevertheless these motions should be confined to submicron domains on the surfaces of many cells.[4251-4255] Assuming the nanodevice penetrators are not very numerous in the cell wall, they should not substantially alter plasma membrane fluidity or viscosity especially if differential shear forces are low, e.g., <1 N/m^2.[4256]

15.5.7.2.4 Organelle Membrane Breach

Immotile submicron particles appear generally mechanocompatible with the intracellular environment. For example, the presence of artificial intracellular particles 20-200 nm in diameter (used as intracellular fluorescent labels or sensors) is not mechanically disruptive to the cell.[4238,4258] Intracellular alumina particles can elicit changes in intracellular elemental composition and a reduction of phagocytic ability in human macrophages,[2596] but there is no evidence that this is a mechanical effect. Silicon microdisks introduced into rabbit white cells were subsequently transported to a site of injury, with no evidence of functional cell impairment during cytocarriage.[4259]

The plasma membrane (Section 8.5.3.2) represents only a tiny fraction of the total membrane present in the cell. Indeed, 99.5% of the cell's lipid bilayer surface lies elsewhere (Table 8.17), mostly in intracellular organelles. The membranes of each type of organelle are structurally distinct (Section 8.5.3) and have different disease susceptibilities.[4260] But all should possess roughly comparable mechanical strength,[4261-4263] so puncture forces should be similar as for plasma membrane. Because the Golgi complex is constructed via an ordered merger and coalescence of isolated intracellular vesicles, and readily reconstitutes itself from a vesiculated state,[4264] it is unlikely that the interposition of a small passive nanorobot into these dynamic structures could mechanically influence their growth. A motile nanorobot locomoting around and through these structures could prove temporarily disruptive, though the structures would probably self-repair as suggested by the 10-minute recovery time for Golgi membranes that have been mechanically disrupted by the forcible interposition of artificial vesicles into the membranes under high g-force centrifugation.[4265] There is some evidence[4266] that the endoplasmic reticulum (ER) may be more sensitive to mechanical membrane damage[4266] or to the physical disruption of the supporting microtubule lattice.[4267] However, the integrity of the ER appears to be maintained during mitosis, with little or no fragmentation and vesiculation.[4304]

The greatest threat to cell viability from organelle membrane rupture and intraorganelle leakage probably comes from the mitochondrion. The careless (or even purposeful) nanorobotic breaching of the integrity of this organelle[5672] could result in the cytosolic release of harmful mitochondrial proteins from the intermembrane space including especially cytochrome c, a 12.3 kD protein that forms part of a complex which directly activates caspase-9,[4268] one of the apical enzymes responsible for the apoptotic dismantling of the cell.[4269] A cytosolic concentration of ~0.1 μM (~0.01 pg/cell)

of cytochrome c appears sufficient to trigger apoptosis,[4270] but the human body contains ~3 mg of iron as cytochrome c[4271] distributed throughout the mitochondria of ~4 x 10^{12} tissue cells (Section 8.5.1), or ~0.20 pg/cell assuming ~20-micron cells. So at least ~5% of all cellular mitochondria probably must be fully ruptured by the mechanical activities of nanorobots, or an equivalent amount of intraorganelle fluid leakage must occur, in order to induce apoptosis, which seems an unlikely event. (Apoptosis may be intentionally aborted by in cyto nanorobots; Section 15.5.7.6.) Proteins attempting to enter the organelle that become stuck across both mitochondrial membranes "jam" protein import sites but do not collapse the potential across the mitochondrial inner membrane.[4272]

What about lysosomes? Although it is normally quite stable, the lysosome membrane can become more fragile: (1) when the cell is injured[4273] or deprived of oxygen;[4274] (2) when excessive amounts of vitamin A (hypervitaminosis A[4275]) or iron[4276] are present; (3) during long-term exposure to gentamicin (though with no increase in cell mortality[4277]); or even (4) in some cases of congenital vascular anomalies.[4278] Lysosomes may undergo drastic shape changes during microautophagocytosis, including invagination of their boundary membrane with scission of vesicles into the lumen of the organelle.[5482] Tubular lysosomes 75 nm in diameter and 2-3 microns long extending outward from the nucleus are common in macrophages, and are fragmented if the supporting microtubule lattice is physically disrupted.[4279] However, if left alone without further disturbance, the fragmented microtubules reassemble and the tubular lysosomes reappear within 10-20 minutes.[4279]

What about mechanical stress damage? One experiment[4280] found possible lysosomal membrane damage in myocardial swine cells from animals subjected to high +Gz accelerations. But another experiment[4281] found that mechanical traction strain applied to cultured retinal pigment epithelium cells and fibroblasts sufficient to break intercellular attachments does not disrupt lysosomal membrane integrity during stretching. Post-phagocytosis *Listeria monocytogenes* bacteria exit the lysosome in which they reside by penetrating through the lysosomal wall, a mechanical disturbance that does not immediately impair host cell function.[4282]

Lysosomes were once called "suicide sacs" because lysosomal rupture can result in self-digestion of the cell, a process known as autolysis. But it is now known that lysosomes are part of the normal cellular digestion apparatus relating the process of endocytosis to the processes of intracellular synthesis, storage, and transport,[1767] even including intraorganelle vesicles.[4283] Structural deterioration of lysosomes does not occur rapidly in ischemic or postmortem cells[4284,4285] or even in cells subjected to microwave irradiation.[4286] Direct damage from organelle fluid leakage, should such leakage occur, may be minimal because most of the digestive enzymes in lysosomes require the relatively low pH of the lysosomal vesicles for activation — just as some proteases require the low pH of the stomach. Peroxisomal membranes appear equally durable.[4287] Lysosomal membrane rupture could release limited amounts of lipofuscin into the cytosol since these organelles are the primary site of lipofuscinosis,[4288] which would probably be reasonably harmless (Section 15.6.3.2).

What about the nuclear membrane? Nuclear-cytoskeletal[4289] manipulations that alter the cellular mechanical force balance can cause the nucleus to change shape[4290,5445] and nuclear envelope fragility increases in the presence of high concentrations of salt.[4291] But micropipette injection of DNA material into cell nuclei is a common biotechnology procedure[4292-4295] which is easily survived by the cell. Normally, the nuclear envelope is reversibly disassembled and reassembled during mitosis, a highly regulated process[4296,4297] that includes the physical tearing apart of the nuclear envelope by extranuclear microtubules that penetrate it.[4304] Reassembly of a nuclear envelope that has been mechanically disrupted, fragmented, or completely disassembled by arbitrary artificial external forces (e.g., due to perinuclear nanorobotic activities) outside of the normal mitotic cycle cannot rely upon the regulated sequential cell cycle process[4298-4304] to guide reassembly. Such disruptions possibly might lead to apoptosis (Section 10.4.1.1), especially if the native chromosomes or their intranuclear moorings are physically damaged in any way,[4421,5465-5467] or to chromatin digestion — e.g., both single- and double-stranded circular plasmid DNA has a 50-90 minute half-life in mammalian cytosol probably due to cytosolic nucleases.[4295,4305,4306] In some circumstances it may be possible for in cyto medical nanorobots to induce reassembly of the disturbed nuclear membranes.[4307] Basic restrictions on the speed of mechanical motions that may safely be applied to chromatin are briefly discussed in Section 8.5.4.7.

15.5.7.3 Mechanical Interactions with Cytoskeleton

Active nanorobots maneuvering inside living cells could disturb or disrupt any of the many functions of the cytoskeleton, including (1) mechanical support (e.g., cell movement, adhesive interaction with ECM and neighboring cells, and stabilization of cell shape including cellular "tensegrity"[5333]), (2) integration of various cellular activities (e.g., intracellular movement including transport and positioning to the appropriate locations of organelles, intracellular particles, RNA and proteins), and (3) intracellular signal transduction (including structural information regarding cellular origin and differentiation state).[4598] In diverse cell types, microtubule and actin filament networks cooperate functionally during many processes, such as vesicle and organelle transport, cleavage furrow placement, directed cell migration, spindle rotation, and nuclear migration.[4308] Nanorobots could mechanically disrupt any or all of these functions during intracellular locomotion and manipulation of cell structures, if cytoskeletal/membrane links are disturbed.[4309]

The two most significant risks appear to be direct mechanical cytoskeletal reorganizations[55] (Section 15.5.7.3.1) and the possible disruption of vesicular transport and related molecular motor diseases (Section 15.5.7.3.2). In both cases, it appears likely that potential problems can be avoided by conservative design.

15.5.7.3.1 Mechanical Cytoskeleton Disorganization

Generalized disruption of the cytoskeleton can be very harmful to living cells. Disorganization of the cytoskeletal architecture has been associated with diseases as diverse as heart failure,[4310,4311] rotavirus infection,[4312] sickle cell anemia,[5676-5678] lissencephaly,[5673] and Alzheimer's disease.[4313-4315,5682] A "collapse transition" of neurofilament sidearm domains may contribute to amyotrophic lateral sclerosis (ALS) and Parkinson's disease.[5679-5681] Stress-related cytoskeletal fracture can be caused by 1-Hz stresses imposed by a mechanical probe on isolated rat ventricular myocytes.[3858] Cancer cells forced through 5- to 12-micron pores in polycarbonate membrane suffer traumatic spatial dissociation between components of the cell periphery, the cytoskeleton, and nucleus, inducing a ~1-week dormant state in the cells due to the mechanical trauma.[4316]

Nanorobots could induce various cell pathologies by mechanically disrupting specialized cytoskeletons consisting of cytoplasmic networks of ~6-nm diameter actin microfilaments, ~10-nm intermediate filaments, ~25-nm microtubules, or their many associated proteins[4317,4334] (Section 8.5.3.11), with effects similar to those of chemical disruption.[4318] Functions of these specialized cytoskeletons that could be disturbed include mechanical integrity and

wound-healing in epidermal cells, cell polarity in simple epithelia, contraction in muscle cells, hearing and balance in the inner ear cells, axonal transport in neurons, and neuromuscular junction formation between muscle cells and motor neurons.[4334]

As a nanorobot enters the cell, the first risk is transmembrane linkage disruptions. Muscular dystrophy may be caused by disorganization of links between the intracellular cytoskeleton and the ECM,[4003] and the disruption of proper adhesive interactions with neighboring cells can lead to fatal defects in extracellular tissue architecture.[4319] Epithelial cells subjected to mechanical strain may release in vivo proteases to cut intercellular adhesions.[4281] Looking inward, cellular mechanoprotective adaptations involve a coordinated remodeling of the cell membrane and the associated cytoskeleton.[4320] For example, the breakage of major cytoskeletal attachments between the plasma membrane and peripheral myofibers in cardiac myocytes predisposes the cell to further mechanical damage from cell swelling or from ischemic contracture.[4321] As another example, when infecting parsley cells, attacking fungus cells extend a penetrating hypha through the cell membrane, eliciting a defensive cytoskeletal reorganization.[4322] A local mechanical stimulus produced by a needle of the same diameter as the fungal hypha inserted through the host cell wall similarly induces the translocation of cytoplasm and nucleus to the site of stimulation, the generation of intracellular reactive oxygen intermediaries, and the expression of some elicitor-responsive genes. Without the mechanical stimulation, the morphological changes are not detected.[4322]

Mechanical disruption of cytoskeleton associated proteins by passing nanorobots could produce various cytopathologies. For instance, plectin is a 580 kD intracellular protein that links intermediate filaments with actin microfilaments, microtubules, and plasma membrane. Disruption of plectin function results in severe skin blistering and muscular degeneration, consistent with plectin's role in stabilizing cells against external mechanical forces[4323] and as a regulator of intracellular actin dynamics.[4324] Disturbance of centrosomes[4325,4326] or other in cyto fixed polarity markers[4327] could result in developmental or morphogenetic defects during subsequent cell division. Mechanical disturbance of cytoskeleton associated proteins could also alter the mechanical properties of cells, such as the ability of the cytoskeleton to deform and flow. One research group[4649] believes cells exist close to a glass transition state, a state regulated by cytoskeletal proteins which modulate the effective noise temperature of the matrix; this state thus could also, in principle, by manipulated by nanorobots.

Actin microfilaments might be disrupted by the mechanical activities of medical nanorobots. In the simplest case, endothelium exposed to shear stress undergoes cell shape change, alignment, and microfilament network remodeling in the direction of flow, though these changes can be blocked with nocodazole.[3803] Glomerular distention is also associated with cellular mechanical strain. A contractile cytoskeleton in mesangial cells, formed by F-actin-containing stress fibers, maintains structural integrity and modulates glomerular expansion. Mesangial cells have a cytoskeleton capable of contraction that is disorganized in long-term diabetes. Disorganization of stress fibers may be a cause of hyperfiltration in diabetes.[4328] Cutting the actin lattice may diminish both cell contractility[4329] and mechanical signal transduction into the nucleus.[4330] Care must also be taken to ensure that the surfaces or activities of intracellular nanorobots do not provide unplanned foci for actin polymerization, given that the kinetics of actin polymerization is autocatalytic and that the actin-based motility of functionalized microspheres can be reconstituted in vitro from only five pure proteins.[4331] Widespread actin disruption might produce symptoms analogous to elliptocytosis[5398-5403] and other inherited hemolytic disorders[5405-5408] that are caused by disorganization of the subsurface spectrin-actin cell cortex in the erythrocyte.[5404]

Intermediate filaments might also be disrupted mechanically. Perturbations in the architecture of the intermediate filament cytoskeleton in keratinocytes and in neurons can lead to degenerative diseases of the skin, muscle cells, and nervous system.[4332-4336] Knockout of the extensive keratin filament network jeopardizes the mechanical integrity of the epidermal cell, producing cell fragility and cytolysis manifesting as blistering skin disorders.[4332] Tissues lacking intermediate filaments fall apart, are mechanically unstable, and cannot resist physical stress, which leads to cell degeneration.[4337] Perinuclear clumping of fragmented keratin intermediate filaments accompanies many keratin disorders of skin, hair, and nails.[4338] In active muscle, intermediate filaments play an important role in the organization and stabilization of myofibril-membrane attachment sites. Their disruption can eliminate the deep membrane invaginations that are normally present in the healthy sarcolemma.[4333] Neuronal intermediate filaments are normally anchored to actin cytoskeleton. If this anchoring fails, the cell displays short, disorganized and unstable microtubules that are defective in axonal transport. Neuronal survival requires viable interconnects among all three cytoskeletal networks.[4336] Impairment of normal axonal cytoskeletal organization in Charcot-Marie-Tooth disease results in distal axonal degeneration and fiber loss.[4339]

The microtubule cytoskeleton could become disorganized due to careless or intentional intracellular operations by nanorobots, possibly: (1) simulating congenital brain malformation;[4340] (2) giving results similar to treatment with vincristine, a microtubule depolymerizing drug that produces peripheral neuropathy in humans accompanied by painful paresthesias and dysesthesias;[4341] or (3) giving results similar to treatment with ethanol, leading to oxidative injury producing a loss of gastrointestinal barrier integrity.[4342] Mechanical disturbance of the microtubule cytoskeleton induces electrophysiological modification of cell-cycle-dependent EAG potassium channels in mammalian tissue cells,[4343] and mechanical strain can induce a major decline in tubulin production in osteoblasts.[4344] Nanorobot mechanical operations could also induce buckling and loop formation of tubulin fibers, as has been observed[5674] inside shrinking vesicles when the surface tension of the shrinking bubble overcomes the Euler buckling strength of the fibers; intracellular tubulin twisted into 5-micron tennis-racquet shapes has also been observed.[5675]

Microtubules allowed to form under microgravity conditions show almost no self-organization and are locally disordered, unlike microtubules formed in 1-g conditions.[4345] Nanorobotic manipulations of cytoskeletal elements that offset, reduce, or cancel the stimulative effects of normal gravity could produce the same sort of cellular architectural disorganization as observed under microgravity conditions (Section 4.4.2 and Chapter 28) that alters the pattern of microtubular orientation.[4346]

A nanorobot with sharp edges that cuts a microtubule probably cleaves the hydrogen bonds between the alpha and beta monomers, rather than the covalent bonds within the monomers. This creates a new "plus" and "minus" end for the microtubule. In most cases this would not be fatal for the cell and in fact normally would have little impact because large-scale microtubule network patterns (e.g., asters, whorls, and interconnected pole networks) are self-assembling and are motor-molecule concentration-dependent.[4347] Nevertheless, in cyto nanorobots should avoid physically severing cytoskeletal elements whenever possible. Simple estimates of mechanical strength (Table 9.3) applied to typical fiber diameters suggest that the

tensile failure strengths are ~170 pN for actin microfilaments, ~300-500 pN for microtubules and ~20,000 pN for intermediate filaments. Nanorobots should avoid applying local forces of these magnitudes or larger in the vicinity of such fibers.

Force thresholds for cellular activation (Section 15.5.4.1) may be considerably less than the indicated tensile failure strengths. In 2002, the absolute force thresholds for failure, the range of mechanical frequency responses, and the threshold fraction of disturbed cytoskeleton required to elicit cellular response all had yet to be precisely determined. For example, during mitosis a force of 15-20 pN is required to detach microtubule-bound chromosomes[4350] but a tensile force of up to 210 pN is required to detach a microtubule from a kinetochore.[4348] Moreover, a nanorobot presenting a 1-micron^2 forward surface during intracellular locomotion through a (20 micron)^3 tissue cell intercepts only ~0.25% of the entire cytoskeleton during each 20-micron of transcellular travel. In cyto medical nanorobots may be restricted to speeds of ~10 microns/sec while traversing intracellular clear paths (Section 8.5.3.12) and ~1 micron/sec during transfilamentary intracellular locomotion, with progressive resealing of cytoskeletal elements that must be temporarily severed to allow the nanorobot to pass (Section 9.4.6). Intranuclear locomotion conservatively should progress no faster than natural chromosomal dragging rates during mitosis,[4349,4350] or ~0.1 micron/sec, applying forces of at most ~50 pN (Section 9.4.6).

15.5.7.3.2 Disruption of Molecular Motors and Vesicular Transport

There are a variety of human disorders associated with dysfunction of cytoskeleton-based molecular motors,[4351] including, for example, the motor-based diseases involving defective cellular myosin motors[4352-4354] (e.g., implicated in Griscelli syndrome,[6219] hearing loss,[6220] hypertrophic cardiomyopathy,[4352] and other myosin myopathies[6221]), spindle assembly- and function-related diseases[4355] or kinesin- and dynein-related motor diseases (e.g., implicated[6222] in Charcot-Marie-Tooth disease type 2A,[6223] Kartagener syndrome[6224] or primary ciliary dyskinesia,[6225] lissencephaly,[6226] polycystic kidney disease,[6227] and retinitis pigmentosa[6228,6229]), and other avenues for cellular malfunction.[4356,4357,6222,6230] Cellular motors also participate in the self-organization of microtubule network structures.[4347] But perhaps the most important function of molecular motors is intracellular vesicular transport, and most particularly axonal transport in neurons.[4358,4359,6231-6234] Typically, organelles, vesicles and granules ~100 nm in diameter or larger are carried at a peak speed of up to ~2 microns/sec on the back of a 60-nm kinesin transport molecule (Figure 9.32) that takes 8-nm ATP-powered steps along microtubule tracks running throughout the cell.[4360-4364] (Mean unloaded kinesin motor speed is usually only 0.5-0.8 microns/sec.) Conventional kinesin is a dimer of identical ~120 kD protein chains[4371] with a diffusion coefficient D ~ 2 x 10^{-11} m^2/sec.[4347] The vesicle-attached kinesin motor molecule steps toward the plus-end of microtubules by converting the energy of ATP hydrolysis to mechanical work.

Could a vesicle be dislodged from its microtubule track after being bumped by a passing intracellular nanorobot? A kinesin molecular mechanical detachment force of F_{detach} ~ 13 pN[4366] requires that a 1-micron^3 diamondoid nanorobot of mass m_{nano} ~ 2 x 10^{-15} kg must impact and carry the cargo vesicle a distance $S_{vesicle}$ ~ 1 nm to detach it at a constant velocity of $v_{nano} >\sim (2\ S_{vesicle}\ F_{detach} / m_{nano})^{1/2}$ ~ 3500 micron/sec, well above the self-imposed 10 micron/sec intracellular locomotion speed limit (Section 15.5.7.3.1) and even slightly exceeding the nanorobot instantaneous thermal velocity of ~2500 microns/sec in water at 37 ºC (Eqn. 3.3). The torsional stiffness of kinesin is so low that the molecule readily twists through more than 360º from its resting orientation,[4368] thus allowing the cargo to easily swivel out of the way of foreign impacting objects. And kinesin motors normally detach from a microtubule after a few seconds of travel anyway.[4369-4371] Still, nanorobots should be able to exert mechanical forces well in excess of 13 pN, so care should be taken to minimize those motions and trajectories which are likely to produce kinesin detachment. Analogously, it has been found experimentally that intracellular microspheres experience enhanced diffusion over short time scales near the nucleus, possibly due to interactions with microtubule-associated motor proteins.[4373]

Could a nanorobot that has clamped or securely bound itself to one location on a microtubule prevent the passage of vesicular cargoes, causing vesicles to bunch up behind or to detach? And could kinesin motor molecules that encounter the obstruction be permanently damaged? Most likely a detached vesicle will reattach to a clear neighboring microtubule and continue its trek,[4374,4375] or will reattach to the original microtubule downstream of the nanorobotic obstruction. In some cases organelles can attach to and move along multiple filaments simultaneously[4376] using multiple motor molecules,[4377] potentially reducing the interference with forward motion from a single-filament blockage.

Coppin, Pierce, Hsu and Vale[4366] have carefully studied the behavior of kinesin molecules whose forward progress is mechanically constrained. Kinesin has a stall load of ~5 pN.[4364-4367] There is an increasing rate of dissociation with increasing load. Specifically, the dissociation rate is ~0.2/sec at 1 pN load, 0.5/sec at 2 pN, 1/sec at 3 pN, and 2/sec at 5 pN load,[4366] rates which can be altered by the presence of microtubule-associated proteins.[4378] However, super stall loads of 5-13 pN do not cause kinesin to walk backwards, "probably because of an irreversible transition in the mechanical cycle." Rather, when super-stalled the kinesin motor most commonly takes a single backward movement and then dissociates (detaches) from the microtubule,* occasionally rebinding to the same microtubule (always at/below the stall load) and resuming its normal movement. This clearly demonstrates that the kinesin motor is still functional after being subjected to a dissociative induced stall. That is, a superload-induced detachment doesn't "break" the motor. The conclusion is that similar mechanical interference by a nanorobot also should not damage a processive protein motor. Interestingly, a mutant form of kinesin with its ATP and microtubule binding sites decoupled has been found that binds so tightly to the microtubule that the motor cannot let go,[4379] crudely analogous to the case of a nanorobot that firmly grasps a microtubule for a period long in comparison to the timescale of kinesin procession.

A nanorobot ambulating along microtubules should endeavor to avoid applying lateral forces exceeding the kinesin detachment load of ~13 pN[4366] which could have the effect of detaching associated vesicles as the nanorobot progresses, like a tree limb being stripped of its leaves as it is pulled through a tight-fitting metal

** Alternating back and forth movements also are observed at super-stall.[4366] The dissociation rate increases with load as long as the motor is moving (up to 2 Hz at 5 pN), but then becomes independent of load once the motor stalls — e.g., the stall time is 0.57 sec, representing a dissociation rate of ~1.8 Hz, for either spontaneous (~5 pN) or induced (~12 pN) stalls. Interestingly, forward loads induce the kinesin motor molecule to step faster under a wide range of ATP concentrations.[4366] Forward loads of 5 pN increase velocity by +200% if ATP concentration is rate-limiting (5-40 μM) or by +50% if ATP is saturated (1 mM), but forward loads >5 pN cause forward velocity to drop off sharply.[4366] A small carboxyl domain acts as a switch that turns the motor off when the kinesin motor is not bound to cargo.[4380]*

ring. (Using a two-dimensional optical force clamp, researchers in Block's group[6172] observed that ambulating kinesin molecules subjected to sideways forces up to 8 pN only slowed by ~30%, and similar forces applied from the rear have only a weak effect on forward speed.) Typically, the processive kinesin molecule only takes a few hundred steps before letting go,[4369-4371] so an occasional early detachment, by itself, should not induce cellular dysfunction. As long as the processive motor protein is not physically damaged, most of the detached vesicles should reattach and continue their journey after the nanorobot has passed by. The minimum spacing (maximum density) of kinesin motors along a microtubule is an axial repeat of 8 nm[4381] and experiments with isolated microtubules gliding on kinesin-coated glass find optimal motility at a 47 nm separation between kinesins.[4382] But the vesicular transport of 100-2000 nm diameter organelles in cyto implies that propulsive kinesin contacts are normally spaced at least 0.1-2 microns apart along the microtubule tracks. This leaves plenty of unoccupied foothold space to allow nanorobots to avoid disrupting processive motor proteins already in transit.

Coordinated groups of in cyto medical nanorobots should avoid inadvertently corralling or bulldozing large numbers of vesicles or motor molecules into relatively small volumes within the cell, as such increases in motor molecule concentration could increase the local microtubule polymerization rate.[4347] Analogously, in motor neuron diseases where vesicular transport is blocked by massive localized accumulations of kinesin molecules, the blockage can produce large axonal swellings in the motor neurons in human spinal cords and can disturb the machinery for anterograde fast axonal transport.[4383] Intracellular traffic jams involving repositioned vesicles and organelles[4384] appear to be initiated by the accumulation of stalled kinesin cargoes[4385] and are most commonly reported in neurons[4386-4389] where their effects are most serious. For example, axonal organelles transported by kinesin molecules that stall can cause organelle jams that disrupt retrograde as well as anterograde fast axonal transport, leading to defective action potentials, dystrophic terminals, reduced transmitter secretion and progressive distal paralysis that parallels the pathologies of motor diseases such as amyotrophic lateral sclerosis.[4388] Stretch injury to axonal cytoskeleton resulting in major loss of microtubules disrupts fast axonal transport resulting in focal accumulation of membranous organelles and axonal swellings,[4387] and a chemically-created microtubule-free region can serve as a trap that causes axonally transported particles to accumulate into a swollen region.[4386] Nanorobots should avoid creating such regions within the cell.

Similar considerations also apply during operations by intranuclear nanorobots, given the presence of myosin-based motors,[4390] RNA polymerase motors,[4391] and other motor molecules inside the cell nucleus.

15.5.7.4 Intracellular Cavitation, Shock Waves, Decompression Nucleation, and Ballooning

Acoustic pistons operated in cyto for nanorobotic power transmission (Section 6.4.1) or communication (Section 7.2.2), or rapidly moving mechanical elements enabling intracellular manipulation (Section 9.3.1) or locomotion (Section 9.4.6), could induce transient cavitation inside the cell. Cavitation bubbles may produce temperature increases of ~1000 °C and pressure spikes of ~1000 atm localized in regions of a few microns in radius, and should be avoided during normal operations because they may elicit cellular apoptosis.[4392] Normal or transient cavitation requires ~10^5 W/m^2 (~5.4 atm or ~550 nN/micron^2) at 30 KHz or ~10^6 W/m^2 (~17 atm or ~1700 nN/micron^2) at 1 MHz in order to form in water.[4393] Intensities less than ~10^4 W/m^2 will not produce transient cavitation in any tissue.[4394]

Intracellular damage may also be caused by acoustic shock waves that could be generated by nanorobots or nanoaggregates. Individual cell components have different measured sensitivities to the energy density of applied acoustic pulses. For example, observable defects are produced in lipid membranes at acoustic energy densities as low as 120 J/m^2; in vimentin (an intermediate filament cytoskeleton attachment protein) at 210 J/m^2; in mitochondria at 330 J/m^2; and in nuclear membranes at 500 J/m^2. A loss of cells growing on a microcarrier was also observed after applying 200 pulses at 210 J/m^2 per pulse.[4395] In another experiment,[4396] pressure waves lasting 0.5-1.5 msec up to 250 KHz impacting on dorsal root ganglion nerve cells of rats showed negative changes in neurite microtubules within minutes. After 6 hours there was swelling of nerve cell cytoplasm and organelles, and some neurofilament tangles were observed. Even loud noise can produce transitory mechanically induced microlesions in the cell membranes of several types of nonauditory cells, a mild membrane wounding from which the cells can survive and functionally recover.[4397]

Can rapid cell decompression cause internal bubbles? Sudden decompressions from up to 200 atm produce no intracellular bubble formation, in the absence of intracellular particles, in red blood cells, microbial cells, or pure water.[4398,4399] Decompression bubbles form in cells of the ciliate *Tetrahymena pyriformis* that have ingested graphite particles from aqueous suspensions when tested with 10-50 atm nitrogen supersaturations, though it is possible to alter the surface of intracellular graphite particles to avoid intracellular gas bubble formation during decompressions from external pressures as high as 25 atm.[4400] Gas tensions of a few atm can cause profuse bubble nucleation if the most effective nucleation particles are used. But ingested effective-bubble-promoter particles lose their ability to induce bubble formation in cells, up to >~175 atm, when added to suspensions of ciliate microbes (and ingested by the microbes). Though we must be cautious extrapolating to human cells, if this result is not merely a property of the cellular interior (e.g., cytoskeletal structure) then it might imply that intracellular bubble formation during decompression is rare because particle surfaces are somehow chemically modified during the ingestion process, by the microbial cell.[4399] If nanorobot surfaces are designed to resist this sort of chemical modification, then the risk of bubble formation in these circumstances rises. When operating in pressurized living cells, nanorobot structure and function should be designed to minimize bubble nucleation during subsequent cellular decompression.

To what degree may an in cyto gas bubble or nanorobotic balloon expand before the cell bursts or is severely damaged? Experimental data are available for just a few unrelated cases. Skalak[4401] found that a red blood cell placed in hypotonic solution swells from its normal biconcave discoid shape into a sphere, reaching its osmotic bursting pressure at ~3.1 x 10^6 N/m^2 (~31 atm). Internally-formed bubbles rupture *Tetrahymena* cells at 25-50 atm,[4400] and mechanical cell homogenizers burst cell membranes by compressing cells to ~1500 atm, then passing them through a rapid decompression nozzle.[4402] A force of 20-220 μN (14-130 atm) was required to burst 0.7- to 7-micron dry microcapsules pressed between two flat surfaces.[4403] A similar experiment performed on relatively fragile wet hybridoma cells produced bursting at only 0.06 atm for 10-micron cells.[4129]

15.5.7.5 Mechanical Disruption of Intracellular Microzones

Intracellular compartmentation of metabolites without enclosure by membranes (i.e., physiologically persistent, localized, and essential intracellular chemical gradients) of low molecular weight species such as O_2,[4405,5935,5936] sodium,[5937,5938] potassium,[5937,5938] calcium,[5939] amino acids,[5937,5940] sugars,[5937,5940] carbohydrate metabolism,[4405] ATP,[4404,4405,5936,5937] and pH[4405,5941] have been measured inside living cells,[4404,4405,5937] although there appears to be no gradient between bulk cytosolic and submembrane ATP in *Xenopus* oocytes.[5942] Even erythrocytes, known to be devoid of intracellular organelles, can sequester ATP.[4406] Intracellular biochemical gradients due to normal physiological processes and protein crowding effects also were discussed in Section 8.5.3.3.

Sequential enzyme interaction complexity gives rise to substrate or metabolite channeling[4407] and compartmentation of macromolecules within specific regions of the cytosol[4408,4409] or in association with specific components of the cytoskeleton.[4410] Regulated intracellular circulation systems may exist with cytoplasmic streaming rates from 1-80 microns/sec.[4411] Even water may be sequestered in microzones.[5937] Observations of transient intracellular hydrodynamics in the microorganism *Dictyostelium discoideum* have revealed the presence of a microscopic region near the cytosolic side of the plasma membrane where the mobility of water molecules is severely restricted.[4412] "The creation of specialized microzones of metabolism in accordance with their association with cellular organelles or membranal structures may be integral to normal function and regulation of adult mammalian cells." [4405] These stable microzones could be disrupted by the passage of intracellular motile nanorobots, possibly causing disorganization of local cell metabolism and temporarily disturbing normal cellular homeostasis. Cytosolic leakage following microinjection (a crude analog to nanorobotic cytopenetration; Section 9.4.5) has also been observed to give rise to artifactual intracellular diffusion gradients.[4413]

Once we fully understand how cells create and maintain microzones or cellular microdomains, we will be able to design nanorobots that can avoid disruption of these natural mechanisms, or repair such disruptions after they have occurred.

15.5.7.6 Mechanically-Induced Proteolysis, Apoptosis, or Prionosis

Might intracellular mechanical or electrical activities of medical nanorobots damage cytosolic proteins leading to locally accelerated proteolysis, or trigger other processes that might increase the protein turnover rate? One recent study[4414] found that bovine pericardium tissue subjected to dynamic stress (such as might be imposed by nanorobot activities) experienced accelerated local proteolysis as compared to the same tissue subjected to static mechanical loads of equal magnitude. For example, the intracellular level of αB-crystallin, a small heat shock protein produced by human trabecular network cells, temporarily declines by 90% one hour after the cells are subjected to a single 10% linear stretch, due to an increased degradation rate of the protein.[4415] Cyclic tension force also induces ECM degradation in cultured chondrocytes.[4416]

On the other hand, the protein turnover rate of myosin heavy chains in cultured rat myocytes is unaffected by changes in the contractile activity of the cell,[4417] and continuous electrical stimulation at 10 Hz does not alter the rabbit muscle protein turnover rate although static stretch significantly increases protein synthesis.[4418] Cells in rat hearts subjected to a doubling of aortic pressure experienced a decrease in protein degradation — mechanical stretch restrained proteolysis[4419] — but another study[4420] found that the net rate of proteolysis in isolated rat hearts is not effected by mechanical workload. More research is required to resolve these issues.

Nanorobot mechanical activities that might lead to unintentional apoptosis (Section 10.4.1.1) must be avoided. For example, detachment of tissue cells from ECM contacts,[3964] manipulation of cell shape,[3965] high intensity (~540,000 W/m^2 at 750 KHz) ultrasound irradiation of cells,[4392] significant physical damage to DNA,[4421] and other mechanical cellular trauma[4422] have been shown experimentally to induce apoptosis. One study[4423] found that mechanical trauma to rat motor neurons increased the production of ubiquitin, which targets many intracellular proteins for degradation, and decreased the production of hsp70, an inhibitor of apoptosis. Cell containerization might trigger apoptosis (Section 15.5.5.4), as might mitochondrial or nuclear rupture (Section 15.5.7.2.4) or intracellular acoustic cavitation (Section 15.5.7.4). Related alternative modes of programmed cell death such as autophagy[5483] must also be avoided.

If apoptosis is triggered, it may be rapidly aborted by in cyto nanorobots. Inhibitors of apoptosis (Section 10.4.1.1) are well known[4424-4430] that jam the caspases and other molecules involved in the cascade, and the anti-apoptotic effects of certain fullerene-based (Section 15.3.2.3) and dendrimeric[5186] pharmaceuticals has already been described. Similar substances could be released, as appropriate, by medical nanorobots. Surface presentation of specific peptides can also prevent apoptotic activity, as in NK cells (Section 15.2.3.1.1). Alternatively, in cyto nanorobots could abort an unwanted incipient apoptotic cascade by using molecular sorting rotors (Section 3.4.2) to quickly extract from the cytosol key apoptotic regulatory, mediator, or trigger molecules (e.g., cytochrome c), analogous to previous discussions of complement (Section 15.2.3.2), inflammatory (Section 15.2.4), coagulation (Section 15.2.5), and pyrogenic (Section 15.2.7) factor depletion by medical nanorobots.

Finally, care must be taken that exterior nanorobot surfaces or mechanical operations do not inadvertently induce pathological protein folding conformations,[5916] as in amyloidosis and prionosis.[4431-4434] It is not yet known whether this still-speculative process is a significant risk in nanorobotic medical missions.

15.5.7.7 Macromolecular Cross-Interface Adhesion

Nanorobots may present to the cytoplasm a variety of working surfaces that must remain free to slide with respect to each other. Examples include telescoping manipulators with adjacent rotating tube segments (Section 9.3.1.4), screw drives with a rotating interface at a fixed housing (Section 9.4.2.5.2), or various metamorphic surfaces with adjacent motile plate segments (Section 5.3.2.2) or telescoping segments (Section 5.3.2.3). Noncovalent adhesion of a large macromolecule (e.g., a free-floating kinesin motor[4347]) at two or more points on either side of the interface would produce an exogenous force that resists free rotation or translation of adjacent segments, leading to immobilization of the mechanism and possible device failure. Similar problems may arise for nanorobots negotiating the extracellular spaces or the vascular system.

A comprehensive analysis is beyond the scope of this book, but a simple example should suffice to illustrate how this situation may be resolved. Consider the 7-interface telescoping manipulator described in Section 9.3.1.4. With zero load at 1 cm/sec travel speed the total of all frictional losses amounts to ~0.1 pW,[10] giving a minimum no-load power density of 10^9 W/m^3 for the 100 nm long, 30 nm diameter tubular manipulator structure. The maximum power

under heavy load was not estimated, but other nanomechanical systems such as the sliding diamondoid logic rods and registers of Drexler's nanomechanical computer[10] assume power densities approximating 10^{12} W/m^3. At this maximum power density, the telescoping manipulator could apply a total of ~70 pW of mechanical power, or ~10 pW per sliding interface or tube segment. A 1.5 nm diameter drive shaft with a tangential velocity of ~1 m/sec turns ~700 times to drive a tube segment through one complete rotation, hence the tube segment rotates at ~2.85 cm/sec and so each tube segment can provide a shearing force of ~350 pN, relative to its neighbor. This exceeds the noncovalent adhesion forces commonly encountered in protein-protein single-molecule interactions (Section 15.5.4.1) by roughly an order of magnitude, and exceeds single-molecule kinesin motor microtubule-microtubule binding forces[4347] by almost two orders of magnitude. Additional protection may be afforded: (1) by constant fine motion (e.g., "jiggling") of all moving segments to reduce cross-interface adhesion, (2) by providing self-scraping exterior housings, and (3) by using anti-adhesive exterior coatings (Section 15.2.2.1).

15.5.8 Nanorobot-Nanorobot Mechanocompatibility

In clinical applications involving large populations of bloodborne diamondoid nanorobots simultaneously present inside the human body, nanorobots will regularly encounter one additional class of objects in their environment towards which mechanocompatibility must be proven: other nanorobots. For example, a maximum nanocrit bloodstream infusion involving a ~1000 terabot dosage (~10^{15} nanorobots) implies a mean collisional frequency for each device with its nanorobotic neighbors of ~40-200 collisions/sec (Section 9.4.2.2), mostly in regions close to vessel walls even at high shear (Section 9.4.1.3). Will such nanorobots survive in sanguo collisions with their neighboring devices?

Consider an elastic collision at relative velocity v_{coll} between two identical spherical nanorobots of radius R_{bot} and density ρ_{bot}, each comprised of a diamondoid structure with failure strength σ_{bot}, producing at the site of interaction a collisional dimple of radius r_{coll} and depth x_{coll}, and imposing a strain s_{coll}. The two nanorobots decelerate in a time $t_{coll} = x_{coll}/v_{coll}$ with a negative acceleration of $a_{coll} = v_{coll}^2 / (2\ x_{coll}) = v_{coll}^2 / (2\ s_{coll}\ R_{bot})$. The collisional force of $F_{coll} = m_{bot}\ a_{coll}$ is distributed over an interaction area of $A_{coll} = \pi\ r_{coll}^2$, producing a collisional pressure $P_{coll} <\sim \sigma_{bot}$ to avoid material failure, with $m_{bot} = (4/3)\ \pi\ \rho_{bot}\ R_{bot}^3$. Hence the stress produced during a nanorobot-nanorobot collision is approximately $s_{coll} = (2\ \rho_{bot}\ R_{bot}^2\ v_{coll}^2) / (3\ \sigma_{bot}\ r_{coll}^2)$. For nanorobots of radius R_{bot} = 1 micron and density ρ_{bot} ~ 2000 kg/m^3, thermal velocity in blood at 37 ºC is ~1 mm/sec (Section 3.2.1) and the anticipated relative collision velocity is 1-2 mm/sec (Section 9.4.2.2). Conservatively taking v_{coll} = 1 cm/sec, σ_{bot} = 1000 atm (~10^8 N/m^2) and r_{coll} = 10 nm, and taking the maximum allowable strain for diamond s_{max} ~ 5%, then the collision time t_{coll} ~ 1 nanosec, deceleration a_{coll} ~ 4 x 10^5 g's, and strain s_{coll} ~ 0.001% << s_{max} ~ 5%, so such collisions appear to be easily survivable. Similar considerations may apply to interactions between individual nanorobots and macroscale nanorobotic organs or nanoaggregates. Interactions between nonspherical nanorobots having protruding surface features, extended manipulators, and the like should be examined in future studies.

Nonspecific aggregation or inelastic "clumping" of nanorobots in vivo should not be a major problem because nonbiological adhesive forces are greatly reduced in fluid environments (Section 9.2.3), and because nanorobot surface adhesive characteristics and biological adhesive forces are subject to design control and therefore to minimization (Section 15.2.2).

CHAPTER 15.6

Nanorobot Volumetric Intrusiveness

Even assuming that nanorobots have biocompatible external surfaces that do not activate any of the body's natural defensive systems, medical nanodevices might still provoke unwanted reactions by physical displacement of critical biological systems or fluids. In nanomedicine, volumetric intrusiveness is a measure of the degree to which artificial nanosystems can safely and harmlessly volumetrically displace natural biological systems. In this Chapter we will briefly consider the acceptable volumetric intrusiveness of nanorobot populations and nanostructured macroscopic objects placed inside the human body (Section 15.6.1), in the human bloodstream (Section 15.6.2), and inside human cells (Section 15.6.3). Issues of functional intrusiveness (Chapter 17) and thermal intrusiveness (Section 6.5.2) are discussed elsewhere, although technological intrusiveness is briefly mentioned in Section 15.6.4.

A more complete analysis would carefully distinguish acute and chronic volumetric intrusions. Acute volumetric loading tests the ability of the current structure (whether whole body, blood vessel, or cellular compartment) to withstand the intrusion. Chronic (i.e., slow, gradual) volumetric loading tests the ability of the structure to adapt to the intrusion. These two processes are quite different in their nature and may result in significantly different tolerance ranges. A. Meretei correctly notes that "nanomedicine should be designed to suit the average organism — deducing ranges from sporadic extremes may make us too bold." Unfortunately, a more comprehensive analysis is beyond the scope of this book.

15.6.1 Somatic Intrusiveness

The issue of somatic intrusiveness arises whenever macroscopic quantities of foreign materials or medical nanorobots must be implanted into the human body. What is the maximum volume of foreign material that the body can safely accommodate?

The 70 kg reference human male has a body volume of 0.06 m^3 (with ~90% of U.S. males between 0.05-0.10 m^3)[5924] but the most rotund man of record, of otherwise normal stature, had a body volume of ~0.50 m^3 (Section 8.2). Hence those portions of the body not enclosed by bone in which skin distension readily permits incorporation of new materials may allow the reference male to add, at most, up to ~0.44 m^3 of foreign material, or up to ~633% volumetric expansion. It is not asserted here that such additions are necessarily healthy or wise,* but merely that they appear possible within the limits of natural human tissue elasticity. Genetic or other permanent artificial modifications to tissue elasticity or body architecture could further increase the expansibility of the human dermal envelope. Additionally, the dermal expansion that accompanies large weight gains occurs slowly over time, so an immediate expansion of equal volume due to the presence of nanorobots or nanoorgans would not be tolerated as well.

The principal natural limit for skin stretching may be estimated from the elasticity of the thick collagenous connective tissue or dermis — a three-dimensional feltwork of continuous collagen fibers embedded in a protein-polysaccharide matrix in which elastin fibers also are present.[4435] The elastin produces a material with rubber-like elasticity at small extensions but is limited at longer extensions by the dimensions of the collagen framework.[4436] Skin is normally under tension even when not being deformed by motion or other forces. For example, the resting strain in human skin varies from 10-30%,[4437] or λ_{skin} = 1.1-1.3 where λ_{skin} is the ratio of the length of stressed to unstressed skin. Distension is dominated by elastin up to λ_{skin} ~ 1.6, but as the tissue is extended further, collagen fibers become aligned in the direction of extension and are stretched by the applied load. By λ_{skin} ~ 1.9 at a tensile stress load of ~10^7 N/m^2 (near the failure strength of abdominal skin, or ~0.4-1.4 x 10^7 N/m^2; Table 9.3), the fiber lattice has a high degree of orientation parallel to the direction of extension and the skin becomes mechanically similar to tendon.[4435,4436] A dermal envelope that encloses a body volume of 0.06 m^3 at λ_{skin} = 1.2 will enclose ~$(1.9/1.2)^3$ (0.06 m^3) ~ 0.24 m^3 at λ_{skin} = 1.9, an addition of ~0.18 m^3 of foreign material or ~300% volumetric expansion. Such extensive and prolonged stretching of the skin (as is common abdominally during pregnancy) can produce dermal itching sensations.[4438]

Nanorobots injected into open tissue volumes dominated by extracellular matrix (ECM) also are limited primarily by the elasticity of collagen and elastin fibers that form the scaffolding of the ECM (Section 9.4.4.2). If these matrix fibers can readily stretch by a linear factor of $\lambda_{ECM} = (\lambda_{stretched} / \lambda_{relaxed})$ ~1.3, where $\lambda_{stretched}$ ~1.6[4435,4436] and $\lambda_{relaxed}$ ~ 1.1-1.3,[4437] then the maximum volumetric expandability of ECM-dominated tissue volumes is ~$(\lambda_{radial}{}^3$ — 1) = 1.2 (120%). These gross limits are not well explored experimentally. One experiment[1848] in which subdermal rat paw tissue received a 0.3% volumetric implantation of 10- to 20-micron diamond particles provoked only a slight increase in volume of the treated paw relative to the control paw and the edematous effect subsided after 30-60 minutes.

** Macroscopic biocompatible foreign bodies such as pacemakers and orthopedic pins and plates may reside inside the body indefinitely without ill effect, as long as they do not migrate (Section 15.4.1). This is true even in the gut. One case presentation[166] of foreign bodies in the alimentary tract proudly reported: "We present a case of a patient who ingested 648 metallic objects that formed an intertwining mass within the stomach, requiring operative removal. Of interest was the absence of symptoms and complications after 11 years of continual ingestion. To our knowledge, this is the second heaviest accumulation of metallic foreign objects removed from the stomach of a living patient." (The absence of symptoms might be explained by psychiatric causes.) Another study[159] involving 8 observed cases found that swallowed foreign bodies could be left in the intestine for years without any noticeable distension (e.g., splanchnomegaly) or pain (splanchnodynia).*

Several organs of the human body regularly expand and contract in volume during their normal functioning. For instance, the two lungs (including the integral tissues) normally cycle between 3.1-3.5 liters in total volume during resting respiration (~13% expansion), but at maximum inspirational capacity the lungs may cycle from 3.1-6.8 liters, a maximum volumetric expansion of ~120%. Similarly, the stomach varies between 0.5 liter when empty to 1.5 liters when full (Section 8.2.3), an expansion of ~200%, and the urinary bladder distends from ~0.15 liter when empty to ~0.65 liter when full (Table 8.9), a ~333% volume expansion. The spleen may vary in size between 80-300 cm^3 largely due to its content of blood, enlarging during digestion (largest in well-fed patients and smallest in starving patients)[5892] — a volume variation of 275%. The uterus of the human female distends massively during pregnancy, enlarging from ~0.1 liter at preconception to >10 liters peripartum (including ~1 liter of uterine wall, ~1 liter of amniotic fluid, and ~3 liters of fetus[4438,4439]), a ~10,000% expansion of the uterine volume itself though only a 14% addition to total body volume. Note that visceral organs are innervated with spinal visceral afferent neurons that respond to distension, contraction, or other mechanical stimuli[5451] — e.g., excessive bladder distension can induce visceral nociception.[5452]) Analyses of nanorobot intrusiveness should add total device volumes to the maximum body system volumes reached in normal functioning if entry and exit take place over one normal functional cycle or longer, with intrusive effect minimized during low-volume phases of the cycle (e.g., during late phases of exhalation and the early phase of inhalation in the lung). The patient's body volumes may also be actively controlled during nanosurgery (Chapter 12).

Some disease conditions can cause dramatic expansions of organ volumes. For example, in Gaucher's disease, the liver can enlarge (hepatomegaly) by up to 9 times its normal size (800% volume expansion); liver function is altered, but the impact is usually minor.[4440] The spleen can enlarge up to tenfold during mononucleosis, and Gaucher's disease also causes an increase in size of the spleen (splenomegaly) up to 20 times its normal size (1900% volume expansion), causing the patient to appear overweight or pregnant.[4440] This splenomegaly is often painless in itself. But the enlarged organ can press on the diaphragm and, indirectly, the lungs, making breathing difficult. It can also press on the stomach and intestines, causing loss of appetite and other digestive problems.[4440] Alcoholic cardiomegaly produces seriously pathological hearts that are enlarged up to 3 times their normal weight (~200% volume expansion).[4441] Of course, if nanorobot intrusiveness causes significant pathology in a given nanomedical mission design, then that mission design is not viable.

Some body compartments may be less tolerant of volumetric expansion. For example, the typical human eyeball has a volume of ~5.4 cm^3 [4442] with an average axial length of 24 mm,[4443] but increasing axial length by just 8% to 26 mm may produce myopia, while decreasing axial length by 17% to 20 mm can produce hyperopia.[4443] (There is one extreme report[4444] of an eyeball expanded to a volume of ~31 cm^3 due to chronic uveitis and secondary glaucoma in an 18-year-old man.) The peritoneal cavity tolerates moderate stretching. Peritoneal infusion of dialysis patients with 2 liters (3% of body volume) or 3 liters (5% of body volume) of dialysate fluid per washout cycle caused intraperitoneal pressure rises of 13.9 mmHg or 16.8 mmHg in males and 12.1 mmHg or 14.5 mmHg in females, respectively. 64% of patients receiving 2.5 liters and 44% of patients receiving 3 liters reported no physical discomfort, suggesting that somewhat higher volumes could be safely employed.[4445]

The interior spaces of joints, bones and the cranial vault in which the brain resides cannot tolerate major intrusions by macroscale foreign objects without surgical assistance. For instance, in joints such as the knee, synovial fluid volume averages 1.1 cm^3 (range 0.13-3.5 cm^3), so it would seem likely that a maximum ~10% volume displacement of synovial fluid, or ~0.11 cm^3 of mechanically-nonirritating foreign objects, would not be intolerably intrusive. One experiment[633] in which canine knee joints received a 0.3% volumetric injection of 3-micron diamond crystals found little evidence of inflammation, with intra-articular pressure and local cell count remaining low. In another experiment,[1849] the synovial fluid of rabbit knee joints received an injection of 10- to 20-micron diamond particles in suspension at 5.7% by volume that produced no inflammation. In yet another experiment,[902] rats survived implantation of 1- to 8-micron carbon particles in knee even at ~25% of synovial volume. Synovial fluid containing mechanically-irritating needle-shaped monosodium urate (MSU) crystals are diagnostic for gout[4446-4448] at concentrations as low as 0.01-1% by volume.* However, most of the pain and physical disruption of gout arises from the long-term buildup of tophi (large crystalline deposits[4453]) within the affected joint that may ultimately displace 10% or more of the original synovial fluid volume. Knees and other joints are well-supplied with nociceptors,[5448] so nanorobots maneuvering in these regions must take care to avoid mechanically inducing sensations of pain.

In the brain, normal cerebrospinal fluid (CSF) and intracranial pressure is ~10 mmHg (~0.013 atm), although experimentally-induced excursions up to 100 mmHg (0.13 atm) in primates[4454] or 152 mmHg (0.2 atm) in pigs[4455] have produced neither ischemia nor death. (Intracranial pressure is regulated by the rate of CSF production and resistance to CSF resorption through the arachnoid villi as determined by venous pressure.[5489]) The isothermal compressibility of water at 1 atm and 37 °C is $\kappa_{water} = 4.492 \times 10^{-5}$ atm^{-1}.[63] If a brain volume-equivalent of $V_{brain} = 1400$ cm^3 of water is placed in a closed incompressible container and pressurized to a maximum safe $P_{foreign} = 0.2$ atm by the insertion of an incompressible foreign body of volume $V_{foreign}$, then $V_{foreign} \sim \kappa_{water} P_{foreign} V_{brain} \sim 0.012$ cm^3. Substantially larger foreign body volumes may be injected safely into the brain if those injected volumes displace mobile fluids such as cranial CSF. MRI studies[4456] reveal that inhalation of 7% CO_2 (producing hypercapnia) induces an average reduction of 9.4 cm^3 (range 0.7-23.7 cm^3) in human cranial CSF volume, whereas hyperventilation with 60% O_2 (producing hypocapnia) induces an average increase in cranial CSF volume of 12.7 cm^3 (range 0.7-26.7 cm^3). This implies that inert foreign bodies (especially if particulate) up to ~10-20 cm^3 in volume (1-2% of brain volume) might safely displace CSF in the brain without ill effect. (Maintenance of blood-brain integrity — a functional intrusiveness issue — is critical.)

Much larger losses of intracranial CSF volume (up to 158.6 cm^3 in one patient,[4457] or ~10% of brain volume) associated with intracranial hypotension, such as may occur after lumbar puncture procedures or dural tear, can often[4457,4458] but not always[4459] produce very painful orthostatic headaches (as sometimes occurs in women receiving an epidural anesthetic for childbirth),

** This estimate assumes that (a) the crystals measure 0.3-1 micron wide and 15 microns long, (b) there are 10 crystals/leukocyte, and (c) there are 5000-50,000 leukocytes/mm^3 of gout-inflamed synovial fluid.[4449] Peritonitis is induced in mice by intraperitoneal injection of ~0.2% by volume of MSU crystals (i.e., 3 mg MSU in a ~1 cm^3 cavity[4450]); gouty serum and synovial fluid concentrations of MSU are ~0.01%,[4451] while the saturating concentration for phagocytic cells is ~0.03% crystals by volume.[4452]*

dural thickening,[4460] and other symptoms.[4461] It would be unwise to crowd out the equivalent of the entire cranial CSF volume because the fluid serves an essential function in the brain (Section 8.2.4) — primarily, to cushion the brain in the cranial cavity. M. Sprintz also notes that intracranial pressure is autoregulated within the CNS, so fluctuations in systemic blood pressure will not alter the intracranial pressure within certain blood pressure limits. The prevention of increased intracranial pressure is dependent not only on the autoregulatory system of the CNS but also on the anatomical functionality of the CNS to allow adequate resorption of CSF, thus preventing hydrocephalus and subsequent increased intracranial pressure.

A whole-body tumor load of ~1000-2000 gm (up to ~3% by weight) is generally required for lethality in patients with systemic cancer, whereas in the central nervous system alone a ~100 gm tumor mass (~6% by weight) is lethal.[4462] Depending on their location, solid brain tumors, cerebral mass lesions or intracranial hematomas may produce altered mental function at sizes from a few millimeters[4463] to a few centimeters in diameter,[4464] or 0.001-1% of brain volume. In cancer research laboratories, federal (U.S.) regulations require a special permission from OSHA's affectionately dubbed "mouse police" before a researcher can grow tumors larger than 10% of body weight[4465,4466] or 1000-2000 mm^3 (5-10% of body volume),[4466,4467] or ascites (serous fluid accumulations in the peritoneal cavity) larger than 20% of body weight,[4465] on laboratory test animals. However, tumor lethality is not strictly mass-dependent but is more the result of a loss of organ function and the toxicity of tumor degradation products — benign tumors such as uterine fibroids or myomas can exhibit masses well in excess of the above limits.

Various particle infusions have been tested experimentally. For example, the LD50 for <44-micron alumina particles injected intraperitoneally in mice lies above >2 gm/kg or >0.1% by volume.[1067] All rats survive intraperitoneal injection of 1- to 8-micron carbon particles at 0.1% of body volume,[902] and the oral LD50 (the lethal dose needed to kill 50% of the subjects) in rats for PVC powder is >0.7% of body weight[4468] and is 0.8% of body weight for methyl methacrylate powder.[4469] Ceramic powders injected intramuscularly or subcutaneously at >0.5% local tissue volume elicited almost no systemic effects in mice.[1067] A table of standard toxicity classes lists as least toxic or "relatively harmless" to rats a dose of foreign substances having an LD50 of >1.5% of body weight for single oral dose or >2.3% of body weight for skin exposures.[4470] Pathological particulate burdens in lymph nodes may range from 0.07-4% of node volume (Section 15.4.3.4).

In sum, the conservative safe limit for somatic intrusiveness of otherwise biocompatible foreign objects — such as medical nanodevices — is probably in the range of 1-10% of local tissue, organ, or body volume, though larger volumetric expansions may be possible without harm.

From a purely aesthetic perspective, in psychology the limit of human perceptual differential sensitivity for otherwise visually equivalent areas is $\Delta A_{perceptual} \sim 0.06$ (6%).[4471,4472] Thus a human body must change by 6% in visual cross-sectional area to be noticeably different, representing a volumetric change of $\Delta V_{perceptual} \sim (1 + \Delta A_{perceptual})^{3/2} - 1) \sim 0.09$ (9%). For example, the volume added to the human male form by tight-fitting clothing should not create a perceptible increase in body size — wrapping the entire ~2 m^2 human skin area with tight-fitting clothing extending ~1.5 mm from the skin surface gives a clothing volume of 0.003 m^3 corresponding to a 5% increase in the apparent body volume. Similarly, the volume of a reference male having maximum cyclic lung, stomach and bladder volume exceeds the volume of a reference male having minimum such volumes by ~0.0052 m^3, an aesthetically acceptable ~9% volumetric expansion. It is not unusual for body volume to change by ~3%/day due to natural variations in fluid balance and fluid retention. The maximum aesthetic intrusiveness limit thus may be conservatively estimated as 5-10% of basal body volume.

15.6.2 Bloodstream Intrusiveness

The vascular system is designed to handle large variations in pressure, with the predominant determinant being volume. The issue of bloodstream intrusiveness arises whenever macroscopic quantities of foreign materials or medical nanorobots must be injected into the vascular system, or must be permanently installed or anchored to the wall of a vessel (e.g., Section 15.5.3.6). What is the maximum volume of foreign material that the vascular compartment (e.g., blood, lymph, etc.) can safely accommodate?

The 70 kg reference human male has a red blood cell volume of 36 cm^3/kg of lean body mass and ~3.6 cm^3/kg of fat.[4473] Assuming the ideal 7% body fat (i.e., typically athletes and models) and a 44% hematocrit (Hct) gives the correct whole blood volume of ~5400 cm^3. If the heaviest known human male (485 kg; Section 8.2) had 80% body fat and a 54% Hct, then his whole blood volume may have been ~9.0 liters, or a ~67% (~4 liter) blood volume expansion. The natural limit for arterial wall distension over the physiological blood pressure range from 0.1-0.2 atm is $\lambda_{radial} \sim 1.2$ radially[4474] and perhaps only $\lambda_{long} \sim 1.1$ longitudinally, and vein walls are a bit more distensible than arterial walls.[3967] Hence the maximum volume expansion (~length distension x areal distension) of the vascular system at maximum pressure would be at least $\sim(1 - \lambda_{long} \lambda_{radial}^2) = 0.6$ (60%). This suggests that a ~4 liter addition to the human blood compartment might be near the maximum limit that natural vascular wall material can accommodate. Again, genetic or other artificial modifications to tissue elasticity or body architecture could further increase the volumetric expansibility of the human vascular compartment.

It is important to note that only a small portion of total body volume is intravascular. A. Meretei speculates that small-gauge intravascular systems can leak access volume to the much larger body volume and thus might become overloaded only very late in the process. Ascites, body-wide edemas and urinary system overload might occur before the vascular systems is stretched to the limits, so the above calculation would be clinically relevant only when we can validly assume no leakage from the intravascular space.

Additionally, minor adjustments occur physiologically:

1. to red cell volume by the splanchnic tissues[4475] and the spleen (~70 cm^3 noncirculating RBC storage volume);
2. to whole blood volume via shifts between microcirculation and macrocirculation as during hemorrhage compensation (~200 cm^3 whole blood[4476]) or dialysis (15.2% whole blood or ~800 cm^3 [4477]); and
3. to blood plasma volume (a) diurnally during sleep (~200 cm^3 plasma decrease),[4478-4480] (b) after drinking 1 liter of water (~200 cm^3 plasma increase),[4480] (c) during heavy exercise (up to –20% plasma volume decrease or ~600 cm^3),[4481-4483] or (d) after endurance training or heavy exercise (up to +25% plasma volume increase or ~760 cm^3)[4484] such as ultramarathons.[4485,4486]

Patients who lose up to ~2 liters of blood may recover if fluid volume is restored by a transfusion of blood or plasma,[4488] or by intravenous infusions of 1.5-2 liters/day of plasma extenders such

as 6% hydroxyethyl starch.[382] Recovery is also possible after a loss of up to ~3 liters during gradual exsanguination over a period of 24 hours.[4487,4488] And plasma volume expansions up to 1.5-3.0 liters are seen in certain pathological conditions such as Waldenstrom's macroglobulinemia.[2484] However, 1 liter is approximately: (1) the asymptomatic blood loss limit;[4488] (2) the plasma volume change in high-altitude-adapted Andean natives with Hct exceeding 60%;[4489] (3) the hemodilution limit for freshwater aspiration in the lungs;[4490] and (4) the maximum blood collection equivalent (on a relative volume basis) allowed from laboratory animals over a 2-week period (15 cm^3/kg or 25% of blood volume[4466]). A volume of 0.5-1.0 liter also is the limit for experimentally-induced[4491] and exercise-induced plasma expansions,[4484] hence 10-20% of blood volume appears to be a liberal upper range for nanorobotic volumetric intrusiveness into the bloodstream.

For a more conservative upper range, we note that the acute toxicity of latex microspheres in various nonhuman animals has been investigated experimentally.[4492-4498] For example, all rabbits receiving an intravenous injection of colloidal carbon[2961] or 0.5-micron latex particles[4492] at a blood volume fraction of ~0.1% survived the treatment, and all rats receiving an I.V. injection of 1- to 8-micron carbon particles at a ~0.2% blood volume fraction also survived.[902] As expected, microsphere toxicity due to vascular occlusion is a function of the total volume of microspheres injected[2679] and follows a power law[2679,4496] of the form $N_{LD50} = M_{body} K / D_{sph}^{b}$, where N_{LD50} is the number of spheres intravenously injected to achieve LD50 in the rat, M_{body} is rat body weight in kg, D_{sph} = microsphere diameter in microns, and the experimentally-determined constants are K = 8.6 x 10^{11} $micron^{3.15}$/kg and b = 3.15. Simply extrapolating to a human body weight of M_{body} = 70 kg, the LD50 whole-body dose of D_{sph} = 1 micron latex microspheres would be N_{LD50} ~ 60 trillion spheres. Consequently taking f_{blood} ~ 0.09 (9%) as the fraction of human body weight represented by blood and ρ_{body} = 1.17 x 10^{-15} kg/μm^3 as the mean human body density, then the human-equivalent LD50 nanocrit (Nct) would be $Nct_{LD50} = \pi \rho_{body} K / (6 f_{blood} D_{sph}^{0.15})$ ~ 1%.

However, the above formula for N_{LD50} is derived mainly from studies of particles >10 microns in diameter (i.e., much larger than medical nanorobots) with varying dimensions and atomically rough surfaces (nanorobots can have identical radii and atomically smooth surfaces), in animal models (rats and beagles) having smaller red blood cell diameters and narrower capillaries than humans. This suggests that humans might be able to tolerate a higher nanocrit of micron-size particles. Additionally, at 0.3% loading with 3-micron microspheres, beagle dogs experienced temporary dyspnea (labored breathing), systemic hypotension and depression of myocardial performance, with the main short-term cause said to be "the large bolus of spheres in the lungs"[2679] The authors speculated that because smaller spheres are rapidly cleared from the lungs, "reduction of toxicity might be obtained by slow infusion, rather than injection, of these microspheres." The use of medical nanorobots specifically designed to avoid geometrical trapping in the lungs (Section 15.4.2.1) and the inclusion of respirocyte-class devices[3573] in the injected nanorobot population to forestall ischemic risk (assuming the circulatory pathway is not permanently occluded) should further reduce toxicity.

The human LD50 for microparticles of any kind has not been reported in the literature. The maximum number of PVC contaminant particles allowed in parenteral IV injectable or infusible fluids, according to the British and U.S. Pharmacopoeias, ranges from 1000/cm^3 for 2- to 5-micron particles to 5/cm^3 for >25-micron particles, or a mere 10^{-6} - 10^{-5} % blood volume fraction.[4499] Air-filled bubbles 3-5 microns in diameter stabilized with 25 nm thick half-denatured albumin shells[4500] are diagnostically injected into human patients in the form of a microbubble infusate called Albunex.[4501] Albunex is used as an ultrasound contrast agent[4502] at a concentration of 3-5 x 10^8 bubbles/cm^3 (infusate bubble volume fraction ~ 1%), and infusate doses up to 0.12 cm^3/kg of body weight (i.e., 2.5-4.2 x 10^9 microbubbles injected into the entire human blood volume, producing a whole-body "bubblecrit" equivalent to Nct ~ 0.002%) are said to be well tolerated in man.[4503] Intraarterial administration of very large (40-micron) degradable starch microspheres produces slight early signs of toxicity (nausea/vomiting) in 50% of patients receiving a ~10^8-particle dose,[4504] yielding a blood volume loading equivalent to Nct ~ 0.06%.[4504] The highest reported bacteremic LD50 is ~10^{10} CFU/ml of blood for an avirulent mutant of *S. aureus* in mice,[4505] an equivalent bacteriocrit to Nct ~ 1% in human blood. Bulk blood viscosity should not be seriously affected by the presence of small microspheres up to Nct ~ 10% (Section 9.4.1.4). We conclude that the safe upper limit of human tolerance for 1- to 3-micron medical nanorobots in the bloodstream probably lies in the range of Nct ~ 0.1-10%. A more exact recommendation must await future laboratory experimental and clinical results.

The intravenous infusion of a maximum 0.540 liter dose (i.e., producing Nct = 10%) of particulate foreign bodies — including all necessary medical nanorobot species required for a particular treatment — suspended in 0.540 liter of aqueous carrier fluid promptly raises blood volume from 5.40 liters to 6.48 liters, elevates blood pressure by ~22 mmHg, and decreases Hct by ~7% (e.g., from 44% to 37%), inducing a temporary mild anemic state unless the foreign particles are oxygen-transporting respirocyte-class[3573] nanorobots (Chapter 22). The addition of >1.0 liter of water to the blood compartment would be required to reduce blood plasma sodium from normal levels at 135-145 mEq/L (3.1-3.3 x 10^{-3} gm/cm^3) to 110-120 mEq/L (2.5-2.8 x 10^{-3} gm/cm^3), sufficient to produce symptomatic hypervolemic hyponatremia and hypokalemia.[4506-4508] Adding just 0.54 liter of excess water should produce only a temporary, nonsymptomatic electrolyte imbalance whose minor effects may be partially offset with ionic amendments to the aqueous carrier fluid. (Utilizing an isotonic aqueous carrier solution should help to avoid causing any electrolyte imbalances.)

As in cases of mild water intoxication,[4509,4510] following infusion of the maximum 0.540 liter dose the osmoregulatory system should respond by eliminating excess water and electrolytes from the bloodstream via the kidneys and urination. This simultaneously eliminates the modest increase in blood pressure and any electrolyte imbalance while re-establishing normal hematocrit at the cost of slightly elevated blood viscosity (Sections 9.4.1.4 and 9.4.1.5). For non-respirocyte-class nanorobots, the post-infusion equilibrium blood state should approach an Hct of 44%, a maximum nanocrit of 10% (Section 9.4.2.6), a plasma volume reduced from 3.02 liters to 2.48 liters, and a whole blood volume of 5.4 liters. The total particle volume load is then 54%, about equal to the high-end range of Hct for male adults and for newborns.[2004] Nanorobot-infused bulk blood viscosity at 37 ºC body temperature rises from ~3.0 x 10^{-3} kg/m-sec to ~4.8 x 10^{-3} kg/m-sec in high-shear conditions (Table 9.4, Figure 9.13), which is insignificantly different from 54% Hct whole blood. This increase is not expected to produce whole blood hyperviscosity[4511-4522] as is characteristic: (1) of some anemias,[4516] inflammatory diseases,[4517] infectious diseases,[4511] cerebrovascular diseases[4514,4519] and certain other conditions;[4515,4520] or (2) of polycythemia patients who present with hematocrits of 75-85%[4521-4523] which leads to disturbances in blood flow as blood viscosity increases

with rising hematocrit. Nor is the viscosity increase likely to induce "blood sludging"[4524] as may occur during shock[4525] or tissue injury,[4526,4527] in which plasma volume is reduced and blood cells tend to agglutinate and form large clumps or masses that move slowly through the vessels, sometimes clogging the smaller vessels.[2004] Osmotic consequences of nanorobot intrusion including ion balance, fluid (and volume) movement, dislocation between body compartments and intracellular, interstitial, and intravascular spaces, and impacts on blood biophysics and chemistry should be systematically addressed, but such a complete analysis is beyond the scope of this text.

Another bloodstream intrusiveness issue is the potential for nanorobot-induced coagulopathy. It is possible that the presence of a sufficiently large concentration of nonadhesive inert microparticles might interfere with the coagulation process by intercalating into the developing thrombus, physically preventing solid clot formation. However, inert polystyrene microspheres are frequently used in coagulation studies[4528] and degradable starch microspheres do not influence platelet aggregation.[4529] The proposed effect has not yet been reported in the literature but could be investigated experimentally.

15.6.3 Cellular Intrusiveness

The issue of cellular intrusiveness arises whenever microscopic quantities of foreign materials or medical nanorobots[29] must be injected into the intracellular spaces, comprising cytosol and nucleus. There are two aspects: First, how much new foreign material can be added to a cell? Second, how much of a cell's existing fluidic volume can be replaced with foreign material with no change in total cell volume, consistent with continuing cellular viability?

Of course, cell "viability" should be rigorously addressed from the standpoint of structural integrity, metabolism, reproduction, cytoskeletal activity, motility, secretory activity, and so forth — since cells may survive intrusion while losing their secretory activity or their ability to divide. Since direct experiments with nanorobots and living cells cannot yet be undertaken, we can only crudely estimate the maximum volume of foreign material that the intracellular compartment can safely accommodate by examining analogous instances of cellular intrusion.

15.6.3.1 Membrane Elasticity and Cellular Expansion

The introduction of foreign material into a cell may cause intracellular volume to expand. Assuming a spherical cell shape, the change in cell volume ΔV_{cell} from the original cell volume V_{cell} is related to the change in plasma membrane area ΔA_{cell} of an unstretched membrane of area A_{cell} by the relations $\Delta V_{cell} / V_{cell} \sim ((1 + \Delta A_{cell}/A_{cell})^{3/2} - 1)$ and $\Delta A_{cell}/A_{cell} = T_{memb} / K_{memb}$, where T_{memb} is the isotropic tension due to membrane expansion, the area compressibility modulus K_{memb} = 0.378 N/m for erythrocyte plasma membrane at 310 K, and K_{memb} = 0.636 N/m for leukocyte plasma membrane (Section 9.4.3.2.1). Taking a conservative lysis limit of $T_{memb} \sim 4 \times 10^{-3}$ N/m for erythrocytes, then $\Delta V_{cell} / V_{cell} \sim$ 1.6% for red cells and ~0.9% for white cells. However, erythrocytes are not spheres but biconcave disks[3967] with a mean volume of 94 micron^3 in isotonic solution (300 mosmol). They absorb water in hypotonic solution, becoming spherical at 131 mosmol with a volume of 164 micron^3, demonstrating a capacity for volumetric expansion of 74% without losing membrane integrity (albeit with some loss of rheological functionality). Other cells may tolerate even greater expansion. For example, taking T_{memb} = 1.7 N/m and K_{memb} = 1.3 N/m for TB/C3 hybridoma cells and T_{memb} = 1.8 N/m and K_{memb} = 1.2 N/m for NS1 myeloma cells,[4530] then $\Delta V_{cell} / V_{cell} \sim$ 250% for hybridomas and ~300% for myelomas. These estimates are crude at best because the lipid population of the plasma membrane is constantly changing and may enlarge or contract over time.[4641,4642]

For more than four decades, microbiologists have routinely extracted or inserted an entire nucleus into a cell using micropipettes without compromising cell viability.[4531] Such nuclear transplantation represents a volumetric change of $\Delta V_{cell} / V_{cell} \sim$ 3.4% for the typical 20-micron human tissue cell (Table 8.17) but in the case of a human leukocyte would represent a volumetric change of $\Delta V_{cell} / V_{cell} \sim$ 18% for an eosinophil, 22% for a neutrophil, 26% for a monocyte, or 51% for a lymphocyte.[4532] Decades of laboratory practice have confirmed that at least ~100 micron^3/cell of foreign material (representing perhaps 1-3% of cell volume) can be safely injected into a somatic cell without any significant effect on cell viability.[4533]

Neutrophils increase in volume by ~15% when stimulated in suspension, and rabbit neutrophils that migrate into the abdominal wall (150 micron^3) are +50% larger than those in the abdominal wall vasculature (100 micron^3). Human neutrophils induced by fMLP to migrate into collagen gels (290 micron^3) are 42% larger than those that did not migrate (204 micron^3).[4534]

15.6.3.2 Intracellular Lipofuscin and Storage Diseases

Insoluble age-pigment lysosomal granules called "lipofuscin" collect in many of our cells, the accumulation starting as early in life as 11 years old and rising with age,[5468] activity level[4535,4536] and caloric intake;[4537] and varying with cell type.[5469,5470] Clumps of these yellow-brown autofluorescent granules — typically 1-3 microns in diameter[4538-4540] — may occupy up to 10% of the volume of heart muscle cells,[4541] and from 20% of brainstem neuron volume at age 20 to as much as 50% of cell volume by age 90.[4542] Lipofuscin concentrations as high as 75% have been reported in Purkinje neurons of rats subjected to protein malnutrition.[4543] Elevated concentrations in heart cells appear not to increase the risk of heart attack,[4541,4544] nor to accelerate cellular aging processes in heart muscle or liver tissues.[5471] Brain cell lipofuscin is not associated with mental[4542,4545] or motor[4546] abnormalities or other detrimental cellular function.[4547] Hereditary ceroid lipofuscinosis[4548] or neuronal ceroid-lipofuscinosis (NCL) diseases[5472] can lead to premature death, though ceroid appears to be pathological only in neurons[5472] or when loaded into human fibroblasts.[5473] There is also considerable evidence that A2E, a hydrophobic fluorophore component[5474] of retinal pigment epithelial lipofuscin,[5475] may contribute to age-related macular degeneration.[6020-6026] But the fact that lipofuscin is an indigestible lipid peroxidation product that cannot be excreted but whose presence appears commonly not directly injurious to the cell argues strongly that cells can tolerate significant volumetric replacements of cytoplasmic fluid with artificial foreign bodies such as medical nanorobots while continuing to function normally.

Other inert intracellular pigments are known,[4549] along with a number of pathological intracellular storage diseases[4550-4554,5476-5478] including Fabrey's, Gaucher's, mannosidosis, Niemann-Pick,[4257] and Tay-Sachs, Lewy bodies in Hallervorden-Spatz disease,[5919-5921] and Hirano bodies.[6145] Accumulation of lysosomal deposits of oxidized low-density lipoproteins in macrophage foam cells may contribute to atherosclerosis.[5479] Intracellular crystalloid bodies have been observed in the skeletal muscle cells of patients with hypothyroid myopathy.[5480] Noninert amyloid deposits average ~12% of pancreatic islet cell volume in patients with maturity onset diabetes.[4555]

15.6.3.3 Intracellular Microspheres and Crystals

Various particulate substances have been introduced intracellularly to observe the effects on the cell. In one study,[4556] up to 500 polystyrene 0.26-micron beads were injected into a tissue cell and this 4.6-micron^3 load did not affect the cell's ability to transport the particles around inside as if they were tiny organelles or vesicles. A few micron^3/cell of engineered nanoparticles are tolerated by living cells when employed as intracellular fluorescent labels.[4238] Cholesterol crystals have been induced to grow inside living J774 mouse peritoneal macrophages, reaching a concentration of ~120 μg cholesterol/mg protein or ~2.4% intracellular crystals by volume[4557] without lethality. However, excessive intracellular crystallization (e.g., of drug molecules) can lead to problems such as acute renal failure,[4558] and intracellular crystals have been found inside chondrocytes in certain crystal deposition diseases.[4559] Cholesterol crystals in macrophage foam cells may also contribute to atherosclerosis.[5481] A useful and simple experiment that could be done today would be to microinject cells with progressively larger loads of chemically inert diamond particles or polystyrene spheres, noting the effect on cell motility, behavior, and metabolic function. Other intracellular crystal deposition diseases are known such as mitochondrial crystalline inclusions[6147-6149] and intermembrane inclusion bodies,[6150] polyglucosan bodies,[6151] and Fardeau-Engel bodies[6152] involved in peripheral neuropathies.

Interestingly, *Pseudomonas stutzeri AG259*, a species of bacterium isolated from silver mines, protects itself from the usual bactericidal effect of silver ions by sequestering triangular and hexagonal insoluble nanocrystals of Ag^0 and Ag_2S (believed to be acanthite, a stable crystalline form of silver sulfide) intracellularly in vacuole-like granules in the periplasmic space.[4560] In one photomicrograph, several crystals ranging from 90-200 nm in diameter are visible inside a living bacterial cell ~800 nm in diameter, suggesting a total inert particulate ~13% volumetric intrusiveness.

15.6.3.4 Phagocyte Ingesta

Phagocytes are specialized cells optimized for ingestion of foreign particles (Section 15.4.3.1). The capacity of a phagocyte for ingestion of chemically inert nanorobots (e.g., Section 15.1.2, Chapter 15.3, Section 15.4.3) or their detritus (Section 15.4.4), without causing its destruction and subsequent re-release of the particulate matter, has already been addressed. Some particles are highly toxic to phagocytes. For instance, just 0.05 μg of silica per 10^6 macrophages,[4561] or 0.002% of cell volume assuming 1166 micron^3 per rat alveolar macrophage,[4562] was cytotoxic.* Asbestos particles are more tolerable. An environment of 6.6-900 μg per 10^6 mouse peritoneal macrophages are required to induce fibrosis,[4561] a volume of ~2.1-280 micron^3 per macrophage, though not all of this material was ingested by the cells. Ultrafine carbon particles were safely administered to rat alveolar macrophages in the amount of 1 μg per 10^6 macrophages or ~1 micron^3/cell,[768] or 0.1% of cell volume.

Latex or polystyrene beads are among the most popular particles for ingestion burden experiments.[778] Guinea pig neutrophils can ingest up to 3.8% of cell volume in 3-micron polystyrene beads, but only 3.0% of cell volume of 0.3-micron beads (Table 15.1). Peritoneal phagocytes from striped bass each ingested an average of four 3.12-micron latex beads during a 30-minute incubation time,[3002] giving a phagocytic capacity of ~64 micron^3/phagocyte or ~4% of cell volume. Rabbit alveolar macrophages cultured in suspensions or on monolayers of latex particles internalized a maximum of 45 1-micron particles (45 micron^3/cell or ~3% of cell volume) and 10 2-micron particles (~80 micron^3/cell or ~5% of cell volume) at saturation.[4563] A study of rat alveolar macrophages confirmed particle burdens exceeding 15 2-micron microspheres (~63 micron^3 or ~4% of cell volume).[4564] Interestingly, murine bone-marrow macrophages that are only 13.8 microns in diameter can ingest IgG-opsonized beads up to 20 microns in diameter,[2876] representing an amazing ~200% of cell volume. Of course, phagocytes that eat too many latex microspheres develop an impaired mobility.[778,4565,4566]

What about inorganic particles? Rat alveolar macrophages can ingest at least ~1 micron^3/cell of iron oxide particles (~0.1% of cell volume) without ill effect,[4567] and another experiment[4568] found up to 72 spherical 2.6-micron iron oxide particles (~663 micron^3) had been nonfatally ingested by human alveolar macrophages each of mean volume 4990 micron^3,[4562] a much larger cell burden of ~13% foreign particles by volume. Murine macrophages suffer only ~10% mortality after ingesting up to 2500 alumina ceramic 0.6-micron particles, or ~10% of cell volume, although mortality rises to ~30% after ingesting a similar volume concentration of 2-micron particles.[1074] Micrographs of live mouse peritoneal macrophages[652] and human monocytes[641] that have been induced to ingest diamond dust particles up to 5 microns in diameter appear to have internalized particles amounting to 10-20% of their cell volume. A particle burden "overload criterion" (i.e., producing complete macrophage immobilization) of ~600 micron^3 per rat alveolar macrophage (a ~50% cellular volumetric burden for 1166-micron^3 cells[4562]) has been proposed by Oberdorster et al.[4566]

15.6.3.5 Intracellular Microbiota

Inside living cells dwell a number cell-like objects of variable volumetric occupancy. Most notably, mitochondria (Section 8.5.3.10) are energy-producing organelles present in virtually all eukaryotic cells that may vary in number throughout the life cycle of the cell. The volume of mitochondria per cell (typically 5-20%) increases in porcine pinealocytes for animals kept in continuous darkness and decreases for animals kept in continuous light.[4569] Mechanical cell injury can cause dramatic mitochondrial enlargement.[3757] Adrenergic innervation of cultured cardiac myocytes over a 96 hour period causes mitochondrial volume to rise +43% (from 521 micron^3 to 744 micron^3) although total cell volume also increases +44% (from 3344 micron^3 to 4816 micron^3), holding volume fraction constant at ~15%.[4570] Myocytes cultured on laminin have a higher mitochondrion count than cells grown on plastic.[4571] Resistance training increases total mitochondrial volume by up to +33% per cell,[4572] and muscle overuse also elicits changes in mitochondrial

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** Extensive in vitro and in vivo research has been conducted to evaluate the effects of crystalline silica on mammalian cells, but the precise molecular mechanism responsible for the cellular injury that precedes the lung disease is unknown.[5982] Four basic mechanisms have been proposed[5983] to explain the cause of the cellular damage:*

1. *direct cytotoxicity of crystalline silica, resulting in lung cell damage, release of lipases and proteases, and eventual lung scarring;*
2. *activation of oxidant production by pulmonary phagocytes, which overwhelms the antioxidant defenses and leads to lipid peroxidation, protein nitrosylation, cell injury, and lung scarring;*
3. *stimulation of the alveolar macrophages and epithelial cells to release inflammatory mediators (e.g., interleukin-8, leukotriene B_4, platelet-activating factor, tumor necrosis factor, platelet-derived growth factor) that recruit polymorphonuclear leukocytes and macrophages, resulting in the production of proinflammatory cytokines and reactive species and further lung injury and scarring; and*
4. *stimulation of the alveolar macrophages and epithelial cells to secrete growth factors (e.g., interleukin-1, tumor necrosis factor, platelet-derived growth factor, fibronectin, and alveolar macrophage-derived growth factor) that initiate fibroblast proliferation and collagen synthesis, with eventual scarring.*

count.[4573] The outer hair cells of the guinea pig cochlea have 1425 mitochondria/cell in the first row but 1963 mitochondria/cell in the third row (which has 2-3 times more nerve endings nearby),[4574] a +38% increase in the count.

Other biota that may live inside of cells include a variety of endosymbionts* [4575-4577] (of which the mitochondrion[4578] and cell nucleus[4579] are possible ancient examples). For instance, endosymbiotic bacteria can infect A*moeba proteus*, quickly reaching the maximum carrying number of 42,000 organisms.[4580] Taking the volume of the bacterium and the amoeba as ~1 micron^3 and ~10^8 micron^3, respectively, the volume fraction occupied by the endosymbionts is only ~0.04%.

Individual lymphocytes (~200 micron^3[4584]) have been observed circulating for hours inside larger living cells (~3-5% volume fraction) with no evident ill effect, a phenomenon originally called emperipolesis (Section 8.5.3.12). Emperipolesis today refers to the temporary presence of one cell within another's cytoplasm and has been associated with tumor cells,[5985-5987] muscle cells,[5984] megakaryocytes,[5987-5991] thymic epithelial cells[5994] (nurse cells[6078]), human fetal liver Kupffer cells,[5995] myeloproliferative disorders,[5990-5993] and both cutaneous[5996-5998] and noncutaneous[5999] Rosai-Dorfman disease — though R. Bradbury notes that emperipolesis may not be a general property of mammalian cells. While neutrophils and macrophages are both found in mammalian lungs and neither cell regularly phagocytoses the other in significant quantities, alveolar macrophages containing neutrophils have been reported.[763] Neutrophils that have undergone apoptosis are taken up by macrophages, with a mean uptake of 3 neutrophils per macrophage.[648] Taking nonmigratory human neutrophils as 204 micron^3,[4534] and human alveolar macrophages as 4990 micron^3,[4562] this uptake represents ~12% of macrophage cell volume. It is unknown whether 12% remains a reasonable limit if the entire population of phagocytic cells in a tissue is burdened by that much foreign material, or if such burdens are tolerable only when a relatively few cells in the population are affected. The first case, analogous to an aggressive bacterial infection, has major implications for the entire multicellular organization, whereas the second case, analogous to emperipolesis, has only a minor volumetric impact.

Cells may also harbor smaller pathogens which are usually volumetrically harmless to the host. Perhaps the best-known example is the case of the bacteriophage T4. A single *Escherichia coli* bacterium injected with a single T4 phage virion at 37 ºC in rich media lyses after 25-30 minutes, releasing 100-200 phage particles that have replicated themselves inside.[4585] (While lysing is clearly harmful to the bacterium, prior to lysing there is no evidence of purely volumetric-related harm to the microbe.) Taking *E. coli* volume as 0.6 micron^3 (Section 10.4.2.5) and phage T4 volume[4586] as ~200,000 nm^3, then the bacteriophage particle load on *E. coli* at lysis is 3-7% of bacterial cell volume.

In human cells, the tuberculosis bacterium enters the alveolar macrophage which transports the intruder into the blood, the lymphatic system, and elsewhere. Each ~1-micron^3 bacillus[4587] that hitches a ride in this manner represents an intrusion of 0.02% of macrophage volume. Other intracellular microorganisms such as *Listeria* (~0.25 micron^3) and *Shigella* (~2 micron^3), once free in the cytoplasm, are propelled "harmlessly" through the cytosol via continuous cytoskeleton-linked actin polymerization (Section 9.4.6). Macrophages infected with *Listeria* have been observed with ~2% of their volume co-opted by the microbes (~100 organisms).[4588] While some motile intracellular parasites such as *Tyzzer*[4589] may cause disarrangement and depopulation of host cell organelles by the movement of their peritrichous flagella, other motile intracellular parasites such as the spotted fever-group *Rickettsiae*[4590] spread rapidly from cell to cell by actin-based movement but do not cause lysis of the host cell. Typhus-group rickettsiae[4590] multiply in host cells to great numbers without profound damage (until cell lysis finally occurs) — providing a more optimistic biological analog for future medical nanorobots.

Harmful pathogens such as malarial schizonts of *Plasmodium falciparum* may multiply to 50-70% of erythrocyte cytoplasmic volume before the red cell bursts.[4591,4592] Other intracellular parasites have been observed at similar cytoplasmic volumetric fractions.[4593-4595]

15.6.3.6 Intracellular Nanorobot Intrusiveness

How much new foreign material can be added to a cell, and how much of a cell's existing volume can be replaced with foreign material (e.g., medical nanorobots)?

To summarize: Membrane elasticity can accommodate variations in cell volume for various cells ranging from 1-300%, nuclear transplantation between cells represents volumetric changes from 3-50%, neutrophils normally vary 15-50% in volume during their adult life cycle, and 1-3% by volume of foreign material can safely be injected into somatic cells (Section 15.6.3.1). Inert lipofuscin deposits can harmlessly occupy 10-50% of cell volume (Section 15.6.3.2), and up to 0.1-2.4% of cell volume has been uneventfully replaced by polystyrene microbeads, nanoparticles, or intracellular crystals (Section 15.6.3.3). Phagocytes nonfatally ingest 0.1-20% of cell volume and a normal maximum of 50% has been proposed, although a 200% volumetric ingestion has been observed (Section 15.6.3.4). Changes in intracellular organelle volume amounting to 20-40% (for mitochondria), intracellular intrusions of leukocytes of up to 3-12% of the volume of the ingesting cell, and intracellular parasite loads of 3-7% (bacterial) and 50-70% (protozoa) of host cell volume have been observed (Section 15.6.3.5).

We conclude that a safe conservative intrusiveness limit for chemically-inert micron-scale medical nanorobots is 1-10% of cell volume, but that in some circumstances nanorobot particle loads of up to 50% of cell volume may be temporarily accommodated. However, tolerance to volumetric intrusiveness and to what degree is ultimately dependent on the individual cell type.

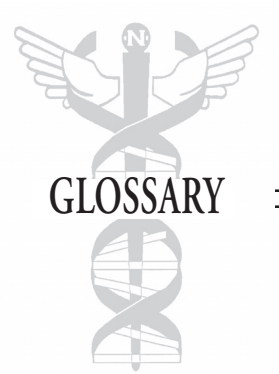
15.6.4 Technological Intrusiveness

The intrusion of nanodevices into the human body can displace both volume and function of our natural biological systems. The consequences of such displacement remain incompletely defined. For example, augmentative nanorobotic systems may establish new equilibrium levels and possibly create new failure modes or instabilities in natural homeostatic processes (Chapter 17). The microbial ecology may react in a number of ways to omnipresent medical nanorobots with whom it has not co-evolved, with the possible emergence of novel pathogenic species displaying unexpected behaviors and abilities (Chapter 17). Specific control protocols are needed to ensure appropriate responses (e.g., when a nanodevice unexpectedly exits the body by being bled out) in various common medical situations (Chapter 12).

** Interestingly, one rickettsial bacterial species called* Wolbachia *is thought to infect the reproductive tissues of as many as 20% of all insect species.[4581,4582] This endosymbiont enhances its own transmission by establishing an active cytoplasmic incompatibility[4583] between egg and sperm cells of host strains or species, e.g., by inducing abortive karyogamy when an uninfected female mates with an infected male.*

Because self-replicating devices[35] might be the most technologically intrusive class of nanorobot, it cannot be emphasized too strongly that mechanical medical nanodevices should not be allowed to self-replicate inside the human body (Section 2.4.2), nor should they have any need for self-replication themselves (Section 1.3.3). Machines that perform medical tasks are fundamentally different from machines that manufacture other machines. Self-replicating systems[35] may be the key to low cost manufacturing but there is no need to allow such systems to function in the outside world. In an artificial and controlled environment these factory systems will manufacture simpler and more rugged applications products which are then transferred to the end user. Medical devices designed to operate in the human body should not self-replicate: such devices can be manufactured in a controlled environment, then injected or implanted into the patient as required. The resulting medical device will be simpler, smaller, more efficient and more precisely designed for the task at hand than a device designed to perform the same function and self-replicate.[9] Given the potential for accident and abuse,[7,8,21] artificial replicators will almost certainly be very tightly regulated by governments everywhere. It is unlikely that the FDA (or its future or overseas equivalent) would ever approve for general use a nonbiological medical nanodevice that was capable of in vivo replication, evolution, or mutation. Guidelines to avoid accidents and foreseeable abuses have been promulgated for biotechnology replicators[38] and have been proposed for nanotechnology replicators.[39]

It is also unlikely, and unnecessary, for individual medical nanorobots each to possess a human-level or even near-human artificial intelligence. Many medical nanorobots will have very simple computers aboard each device. For artificial nanorobotic red cells (respirocytes[3573]), a ~10^3 operations/sec computer may suffice — far less computing power than an old Apple II machine — while nanorobotic white cells (microbivores[2762]) may need only ~10^6 ops/sec of onboard capacity. Still more sophisticated cellular repair nanorobots should demand no more than 10^6-10^9 operations/sec of onboard computing capacity to do their work. This is a full 4-9 orders of magnitude below even the potential for true human-equivalent computing which is conservatively estimated as 10-1000 teraflops (~10^{13}-10^{15} operations/sec).[40-42] Faster computing capacity is simply not required for individual medical nanorobots. The potential for unexpected emergent behaviors (as suggested in both the scientific[43-47] and science fiction[48-50] literature) among large in vivo populations of small-capacity fixed-program individual nanodevices seems low but should be investigated further.



GLOSSARY

Existing glossaries for the fields of biocompatibility and biomaterials science include the works of Black[234] and especially Williams,[230,5869,5870] the latter work containing over 6000 entries; other entries here are from Taber's Medical Dictionary[2004] and elsewhere.

Abscess — a circumscribed collection of pus appearing in acute or chronic localized infection, and associated with tissue destruction and frequently with swelling; a cavity formed by liquefaction necrosis within solid tissue.

Acetylcholine — a chemical neurotransmitter.

Acidosis — excessive acidity of body fluids due to acid accumulation or excessive bicarbonate loss.

ACTH — adrenocorticotropic hormone; stimulates adrenal gland cortex to produce adrenal cortical hormones.

Actin — structural protein derived from actomyosin in muscle and the most abundant protein in most cells, usually comprising more than 5% of the total cellular protein.

Acute — duration of less than 30 days; durations associated with clinical treatment are usually termed short-term or intraoperative.[234] Compare chronic.

Adamantane — the smallest repeating cage unit of the diamond lattice ($C_{10}H_{16}$).

Adhesion antenna — in medical nanorobotics, partially selective binding tips that are swept through the environment, whereupon desired moieties or particles adhere and can be removed from the environment or drawn into the nanodevice (Section 10.4.2.5.2).

Adhesioregulatory — in medical nanorobotics, active regulation of the adhesive characteristics of the nanorobot surface (Section 15.2.2.4). See also sorboregulatory.

Adipose — fatty; pertaining to fat.

Adjuvant — in pharmacology, a drug added to a prescription to hasten or increase the action of a principal ingredient; in immunology, a variety of substances (e.g., alum, aluminum hydroxide, aluminum phosphate inorganic gels) that increase the antigenic response.

ADME — Absorption, Distribution, Metabolism, and Excretion screening tests for drug discovery.[6079] See also pharmacokinetics.

ADP — adenosine diphosphate; has one energy-rich phosphate bond.

Adrenergic — activated or energized by adrenalin (epinephrine).

Adsorption — adhesion of a substance to the surface of another material.

Aerobot — flying robot.

AFM — atomic force microscope.

Afferent — in relation to nerves or blood vessels, conducting toward structure or organ; carrying impulses toward a center, as when sensory nerves carry sensory information toward the brain or spinal cord.

Affinity — the strength of the binding of a ligand to a receptor, or the reciprocal of the dissociation rate constant; a measure of the binding energy of a ligand in a receptor; the greater the affinity, the more securely the receptor binds the ligand.

Agenesis — failure of an organ (or part thereof) to develop or grow.

Agglutination — one type of antigen-antibody reaction in which a solid antigen clumps together with a soluble antibody; often in reference to red blood cell typing.

Agonist — in pharmacology, a drug which binds to a receptor and thus stimulates the receptor's function, possibly mimicking the body's own regulatory function. Compare antagonist.

Agranulocyte — a nongranular leukocyte; see monocyte, lymphocyte.

Albumin — the most abundant blood protein.

Alginate — any salt of alginic acid; derived from kelp; used in pharmaceuticals, dentistry, and foods.

Alimentary — pertaining to the digestive tract.

Alkanethiol — a class of organic compounds which consist of a carbon chain (alkane) attached to a sulfur-based chemical group (thiol).

Allergen — any substance that causes manifestations of allergy.

Allergy — an acquired, abnormal immune response to a substance (allergen) that does not normally cause a reaction.

Alloantigen — a substance present in certain individuals that stimulates antibody production in other members of the same species, but not in the original donor.

Allodynia — a condition in which an ordinarily painless stimulus, once perceived, is experienced as being painful (Section 15.5.1.2).

Allogeneic — having a different genetic constitution but belonging to the same species.

Allograft — transplant tissue obtained from the same species as the host.

Alloknesis — a state of spinal sensitization, similar to secondary hyperalgesia/allodynia,[3677,5837] wherein strong itching stimuli induce a cutaneous halo and itchy skin in which innocuous light touch can easily elicit itch.[5835,5836] Alloknesis depends on the magnitude of the inducing itch stimulus, is controlled by nociceptive input from the peripheral itch focus, and is fully blocked by cooling the itch focus.[3677,5838])

Alloplast — inert implanted material, used in plastic surgery.

Allosteric control — the ability of an interaction at one site of a protein to influence the activity of another site.

Allotype (allotypic) — genetic variants of protein that occur in a single species; each variant can be antigenic to members of the same species possessing different variants.

Alveolus (alveolar) — in anatomy, a small cell or cavity; a saclike dilation. Most commonly, a small air sac found at the lowest levels of the branching tube system comprising the lungs.

Alveolitis — inflammation of alveolus.

Alzheimer's disease — a chronic, organic mental disorder; a form of presenile dementia.

Amebiasis — infection with amebae.

Amniotic (amnion) — pertaining to the amnion (the innermost of the fetal membranes).

Amphipathic — molecular structures which have two surfaces or ends, one of which is hydrophilic and the other of which is hydrophobic. Lipids are amphipathic, and some protein regions may form amphipathic helices with one charged face and one neutral face.

Amphiphile — a molecule having both hydrophobic and hydrophilic components (e.g., soap).

Amphoteric — ability to react as both an acid and a base.

Amyloid(osis) — metabolic disorder marked by deposition of amyloid (a protein-polysaccharide complex) in tissues and organs.

Amyotrophic lateral sclerosis (ALS) — a syndrome marked by muscular weakness and atrophy due to degeneration of motor neurons of spinal cord, medulla, and cortex.

Analgesia — absence of normal sense of pain.

Analyte — sample substance whose chemical composition is being analyzed.

Anaphylaxis — the immediate transient kind of immunologic (allergic) reaction characterized by contraction of smooth muscle and dilation of capillaries due to release of pharmacologically active substances (e.g. histamine, bradykinin, serotonin, etc.); a powerful allergic response (Section 15.2.6.1). Anaphylaxis is classically initiated by the combination of antigen (allergen) with mast cell-fixed, cytophilic antibody (chiefly IgE immunoglobulin), but can also be initiated by relatively large quantities of serum aggregates (antibody-antigen complexes, and other) that seemingly activate complement leading to production of anaphylatoxin.

Anaphylatoxin — a substance composed of the C3 and C5 components of complement.

Anastomosis (anastomotic) — to open one structure into another directly or by connecting channels, usually said of blood vessels, lymphatics, and hollow viscera; to unite by means of an anastomosis, or a connection between formerly separate structures.

Anemia (anemic) — reduction in the number density of circulating red blood cells.

Anergic — unresponsive; inactive; lacking energy.

Aneurysm — localized abnormal dilation of a blood vessel, usually an artery, due to congenital defect or weakness in the vessel wall.

Angina pectoris — severe pain and sensation of constriction around the heart, caused by cardiac ischemia.

Angioedema — a condition characterized by development of urticaria (hives) and edematous (swollen with excessive fluid) areas of skin, mucous membranes, or viscera.

Angiogenesis — growth of new blood vessels, especially capillaries.

Angioplasty — altering blood vessel structure, either by a surgical procedure or by dilating the vessel using a balloon inside the lumen.

Anhydrobiotic — ability of an organism to survive almost complete desiccation.

Anion — a negatively charged ion; acidic. Compare cation.

Anophthalmic — congenital absence of one or both eyes.

Antagonist — in pharmacology, a drug that prevents receptor function. Compare agonist.

Anterior — the front of the human body, on or nearest the abdominal surface; the front of something.

Anterograde — moving frontward.

Anthrax — acute infectious disease caused by *Bacillus anthracis*.

Antibody — a protein (immunoglobulin) produced by B-lymphocyte cells that recognizes a particular foreign antigen, thus triggering the immune response (Section 15.2.3.3).

Anti-emetic — inhibiting vomiting.

Antigen — a foreign macromolecule capable of eliciting antibody formation; any molecule or foreign substance that, when introduced into the body, provokes synthesis of an antibody, thus stimulating an immune response; an agent that can bind specifically to components of the immune response; not all antigens are immunogens.

Antipyretic — reducing fever.

Antisense oligonucleotide — a nucleotide polymer having a sequence complementary to a target nucleotide sequence.

Aorta (aortic) — the largest artery in the human body, leading away from the heart.

Apheresis — removal of blood from an individual patient, separating certain elements (e.g. red cells, platelets, white cells) for use elsewhere, and reintroducing the remaining components into the patients; also known as cytapheresis, hemapheresis, leukapheresis, pheresis, and plasmapheresis, depending on the type of cells being harvested.

Apical — pertaining to the apex (e.g. the point of a cone) of a structure.

Apoptotic — undergoing apoptosis (programmed cell death).

Apoptosis — an orderly disintegration of eukaryotic cells into membrane-bound particles that may then be phagocytosed by other cells (Section 10.4.1.1).

Apposition — condition of being side by side or fitted together.

Aptamers — single-stranded nucleic acids that directly inhibit a protein's function by folding into a specific three-dimensional structure that dictates high-affinity binding to the targeted protein.[5810]

Area compressibility modulus — a mechanical property characteristic of a membrane, defined as the isotropic tension per unit fractional change in area.

Aromatic compounds — in chemistry, ring or cyclic compounds related to benzene, many having a fragrant odor.

Arthropathy — any joint disease.

Arthroplasty — the operative procedure of reshaping or reconstructing a diseased joint.

Artificial organ — a medical device that replaces, in whole or in part, the function of one of the natural organs of the human body.

Artificial organ, hybrid — an artificial organ that is a combination of viable cells and one or more biomaterials.[230]

Ascites — accumulation of serous fluid in the peritoneal cavity.

Aseptic — characterized by the absence of living pathogenic organisms; a state of sterility.

Asialo- — a molecule lacking a sialyl group; see sialyl.

Aspiration — drawing in or out, as by suction.

Asperities — protruding elements of roughness on a surface, e.g., burrs or spurs.

Asplenic — without a spleen.

Asters — stellate rays forming around the dividing centrosome during mitosis.

Asthma — disease caused by increased responsiveness of the tracheobronchial tree to various stimuli, with paroxysmal constriction of the bronchial airways.

Astrocyte — a star-shaped neuroglial cell with many branching processes.

Astroglioma cells — neoplastic or tumor cells associated with astrocytes making up neuroglial tissue.

Atelectasis — condition in which fetal lungs remain unexpanded at birth.

Atherectomy — a procedure to remove plaque from arteries; e.g., using a laser catheter or a rotating "burr" shaver.

Atherosclerosis (atherosclerotic) — the most common form of arteriosclerosis (thickening, hardening, and loss of elasticity of arterial walls).

ATP — adenosine triphosphate; has two energy-rich phosphate bonds.

Atrial natriuretic peptide — hormone secreted by atrial tissue of the heart in response to an increase in blood pressure.

Atrium (atrial) — chamber or cavity communicating with another structure.

Atrophy — decrease in size of organ or tissue; to waste away.

Auricle — portion of the external ear not contained within the head; the pinna.

Austenitic — a higher-temperature body-centered cubic structure with the characteristic stress-strain curve of most metals; compare martensitic.

Autocatalysis (autocatalytic) — increase in the rate of chemical reaction resulting from products that are produced in the reaction acting as catalysts.

Autologous — having its origin within the host organism.

Autolysis — self-dissolution or self-digestion of tissues or cells, by endogenous enzymes.

Autophagy — self-consumption by a cell.

Autosome (autosomal) — any of the chromosomes other than the XY sex chromosomes.

Avirulent — without virulence.

Azurophilic — staining readily with azure dye.

Babesiosis — a rare and often severe or fatal disease of man caused by an intraerythrocytic protozoan, *Babesia microti*, transmitted by ticks.

Bacteremia (bacteremic) — bacteria in the blood.

Bacteriophages — viruses that infect selected bacteria; often abbreviated as phages.

Barosensor — pressure-detecting sensors in cells.

Basal lamina — basement lamina, e.g. basement membrane.

Basal rate — in metabolism, a measure of the metabolic rate taken with the patient fasting and at rest. The oxygen consumed in breathing under these conditions indicates the minimum rate of chemical reactions in the body.

Basement membrane (basement lamina) — a thin layer of delicate noncellular material of a fine filamentous texture underlying the epithelium; its principal component is collagen.

Base pair (bp) — a complementary purine-pyrimidine hydrogen-bonded residue pair, one from each strand of DNA double helix, designating one unit (bp) of sequence. A partnership of adenine (A) with thymine (T) or of cytosine (C) with guanine (G) in a DNA double helix; other pairs can be formed in RNA under certain circumstances.

Basophil — a type of granulocytic white blood cell comprising less than 1% of all leukocytes, that is essential to the nonspecific immune response to inflammation because of its important role in releasing histamine and other chemicals that act on blood vessels.

Biliary — pertaining to bile.

Billroth's cords — splenic cords found in the red pulp between the sinusoids, consisting of fibrils and connective tissue cells with a large population of monocytes and macrophages.

Bioactive — the ability of a biomaterial surface or coating to adhere directly to soft or hard tissue without an intermediate layer of modified tissue.[234]

Bioactive material — a biomaterial that is designed to elicit or modulate biological activity;[5870] Section 15.2.1.3.

Bioadhesion — the adhesion of cells or tissue to the surface of a material.[230]

Bioattachment — the fastening of cells or tissue to the surface of a material, including mechanical interlocking.[230]

Biocompatibility — biological performance in a specific application that is judged suitable to that situation;[234] the ability of a material to perform with an appropriate host response in a specific situation.[230]

Biocompatible material — one having acceptable host and material response in a specific application.[234]

Biodegradation — the breakdown of a material mediated by a biological system;[5870] the passive response of a material to the physico-chemical conditions found in living systems, involving actual cellular effects on the pericellular environment.[234]

Biodistribution — distribution of a substance, after in vivo administration, throughout the organs and tissues of the body.

Biofilm — bacteria embedded in a film of adhesive polymer (especially on implanted devices); bacteria within the film are protected from the action of antibiotics (Section 15.2.1.4).

Biological performance — the interaction between materials and living systems;[234] preferred term is biocompatibility.

Biomaterial — a material intended to interface with biological systems to evaluate, treat, augment, or replace any tissue, organ, or function of the body;[5870] a nonviable material used in a medical device, intended to interact with biological systems.[230]

Biomaterials, inert — implantable materials that elicit little or no host response.[234]

Biomaterials, interactive — implantable materials designed to elicit specific, beneficial responses, such as ingrowth, adhesion, etc.[234]

Biomaterials, replant — implantable materials consisting of native tissue, cultured in vitro from cells obtained previously from the specific implant patient.[234]

Biomaterials, viable — implantable materials, incorporating or attracting live cells at implantation, that are treated by the host as normal tissue matrices and are actively resorbed or remodeled.[234]

Biomaterials engineering — the application of the principles of biomaterials science and its foundation sciences to the solution of practical problems of human health, disability, and disease.[234]

Biomaterials field — the organized study of the materials properties of the tissues and organs of living organisms; the development and characterization of pharmacologically inert materials to measure, restore, and improve function in such organisms; and the interaction between viable and nonviable materials.[234] Biomaterials is: (1) a materials science, the central issue being the dependence of physical properties on composition and structure; (2) an interdisciplinary science, its unique feature being a consideration of the interactions between living and nonliving materials; and (3) a medical science, whose ultimate goal is the improvement of human health and quality of life.[234]

Biomaterials science — the study and knowledge of the interaction between living and nonliving materials.[234]

Biomimetic — an approach to bioengineering in which artificial materials are selected to mimic as closely as possible the desired structure or function of natural biological components.

Bioresorbable — the ability of a biomaterial to be digested by or as a consequence of cellular activity, and thus dissolve or disappear in part or in whole after implantation; implies specific action of cells or tissues.[234] See also resorbable.

Blockade — prevention of the action of something, such as the effect of a drug or of a body function, e.g. halting immune system blood cleansing by overloading the RES (Section 15.4.3.6.10).

B-lymphocytes (B-cells) — thymus-independent white blood cells responsible for synthesizing antibodies.

Bolus — mass of masticated food ready to be swallowed; concentrated mass of a diagnostic substance given rapidly intravenously.

Bone bonding — the establishment, by physicochemical processes, of continuity between implant and bone matrix.[5870]

Bowman's capsule — a visceral layer closely applied to the glomerulus and an outer parietal layer that functions as a filter in the formation of urine in the kidney.

bp — see base pair.

Brachiation — in medical nanorobotics, by alternately swinging the arms (e.g. swinging hand-over-hand).

Brachymetatarsia — abnormal shortness of one of the metatarsals (the five long bones of the foot), resulting in a short toe.

Bradykinin — an end product of contact system activation (Section 15.2.5).

Bronchoconstriction — constriction of the bronchial tubes.

Broncholithiasis — bronchial inflammation or obstruction caused by calculi in the bronchi.

Bronchopulmonary — pertaining to bronchi and lungs.

Bronchus (bronchi) — one of the two large branches of the trachea.

Brownian motion — random motion of small particles in a fluid owing to thermal agitation.

BSA — bovine serum albumin. See also albumin.

Buckyballs — ball-like molecules of fullerene carbon, C_{60} (Section 2.3.2).

Buckytubes — carbon nanotubes (Section 2.3.2).

Calciphylaxis — state of induced tissue sensitivity characterized by calcification of tissue when challenged by an appropriate stimulus.

Calculus (calculi) — commonly called stone; any abnormal concretion within the animal body, though usually composed of mineral salts.

Calmodulin — a 17,000-dalton protein that binds calcium ions in eukaryotic cells, thereby becoming the agent for many or most of the cellular effects ascribed to calcium ions.

Calor — local tissue temperature rise, one of the four classic signs of inflammation (Section 15.2.4); see also dolor, rubor, tumor.

cAMP — cyclic AMP (adenosine monophosphate), an intracellular messenger molecule.

Canaliculus (canalicular) — small channel or canal.

Cancer — a disease of multicellular organisms characterized by uncontrolled multiplication and spread of abnormal forms of host cells.[234]

Canine — pertaining to dogs.

Cannula — tube or sheath enclosing a trocar (a transdermal punch), the tube allowing escape of fluid after withdrawal of the trocar from the body.

Capacitance, electrical — ability to store electric charge.

Capacitance, phagocytic — ability of phagocyte to ingest phagocytic targets.

Capillaritis — inflammation of the capillaries.

Capsule — tissue surrounding an implant produced by local host response.[234] See also granuloma, incapsulation.

Carbon black — finely divided amorphous carbon particles (Section 15.3.3.5).

Carcinogen — an agent capable of causing cancer (Section 15.2.8).

Carcinoma — a new growth or malignant tumor that occurs in epithelial tissue; can metastasize throughout the body.

Cardiac — pertaining to the heart.

Cardiomegaly — abnormal enlargement of the heart.

Cardiomyopathy — disease of the myocardium (heart muscle).

Cardioplegia — intentional arrest of the cardiac function using cold, electrical stimuli, or medication to greatly reduce the need of the myocardium for oxygen; often done during cardiopulmonary bypass.

Carotid — principal arteries supplying oxygenated blood to the head and neck, originating in the aorta.

Cartilage — specialized type of dense connective tissue consisting of cells embedded in a firm, compact fibrous collagenous matrix.

Catheter — a tube passed through the body for evacuating or injecting fluids into body cavities.

Cation — a positively charged ion. Compare anion.

Caveolae — structural indentations (~50 nm) in plasma membrane of the cell, serving to draw substances such as vitamins and signal transduction molecules into the cell's interior.

Cavitation — in physics, the formation of bubbles in a fluid during high-power sonication of that fluid; in medicine, formation of a cavity by either normal or pathological biological processes. See Section 6.4.1.

CB — see carbon black.

CD- — cluster of differentiation, designating surface marker proteins that distinguish various T cell subpopulations (Section 15.2.3.1.2).

Cecum — a blind pouch that forms the first portion of the large intestine, located below the entrance of the ileum at the ileocecal valve (Figure 8.16).

Celiac — pertaining to the abdominal regions.

Cellulitis — inflammation of cellular or connective tissue, spreading as in erysipelas.

Centrosomes — the regions from which microtubules are organized at the poles of a mitotic (dividing) cell.

Ceramide — a class of lipids, derived from a sphingosine (a long-chain base present in sphingolipids), that do not contain cholesterol.

Cervix — the neck, or part of an organ resembling the neck; usually refers to neck of the uterus.

CFRC — carbon fiber-reinforced carbon.

CFU — colony forming units (e.g., number of microbes).

Chaotropic agents — structure-breaking ions, salts, and other agents that weaken hydrophobic associations, denature proteins, increase membrane permeability to protons, and can promote cell lysis.

Charcot-Marie-Tooth disease — a form of progressive neural muscular atrophy.

Chelation — combining of metallic ions with certain heterocyclic ring structures so that the ion is held by chemical bonds from each of the participating rings; chelating agents are commonly used to remove toxic metals from the body.

Chemisorption — adsorption with the formation of tight covalent bonds.

Chemokines — compounds that draw cells and other factors to sites of injury in the body.

Chemokinesis — general random movement or nondirected cell locomotion.

Chemorepellents (chemorepulsion) — chemotaxis antagonists or negative chemokinesis agents.

Chemotactic — pertaining to chemotaxis.

Chemotaxis — the movement of additional white blood cells to an area of inflammation in response to the release of chemical mediators by neutrophils, monocytes, or injured tissue; orientation or movement of cells toward a chemical source; movement along a spatial gradient or directed cell locomotion.

Chiggers — six-legged larvae of mites of the family *Trombiculidae*; redbugs.

Chimeric molecule — combining in one molecule dissimilar components from two or more different molecules.

Cholesterol — a sterol (a group of substances related to fats) widely distributed in animal tissues; a monohydric alcohol with a cyclic nucleus.

Cholinergic — activated or energized by acetylcholine.

Cholelithiasis — formation or presence of calculi or bilestones in the gallbladder or common duct.

Chondrocyte — a cartilage cell.

Chondrogenesis — formation of cartilage.

Chorioamnionitis — inflammation of the membranes that cover the fetus.

Chomatin — the complex of DNA and protein in the nucleus of the interphase eukaryotic cell; individual chromosomes cannot be distinguished in it.

Chronic — duration of 30 days or longer.[234] Compare acute.

Chrysotile — a flexible, chemically-resistant, nonflammable fibrous mineral with high tensile strength.

Chylomicron — submicron-sized protein-lipid aggregates produced by the intestine and carried by the lymph system into the blood (Section 15.4.2.2).

Chyme — a semifluid mixture of partly digested food and digestive secretions found in the stomach and small intestine during digestion of a meal.

Circadian — pertaining to physiological events that occur at approximately 24-hour intervals.

Circumvascular — surrounding or wrapping around the exterior of a blood or lymph vessel.

Cirrhosis (cirrhotic) — a chronic liver disease involving loss of functioning liver cells, increased resistance of blood flow through the organ, and disturbance of normal tissue architecture; in serious cases, leads to ammonia toxicity.

Clathrin — cell-type specific 180,000-dalton protein that coats intracellular transport vesicles, forming a basket or cage around the vesicle. See vesicles (endocytotic).

Clinical — founded on actual observation and treatment of patients, as distinguished from data or facts obtained by experimentation or pathology; or, pertaining to a clinic.

Clottocytes — in medical nanorobotics, artificial mechanical platelets[22] (Chapter 24).

CNS — central nervous system.

Coagulation — sequential process in blood leading to thrombus formation (Section 15.2.5).

Coagulopathy — defect in the blood clotting mechanisms.

Coarctation — compression of the walls of a vessel; a stricture.

Cochlea (cochlear) — the coiled, fluid-filled structure of the inner ear that transduces sound, allowing hearing.

Colitis — inflammation of the colon.

Collagen — the major protein of the white fibers of connective tissue, cartilage, and bone, rich in glycine, alanine, proline, and hydroxyproline (amino acids), low in sulfur, and completely lacking in tryptophan (another amino acid); the collagen family comprises ~25% of all mammalian protein.

Collagenase — an enzyme that catalyzes the hydrolysis of collagen.

Colon (colonic) — the large intestine (Figure 8.16).

Colostrum — breast fluid that may be secreted from the second trimester of pregnancy onward, preceding true lactation.

Commissure — the coming together across the midline or dividing space of two structures.

Communicyte — in medical nanorobotics, a theorized mobile, mass-storage (nanorobotic) device that can be used for information transport throughout the human body (Section 7.3.2).

Complement — a group of proteins in the blood that influences the inflammatory process and serves as the primary mediator in the antigen-antibody reactions of the B-cell mediated immune response. Components of complement are labeled C1-C9; C3 and C5 are most commonly involved in promoting vasodilation, chemotaxis, opsonization of antigens, lysis of cells, and blood clotting (Section 15.2.3.2).

Compliance, mechanical — the reciprocal of stiffness; in a linear elastic system, displacement equals force times compliance.

Concussion (concussive) — injury resulting from impact with an object.

Condyle — a rounded protuberance at the end of a bone forming an articulation.

Conformation — molecular folding; a molecular geometry that differs from other geometries chiefly by rotation about single or triple bonds; distinct conformations (termed conformers) are associated with distinct potential wells. Typical biomolecules and products of organic synthesis can interconvert among many conformations. Typical diamondoid structures are locked into a single potential well, and thus lack conformational flexibility.

Congestive heart failure — weakness, breathlessness, abdominal discomfort and lower-body edema resulting from venous stasis and reduced outflow of blood from the left side of the heart.

Conjugated — in chemistry, a conjugated pi system is one in which pi bonds alternate with single bonds; the resulting electron distribution gives the intervening single bonds partial double-bond character, the pi electrons become delocalized (useful in molecular wires), and the energy of the system is reduced. More generally, joined or paired.

Control material — see reference material.

Contusion — injury in which skin is not broken; bruise.

Cornea — the clear, transparent anterior portion of the fibrous coat of the eye comprising about one-sixth of its surface.

Coronary — refers to the heart and to coronary heart disease; encircling the heart.

Corpus callosum — the great commissure of the brain between the cerebral hemispheres.

Cortex (cortical) — the outer layer; compare medulla.

Costimulatory — costimulatory molecules are required on a target surface (e.g., of a cell to be phagocytosed) before T cells may become activated.

Costochondral — pertaining to a rib and its cartilage.

Covalent bond — in chemistry, a bond formed by sharing a pair of electrons between two atoms.

Cranium (cranial) — pertaining to the portion of the skull enclosing the brain.

Creatinine — end product of creatine metabolism, found in urine; increased quantities indicate advanced stages of renal disease.

Cricothyroid — pertaining to the thyroid and cricoid cartilages.

Crinal — pertaining to hair.

Crosslinks — in biochemistry, additional bonds formed between normally separate parts of a polymer, typically increasing the tensile strength and stiffness of the chain.

Cruciate — cross-shaped.

Crystallescence — in medical nanorobotics, the crystallization of solid solute that is offloaded by nanorobot sorting rotors at a concentration that exceeds the solvation capacity of the surrounding solvent (Section 9.2.6).

Crystalluria — appearance of crystals in the urine.

CSF — cerebrospinal fluid.

Cutaneous — pertaining to the skin.

CVD — chemical vapor deposition.

Cyanosis — bluish or grayish skin discoloration due to abnormal amounts of reduced hemoglobin in the blood.

Cycloaddition — a chemical synthesis reaction in which two unsaturated molecules (or moieties within a molecule) bond to form a ring.

Cystic fibrosis (CF) — inherited disease of exocrine glands characterized by chronic respiratory infection, pancreatic insufficiency, and increased electrolytes in sweat.

Cytoambulation (cytoambulatory) — in medical nanorobotics, cell surface walking (Section 9.4.3).

Cytocarriage — in medical nanorobotics, the commandeering of a natural motile cell, by a medical nanorobot, for the purposes of in vivo transport (of the nanorobot), or to perform a herding function (of the affected cell), or for other purposes (Section 9.4.7).

Cytochrome — a class of cellular respiration hemoprotein pigments.

Cytocide — the killing of living cells (Section 10.4).

Cytocompatibility — biocompatibility with cells.

Cytokines — a group of extracellular biochemical substances that may be produced by a variety of cells, for the purposes of chemical messaging, regulation, and control; proteins that exert changes in the function or activity of a cell, such as differentiation, proliferation, secretion, or motility; chemical species used for intercellular signaling.[234]

Cytopathology — pathology of the cell.

Cytopenetration — in medical nanorobotics, entry into cells by penetrating the plasma membrane (Section 9.4.5).

Cytoplasmic — pertaining to, or residing in, the cell cytoplasm.

Cytoskeleton — the internal structural framework of a cell consisting of at least three types of filaments (microfilaments, microtubules, and intermediate filaments), forming a dynamic framework for maintaining cell shape and motion and allowing rapid changes in the three-dimensional structure of the cell (Section 8.5.3.11).

Cytosurgery — surgical procedures performed on individual cells.

Cytotoxic — having a deleterious or adverse effect on cells, up to but not always implying cell death; tending to kill cells.

Dacron — polyethylene terephthalate.

Dalton — unit of molecular weight (1 dalton ~ 1 proton).

Decubitus — a bedsore.

De-differentiation — the loss by mature cells of some of their specialized properties and reversion to a less developed state.[5484] De-differentiation is a normal part of healing and regeneration,[5485] can be induced mechanically,[5486] and is often a part of early tumor development.[5487] Artificial de-differentiation, or cellular reprogramming, aims at getting specialized body cells to revert to a primordial state, like stem cells, so they can be turned into various types of tissues.[6028]

Degranulation — loss of granules, especially in a phagocytic cell.

Denaturation — conversion of a protein from the physiological conformation to some other (possibly inactive) conformation.

Dendrimers — large, regularly-branching molecules (Section 15.3.6.4).

Dendrite — a branched protoplasmic process of a neuron that conducts impulses toward the cell body. There are usually many to a cell, forming synaptic connections with other neurons.

Dendritic cells (DCs) — leukocytes of bone marrow origin; antigen presenting cells scattered throughout the body in immature form as immunological sensors; subsets of DCs differ in phenotype, function, and locale.

Denudation — removal of a protecting layer or covering through surgery, pathological condition, or trauma.

Deoxyribonucleic acid (DNA) — a complex molecule of very high molecular weight encoding genetic information. DNA consists of deoxyribose (a sugar), phosphoric acid, and four bases (purines or pyrimidines), arranged as two long chains that twist around each other to form a double helix joined by bonds between the complementary purine and pyrimidine components (analogous to rungs on a twisted ladder). DNA is present in the chromosomes of all cells and is the chemical basis of heredity and the carrier of genetic information for almost all organisms (e.g. except the RNA virus, etc.).

Dermatitis — inflammation of skin evidenced by itching, redness, and various skin lesions.

Dermis — inner layer of the skin that lies below the epidermis.

Desialylated — molecules from which sialyl chemical groups have been removed.

Desiccate — removal of water; dehydration.

Detritus — broken down or degenerative matter produced by disintegration.

Device, medical — an instrument, apparatus, implement, machine, contrivance, in vitro reagent, or other similar or related article, including any component, part, or accessory, intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease in humans.[230]

Dialysate — a fluid that has been dialyzed.

Dialysis (dialyzer) — the passage of a solute through a membrane; process of diffusing blood across a semipermeable membrane to remove toxic materials and to maintain fluid, electrolyte, and acid-base balance in cases of impaired kidney function.

Diamondoid — structures that resemble diamond in a broad sense; strong, stiff structures containing dense, three-dimensional networks of covalent bonds, formed chiefly from first and second row atoms with a valence of three or more. Many of the most useful diamondoid structures will be rich in tetrahedrally coordinated carbon.

Diapedesis — transendothelial migration (passing through blood vessel endothelial coated walls) to exit the bloodstream and enter the surrounding tissues (Section 9.4.4.1).

Diaphysis — the shaft or middle part of a long cylindrical bone.

Diastole (diastolic) — the normal period in the heart cycle during which the muscle fibers loosen and lengthen, the heart dilates, and the cavities fill with blood; roughly, the period of relaxation alternating with systole or contraction.

Diathermy — local elevation of temperature within the tissues, produced by high-frequency (~MHz) current, ultrasonic waves, or microwave radiation.

DIC — see disseminated intravascular coagulation.

Dielectrophoresis — the lateral motion imparted on uncharged particles as a result of polarization induced by non-uniform electric fields.

Differentiation — acquisition of character or functions that are different from those of the original type; specialization of cell type within a cell line of increasingly specialized types, by a change in physical form of a cell.

Diffusion — a process by which populations of molecules intermingle and become mixed as a result of their incessant thermal motions.

Disseminated intravascular coagulation (DIC) — a pathological form of coagulation that is diffuse rather than localized (as in normal coagulation), with several clotting factors so heavily consumed that generalized bleeding may occur.

Disse space — fluid-filled space outside hepatic endothelial cells (Figure 8.27).

Distal — away from a source or a point of attachment or origin; in the extremities, farthest from the trunk.

Diverticulum — a sac or pouch in the walls of a canal or organ.

DLC — diamond-like carbon.

DNA — see deoxyribonucleic acid.

Dolor — local pain, one of the four classic signs of inflammation (Section 15.2.4); see also calor, rubor, tumor.

Dopaminergic — activated or energized by dopamine.

Dorsal — pertaining to the backside.

Duodenum — the first ~12 inches of the small intestine.

Dura mater — outer membrane covering the spinal cord and brain.

Dust cells — alveolar macrophages.

Dysentery — intestinal disorders, especially of the colon, characterized by inflammation of the mucous membrane.

Dysesthesia — abnormal sensations on the skin, including feelings of numbness, tingling, prickling, burning, or cutting pain.

Dysopsonic — tending to remove opsonization molecules that have become adhered to an exposed in vivo surface.

Dysphonia — difficulty in speaking; hoarseness.

Dystrophia (dystrophic) — disorder caused by defective nutrition or metabolism.

EAG — "ether a go-go," a distinct type of voltage-activated potassium (K^+) channel.

EC — endothelial cells.

Ecchymosis — skin discoloration consisting of large, irregularly formed hemorrhagic areas, caused by extravasation of blood into skin or mucous membrane.

Eclampsia — Coma and compulsive seizures between the 20^{th} week of pregnancy and the end of the first week postpartum; usually fatal if untreated.

ECM — see extracellular matrix.

Edema (edematous) — swollen with excessive fluid.

Edentulous — without teeth.

Efferent — in relation to nerves or blood vessels, conducting away from a structure or organ; carrying impulses away from a center, as when motor nerves carry impulses from the brain and spinal cord to an effector (e.g., a muscle).

Effervescence — in medical nanorobotics, bubble formation by a gaseous solute that is offloaded by nanorobot sorting rotors at a concentration that exceeds the solvation capacity of the surrounding solvent (Section 9.2.6).

Effluent — discharged fluid material; a flowing out.

Elasticity — a property of an object or material, wherein the object or material returns to its original shape after a force is applied and then removed.

Elastin — extracellular connective tissue protein; principal component of elastic fibers.

Electret — a material that retains a permanent charge.

Electrocautery — cauterization (destruction of tissue) by heated wire.

Electrochemistry — science of chemical changes produced by electricity.

Electrocompatibility — the electrical biocompatibility of nanodevices or nanorobotic systems as they interact with the organs, tissues and cells of the human body (Chapter 15.3.8).

Electrolyte — a substance that, in solution, conducts an electric current and is decomposed by the passage of an electric current; a solution that is a conductor of electricity.

Electron affinity — the energy liberated when an extra electron is attached to an atom to form an anion.

Electronegativity — a measure of the tendency of an atom (or moiety) to withdraw electrons from structures to which it is bonded. In most circumstances, sodium (Na) tends to donate electron density (low electronegativity) whereas fluorine (F) tends to withdraw electron density (high electronegativity); nitrogen (N) and oxygen (O) are also electronegative atoms.

Electrophoresis — the movement of charged colloidal particles through the medium in which they are dispersed as a result of changes in electrical potential; used in the analysis of protein mixtures because protein particles move with different characteristic velocities dependent principally on the number of charges carried by each particle.

Electroporation — insertion of macromolecules (e.g. DNA) into cells by employing a brief intense pulse of electricity to open cellular pores.

Electrostatic — pertaining to the static electric fields produced by charged objects.

Elliptocytosis — increased number of elliptocytes (oval-shaped red blood cells); occurs in some forms of anemia.

Elution — in chemistry, separation of one material from another by washing.

Embolus — a mass of undissolved matter (solid, liquid, or gaseous) present in a blood or lymphatic vessel, brought there by the blood or lymph current.

Emesis — vomiting; may be chemically induced using an emetic.

Emetogenesis — eliciting vomiting (Section 15.2.6.3).

Emperipolesis — temporary presence of one cell within another's cytoplasm.

Encapsulation — formulation of granulation tissue with a fibrotic capsule surrounding the foreign body.

Encephalitis — inflammation of the brain.

Endarterectomy — surgical removal of the lining of an artery.

Endocarditis — a life-threatening inflammation of the heart's inner lining.

Endocardium — serous lining membrane of the inner surface and cavities of the heart.

Endocytosis (endocytotic) — a process by which proteins arriving at the surface of a cell are internalized, being transported inside the cell within membranous vesicles.

Endogenous — originating inside an organ, part, or system.

Endohedral — lying entirely within a (fullerene) cage molecule.

Endometrium (endometrial) — pertaining to the lining of the uterus.

Endoplasmic reticulum — in cell biology, a highly convoluted sheet of membranes, extending from the outer layer of the nuclear envelope into the cytoplasm (Section 8.5.3.5).

Endoprosthesis — an internally-worn permanently-attached device that replaces a limb, organ, or tissue of the body.[234] See also prosthesis.

Endoscopy — inspection of body organs or cavities using the endoscope (device consisting of a tube and optical system).

Endosome — the vacuole formed when material is absorbed into a cell by the process of endocytosis; the vacuole fuses with lysosomes.

Endosteum (endosteal) — membrane lining the medullary cavity of a bone.

Endosymbiont (endosymbiotic) — an organism or cell that lives inside another organism or cell, in a state of symbiosis.

Endothelium — a form of squamous epithelium consisting of flat cells (endothelial cells) that line the blood and lymphatic vessels, the heart, and various other body cavities.

Endotoxin — bacterial toxin confined within the body of a bacterium, freed only when the bacterial cell wall is lysed.

Endotracheal — within the trachea.

Enophthalmos — recession of eyeball into orbit.

Enteric — pertaining to the small intestine.

Enterocyte — intestinal (duodenum and jejunum) lining cells, important in the final phases of digestion and for absorption of protein, fat and carbohydrate.

Enterotoxin — toxin produced in or originating in the intestinal contents, exotoxin specific for the cells of the mucosa, or exotoxin produced by bacteria that cause food poisoning and toxic shock syndrome.

Enthalpy — in thermodynamics, the internal energy of a system plus the product of its volume and the external pressure.

Entropy — in the physical sciences, a measure of uncertainty regarding the state of a system; free energy can be extracted by converting a low-entropy state to a high-entropy state. In other contexts, the term is often used by analogy to describe the extent of randomness and disorder in a system and the consequent lack of knowledge or information about it.

Enucleated cell — a cell from which the nucleus has been removed.

Envasculoided — permeated with a vasculoid[4609] appliance implant.

Enzyme — a protein molecule that often acts as a specific catalyst, facilitating specific chemical or metabolic reactions necessary for cell growth and reproduction; a biological chemosynthetic molecular machine.

Eosinophil — a type of granulocytic white blood cell comprising 1%-4% of all leukocytes, that is known to destroy parasitic organisms and to play a major role in allergic reactions (some of the major chemical mediators that cause bronchoconstriction in asthma are released by eosinophils).

EPA — Environmental Protection Agency (U.S.).

Epidermis (epidermal) — the outer epithelial portion of the skin.

Epidermalgia — sensation of pain in the epidermis (Section 15.5.1.2).

Epidural — located over or upon the dura.

Epimysium (epimysial) — outermost sheath of connective tissue that surrounds a skeletal muscle.

Episclera (episceral) — outermost superficial layer of the sclera of the eye.

Epithelium (epithelial tissue) — the avascular layer of cells forming the epidermis of the skin and the surface layer of mucous (secreting mucus) and serous (secreting serum or serumlike fluid) membranes, including the glands. The cells rest on a basement membrane and lie closely approximated to each other with little intercellular material between them. Skin and the lining of natural internal body cavities.[234]

Epitope — the particular site on the macromolecular surface of an antigen which elicits specific affinity of an antibody; the antigenic determinant; any component of an antigen molecule that functions as an antigenic determinant by permitting the attachment of certain antibodies.

ER — emergency room.

Erysipelas — acute febrile disease with localized inflammation, with redness of skin and subcutaneous tissue accompanied by systemic signs and symptoms.

Erythema — redness; see rubor (inflammation).

Erythroblastosis fetalis — a hemolytic disease of the newborn characterized by anemia, jaundice, enlargement of liver and spleen, and generalized edema.

Erythrocyte — red blood cell.

Erythropathy — disease of the red blood cells.

Erythropoietic — producing erythrocytes.

Erythropoietin — a hormone that controls the production rate of red blood cells in the human body.

Esophagus (esophageal) — muscular canal extending from pharynx to stomach.

Esthesiometer — device for measuring tactile sensitivity.

Ethmoidal — pertaining to ethmoid bone (spongy bone forming roof for the nasal fossae and part of floor for anterior fossa of the skull) or sinuses.

Eukaryote (eukaryotic) — an organism or cell that contains its genome within a nucleus.

Euler buckling — force required to cause a structure to buckle under compression.

Euvolemic — normal blood volume.

Exocrine — external secretion of a gland; glands whose secretion reaches an epithelial surface either directly or through a duct.

Exocytosis (exocytic) — the process of secreting proteins from a cell into the surrounding medium, by transport in membranous vesicles from the endoplasmic reticulum, through the Golgi, to storage vesicles, and finally (upon a regulatory signal) through the plasma membrane.

Exogenous — originating outside an organ, part, or system.

Exoprosthesis — an externally-worn device that replaces a limb, organ, or tissue of the body. See also orthosis.

Exsanguinate — loss of blood to the point at which life can no longer be sustained; expressing blood from a part.

Extracellular — outside of the cell.

Extracellular matrix (ECM) — an extracellular fibrous scaffolding that helps organize cells into tissues (Section 9.4.4.2).

Extrahepatic — outside the liver.

Extranuclear — outside the cell nucleus.

Extravasation — exiting the bloodstream; see diapedesis.

Extravascular — outside a vessel.

Extrusion (implants) — resolution of inflammation, in which implants in contact with epithelial tissue are surrounded by a down-growing extension of such tissue, directed toward extruding the implant from the body; also termed marsupialization, due to the resemblance of the newly formed tissue to a kangaroo's pouch.[234]

Exudate — accumulation of a fluid in a cavity; matter that penetrates through vessel walls into adjoining tissue; the production of pus or serum.

Ex vivo — outside of the living human body.

Fabrey's disease — an inherited metabolic disease in which a glycolipid (ceramide trihexoside) accumulates in the organs and tissues, impairing function of kidneys and other organs.

Fascia — a fibrous membrane covering, supporting, and separating muscles; also, unites the skin with underlying (e.g. muscular) tissue.

Fascicles — a small bundle, especially of nerve fibers.

FBGC — multinuclear foreign body giant cell.

FDA — Food and Drug Administration (U.S.).

Febrile — pertaining to fever (Section 15.2.7).

Feline — pertaining to cats.

Femur (femoral) — thigh bone; longest and strongest bone in human skeleton.

Fenestrated — having openings.

FEP — fluorinated ethylene propylene (a form of Teflon).

Ferrofluid — a stable colloidal liquid-carrier suspension of sub-domain magnetic particles of average size ~10 nm that are coated with a stabilizing dispersing agent (surfactant) to prevent particle agglomeration even when a strong magnetic field gradient is applied.

Fetotoxic — toxic to the fetus.

Fibrinogen — a blood protein molecule that is ultimately converted to the active protein, fibrin, after foreign surface contact during blood clotting (Section 15.2.5).

Fibroblast — a stellate or spindle-shaped motile cell with cytoplasmic processes present in connective tissue, capable of forming collagen fibers.

Fibroid — colloquial term for fibroma (a fibrous, encapsulated, connective-tissue tumor), especially a fibroma of the uterus.

Fibromyalgia — chronic pain in muscles and soft tissues surrounding joints.

Fibronectin — any one of a group of fibrous linking proteins present in blood plasma and extracellular matrix.

Fibrosis — abnormal formation of fibrous tissue.

Fimbria (fimbral) — any structure resembling fringe or border.

Fission, cell — in microbiology, a method of asexual reproduction in bacteria, protozoa, and other lower forms of life; in cell biology, the partition of one organelle into two, as for example the fissioning mitochondrion.

Fistula — in anatomy, an abnormal tubelike passage from a normal cavity or tube to a free surface or to another cavity; may be due to congenital incomplete closure of parts, or may result from abscesses, injuries, or inflammatory processes.

Fluorophore — peptide sequence that mediates fluorescence; fluorescent probes use a fluorophore are conjugated to antibodies or other molecules designed to localize within a specific region of a cell or to respond to a specific stimulus such as pH.

Flux (fluence) — generally, a rate of flow.

fMLP — N-formyl-methionyl-leucyl-phenylalanine, a known chemoattractant for granulocytes and macrophages.

Foreign body reaction — a variation in normal tissue behavior caused by the presence of a foreign material.[234]

Frustrated phagocytosis — see Phagocytosis, frustrated.

Fullerene — a closed-cage molecule consisting of linked pentagons, hexagons, heptagons, or other polygonal elements; originally referred to carbon-only structures but may also represent the entire class of molecules having this geometry, regardless of atomic constituency (Section 2.3.2).

Functionalized — in chemistry, an otherwise chemically inert structure is functionalized when a chemically active ligand or moiety is covalently bonded to it.

Fundus, gastric — uppermost portion of the stomach, posterior and lateral to the entrance of the esophagus.

Fusion, cell — in cell biology, fusion is the merging of vesicles budded from the ER into the Golgi complex, or of endosomes with lysosomes, or of the contents of two cells by artificial means without the destruction of either, resulting in a heterokaryon that, for at least a few generations, will reproduce its kind (this was once an important method in assigning loci to chromosomes).

Fusogen (fusion protein) — specialized proteins that facilitate penetration of plasma membrane.

g — unit of gravitational acceleration (9.81 m/sec^2); describes the mean gravitation force experienced by a mass at rest on Earth's surface.

Galvanic — pertaining to electrical direct current, usually chemically generated.

Galvanotaxis, cellular — electric field-induced cell migration.

Ganglion — a mass of nervous tissue composed principally of nerve-cell bodies and lying outside the brain or spinal cord (e.g. the chains of ganglia that form the main sympathetic trunks, or the dorsal root ganglion of a spinal nerve).

Ganglioside — a particular class of glycosphingolipid present in nerve tissue and in the spleen.

Gastro- (gastric) — pertaining to the stomach.

Gastrointestinal — pertaining to the stomach and intestine.

Gaucher's disease — a chronic congenital disease of lipid metabolism caused by a deficiency of the enzyme beta-glucocerebrosidase, wherein glycosphingolipids accumulate in the reticuloendothelial cells.

Gavage — feeding with a stomach tube or with a tube passed through the nares, pharynx, and esophagus into the stomach.

Genotoxicity — toxic to the genetic material in cells.

Gentamicin — an antibiotic derived from the fungi of the genus *Micromonospora*.

Giant cells (phagocytic) — a large cell with several nuclei, appearing to be made up of many cells (Section 15.4.3.5).

Gingiva (gingival) — the gum; the tissue that surrounds the necks of the teeth.

Glaucoma — a group of eye diseases characterized by increase in intraocular pressure, resulting in atrophy of the optic nerve and may produce blindness.

Glia cells — neuroglial cells including astrocytes, oligodendroglia and microglia.

Gliosis — proliferation of neuroglial tissue in the central nervous system.

Glomerulonephritis — a form of nephritis in which the lesions involve primarily the glomeruli.

Glomerulus, renal — one of the small structures in the malpighian body of the kidney made up of capillary blood vessels in a cluster and enveloped in a thin wall.

Glucan — polyglucose particles.

Glucosyl — a glycoprotein moiety.

Glycocalyx — a thin layer of glycoprotein and polysaccharide that covers the surface of some cells, such as muscle cells, fibroblasts, pericytes, and epithelial cells, and contributes to the basal lamina (Section 8.5.3.2).

Glycolipids — patterns of glucose residues attached to membrane lipids.

Glycoprotein — a protein molecule with carbohydrate moieties attached.

Glycosylation — the covalent bonding of carbohydrate moieties to another molecule.

Golgi complex/apparatus — in cell biology, individual stacks of membranes near the endoplasmic reticulum involved in glycosylating proteins and sorting them for transport to different intracellular locations (Section 8.5.3.6).

Goodpasture's syndrome — progressive glomerulonephritis, hemoptysis, and hemosiderosis.

Gout — hereditary metabolic disease that is a form of acute arthritis and is marked by inflammation of the joints.

Graft — tissue that is transplanted or implanted in a part of the body to repair a defect.

Gram-negative — losing the stain and taking the color of the red counterstain in Gram's method of staining.

Gram-positive — retaining the color of the gentian violet stain in Gram's method of staining.

Granule — a small, grainlike body. Small granules may be found in cells, containing stores of nutrients; large granules may be formed in tissues following a granulomatous reaction.

Granulocyte — a granular leukocyte; a polymorphonuclear (nucleus composed of two or more lobes or parts) leukocyte, including basophils, eosinophils, and neutrophils.

Granuloma — a nodular inflammatory lesion, usually small or granular, that is firm, persistent, and contains compactly grouped mononuclear phagocytes. Actively growing provisional soft tissue that precedes remodeling phase of inflammatory response; may become chronic in the absence of resolution.[234]

Granulomatous reaction — producing a granuloma, a granular tumor or growth, usually of lymphoid and epithelioid cells; an encapsulation reaction to the presence of a foreign object in the body that cannot be readily phagocytosed (Section 15.4.3.5).

Granulopoietic (granulomatogenesis) — producing granulocytes.

Graphene — monoatomic graphite sheet that forms the walls of fullerenes and carbon nanotubes.

Growth factors — biochemicals that promote division and proliferation of specific cell types.

GTP — guanosine triphosphate.

HA — see hydroxyapatite.

Hageman factor — clotting factor XII, a human plasma protein.

Hallervorden-Spatz disease — progressive, degenerative disease, beginning in childhood, of the globus pallidus, red nucleus, and reticular part of the substantia nigra of the brain.

Hamaker constant — in surface science, a physical constant that describes the strength of van der Waals attractive forces between different materials as a function of the radius of curvature and separation distance between two surfaces (Section 9.2.1).

Haptic — operated by, or pertaining to, the sense of touch.

Haptotaxis — directed migration of cells along surfaces with gradients of immobilized factors.

Hct — see hematocrit.

Heat capacity — the ratio of the heat input to the temperature increase in a system.

Heat shock proteins (HSPs) — present in all normal living cells; act as "chaperones" to assist new or distorted proteins to properly fold, and help to shuttle proteins from one cellular compartment to another and to transport old proteins to intracellular "garbage disposal" sites; are also induced when a cell undergoes various types of environmental stresses like heat, cold or oxygen deprivation.

Heinz bodies — granules in red blood cells due to damage of the hemoglobin molecules.

HEMA — hydroxyethylmethacrylate (e.g., polymer).

Hemato- — pertaining to blood.

Hematocrit (Hct) — volume-fraction or bloodstream concentration of erythrocytes (red blood cells), expressed as a percentage.

Hematoma — a swelling or mass of blood (usually clotted), confined to an organ, tissue, or other space, caused by a break in a blood vessel.

Hematopoietic — pertaining to the production and development of blood cells.

Hemidesmosome — the half of a desmosome (structure binding adjacent epithelial cells) produced by epithelial cells for attachment of basal surface of the cell to the underlying basement membrane or the enamel or cementum tooth surface in the case of junctional epithelium.

Hemocompatibility — biocompatibility with the blood.

Hemodialysis — a method for providing the function of the kidneys by circulating blood through tubes made of semipermeable membranes.

Hemoglobinuria — presence of hemoglobin in the urine, but free from red blood cells.

Hemolysis (hemolytic) — fragmentation of red blood cells, liberating hemoglobin.

Hemolytic-uremic syndrome — an acute condition consisting of microangiopathic hemolytic anemia, thrombocytopenia, and acute nephropathy.

Hemoptysis — expectoration of blood arising from the oral cavity, larynx, trachea, bronchi, or lungs.

Hemorrhagic — pertaining to bleeding.

Hemosiderosis — condition characterized by deposition, especially in liver and spleen, of hemosiderin (an iron-containing pigment).

Hemostasis — arrest of bleeding.

Heparin — a polysaccharide that inhibits coagulation by preventing conversion of prothrombin to thrombin by forming an antithrombin.

Hepatic — pertaining to the liver.

Hepatocarcinogenic — tending to cause liver cancer.

Hepatocyte — the most common tissue cell found in the liver.

Hepatomegaly — abnormal enlargement of the liver.

Hernia — protrusion or projection of a part of an organ through the wall of the cavity that normally contains it.

Hilus (hilar) — depression or recess at entrance or exit of a duct into a gland, or of nerves and vessels into an organ.

Hippocampus (hippocampal) — the complex, internally convoluted structure that forms the medial margin of the cortical mantle of the cerebral hemisphere.

Histamine — a chemical substance, produced from the amino acid histidine, normally present in the body; exerts a pharmacological action when released from injured cells.

Histiocyte — a macrophage present in all loose connective tissues; part of the RES.

Histiocytosis — excessive multiplication of histiocytes, which appear in the blood in unusual numbers.

Histiocytoma — a tumor containing histiocytes.

Histology — the study of tissues.

Histonatation — in medical nanorobotics, locomotion (swimming) through tissues by a nanorobot (Section 9.4.4)

Histopenetration — in medical nanorobotics, penetration through dermis and internal tissue spaces by motile nanorobots.

HLA complex — Histocompatibility Locus Antigens, formerly known as Human Leukocyte Antigen (or Associated) complex.

Homeostasis — in physiology, a state of equilibrium of the internal environment of the body that is maintained by dynamic processes of feedback and regulation; homeostasis is a dynamic equilibrium (changing balance), keeping cells within the physical and chemical limits that can support life.

Homologous — similar in form (e.g. fundamental structure and origin), but not necessarily in function.

Homotypic — of the same form and type.

Hormone — a chemical substance that originates in an organ, gland, or part and is conveyed through the blood to another part of the body, stimulating that other part by chemical action to increase functional activity or to increase secretion of another hormone.

Host response — the local and systemic response, other than the intended therapeutic response, of living systems to the material;[234] the reaction of a living system to the presence of a material.[230]

Host response, local — the response, other than the intended therapeutic response, of tissue and organs contacting a biomaterial.[234]

Host response, remote — the response, other than the intended therapeutic response, of remote tissue and organs in an individual with one or more implants.[234]

Host response, systemic — the distributed or disseminated response, response, other than the intended therapeutic response, of tissue and organs in an individual with one or more implants.[234]

HSA — human serum albumin. See also albumin.

Humoral — pertaining to body fluids or substances contained in them.

Hyaline — material deposited in the glomerulus in certain forms of glomerulonephritis.

Hyaline bodies — homogeneous substance; the result of colloid degeneration, found in degenerated cells.

Hyaluronic acid — tissue cement or "ground substance" found in human connective tissue.

Hybrid artificial organ — see artificial organ, hybrid.

Hybridization — combination of different electron bonding orbitals to form four equivalent tetrahedral bond orbitals, esp. in carbon.

Hybridoma — the cell produced by the fusion of an antibody-produced cell and a multiple myeloma cell, capable of producing a continuous supply of identical antibodies.

Hydrocarbon — a molecule consisting only of H and C.

Hydrocephalus — the increased accumulation of cerebrospinal fluid within the ventricles of the brain.

Hydrodynamics — in physics, the study of the action of and motion of (and in) water and other liquids.

Hydrogen bond — the weak bond between a positively charged hydrogen atom that is covalently bound to one electronegative atom, and another electronegative atom.

Hydrolysis — a (hydrolytic) reaction in which a covalent bond is broken with the incorporation of a water molecule.

Hydrophilicity — tending to mix with water; wettable; nonpolar. Hydrophilic groups interact with water, so that hydrophilic regions of protein or the faces of a lipid bilayer reside in an aqueous environment. Compare hydrophobicity.

Hydrophobic force — water molecules are linked by a network of hydrogen bonds; a nonpolar nonwetting surface such as wax cannot form hydrogen bonds, hence repels water.

Hydrophobicity — tending not to mix with water; nonwetting; polar. Hydrophobic groups repel water, so that they interact with one another to generate a nonaqueous environment. Compare hydrophilicity.

Hydrostatic — pertaining to the pressure of fluids or to fluid properties when in equilibrium.

Hydroxyapatite — the apatite form of calcium phosphate present with calcium carbonate in the bones and skeleton.

Hydroxyl — an OH^- group or ion.

Hyperalgesia — excessive sensitivity to pain.

Hyperbaric — exposure to, or having pressure greater than, normal atmospheric pressure.

Hypercapnia — increased amount of carbon dioxide in the blood.

Hyperhidrosis — abnormally excessive sweating.

Hyperopia — farsightedness.

Hyperplastic (hyperplasia) — excessive proliferation of normal cells in the normal tissue arrangement of an organ.

Hypersensitivity reactions — the reaction of the body to antigens.

Hypertension — abnormally high blood pressure.

Hyperthermia — unusually high fever.

Hypertrophy — increase in size of an organ or structure that does not involve tumor formation.

Hyperventilation — increased lung ventilation leading to abnormally low carbon dioxide in blood.

Hypervolemic — abnormal increase in the volume of circulating blood.

Hypha — a filament of mold, or part of a mold mycelium (mass of filaments constituting the vegetative body of fungi).

Hypocapnia — decreased amount of carbon dioxide in the blood.

Hypokalemia — extreme potassium depletion in the circulating blood.

Hyponatremia — extreme sodium depletion in the circulating blood.

Hypotension — low blood pressure.

Hypothalamus — part of the brain lying below the thalamus.

Hypothermia — having a body temperature below normal.

Hypothyroid — marked by insufficiency of thyroid secretion.

Hypotonic — see isotonic.

Hypotonia — reduced tension; relaxation of arteries; loss of tonicity of the muscles or intraocular pressure.

Hypovolemic — diminished blood volume.

Hypoxia — a condition in which the tissues are not receiving enough oxygen to sustain their metabolic activity.

Hysteresis — failure of related phenomena to keep pace with each other.

IAP — inhibitor of apoptosis.

Iatrogenic disorder — an adverse condition induced in a patient by the actions of a physician.

ICD patch — implantable cardioverter defibrillator (e.g., with epicardial patch electrodes).

Idiopathic — pertaining to conditions without clear pathogenesis.

Idiotype — in immunology, the specific region of the antibody-binding (Fab) region of the immunoglobulin molecule to which the specific antigen binds.

Ig — immunoglobulin (IgG, IgA, IgM, IgD, IgE); see antibody.

IJE — peri-implant junctional epithelium.

Ileum (ileal) — lower three-fifths of the small intestines from the jejunum to the ileocecal valve.

Immune response — host response involving either humoral or cellular specific immune mechanisms.[234]

Immunofixation — a laboratory technique used to identify proteins in which immunoglobulins (which appear as a "gamma" band in protein electrophoresis) are separated, allowing the individual immunoglobulins to be identified; immunofixation electrophoresis consists of an electrophoretic phase followed by a fixation phase in which antiserum is used to precipitate the protein, thus enhancing the results of standard protein electrophoresis, giving more rapid results and greater sensitivity.

Immunogen — an agent that can induce an immune response; all immunogens are antigens.

Immunoglobulins — a class of glycoproteins; see antibody.

Immunoradiometric assay — an assay based on the reversible and non-covalent binding of an antigen by a specific antibody labeled with a radioactive nuclide as a tracer.

Immunosuppression — prevention of formation of an immune response.

Immunotoxin — toxic agent attached to an antibody molecule, used to specially target tumor cells.

Impedance — opposition to flow (e.g. fluid, electrical, etc.) when flow is steady, or the driving pressure per unit flow when flow is changing; the resistance of an acoustic system to being set in motion.

Impermeant — incapable of permeating.

Implant — a device placed within an animal or human body by the act of implantation;[234] a medical device made from one or more biomaterials that is intentionally placed within the body, either totally or partially buried beneath an epithelial surface.[230]

Implantation — placement of a device or material within the body of an animal or human by a medical or surgical professional, in such a way as to breach one or more epithelial layers, and to leave materials or components in place after the initial procedure is completed.[234]

Incapsulation — resolution of inflammation, in which the implant is surrounded and walled off from normal tissue by a collagenous, relatively acellular tissue called a capsule, which resembles scar tissue; in a bony location, the capsule may be mineralized and is called a sequestrum.[234]

Incontinence — inability to retain urine, semen, or feces, through loss of sphincter control or because of cerebral or spinal lesions.

In cyto — within a biological cell.

India ink — a black ink consisting of an aqueous suspension of natural black pigment usually made from bone black, lampblack, or amorphous carbon from combustion (soot); aka. China ink.

Inert biomaterials — see biomaterials, inert

Infarct — an area of tissue in an organ or part that undergoes necrosis following cessation of blood supply.

Inferior — beneath or lower; often refers to the undersurface of an organ or indicates a structure below another structure.

Inflammatory response — the cell-mediated local and regional response directed toward stabilizing injured tissue, restoring physiological status quo ante, removing dead or damaged tissue elements and foreign material, and correcting structural and functional loss due to the initial insult (Section 15.2.4). The four classical signs of inflammation are redness (rubor), swelling (tumor), pain (dolor), and heat (calor).[234]

Infraorbital — beneath the orbit (the cavity in the skull containing the eyeball).

Infrarenal — below the kidney.

Ingrowth — formation of tissue within pores, etc. in the body of an implant.[234]

In sanguo — within the bloodstream.

Insufflation — the act of blowing a gas, vapor, or powder into a cavity, such as the lungs.

Integral membrane protein — in cell biology, an amphipathic protein embedded in the lipid bilayer of the cell which cannot be extracted from the membrane without disrupting the lipid bilayer; most integral proteins are transmembrane proteins.

Integration — resolution of inflammation, in which the implant becomes well-integrated with the adjacent biological tissues; occurs for a very limited number of materials, such as bioactive glasses of selected compositions and some metals such as pure titanium for which direct bonding or apparent adhesion to normal tissue may take place.[234]

Integrins — cell surface adhesion receptors (~200 kilodalton) that mediate cellular connection to the extracellular matrix and are expressed on a wide variety of cells. Most cells express several integrins; most integrins are involved in attachments to the cytoskeletal substratum.

Integument — the skin, consisting of the dermis and epidermis; a covering.

Interactive biomaterials — see biomaterials, interactive.

Intercalated — inserted between two others, as something interposed.

Intercostal — between the ribs.

Intermediate filament — the most stable of the cytoskeletal elements; high tensile strength and comparative positional stability; serve as internal guy wires to resist mechanical stress on the cell, providing a scaffold supporting the entire cytoskeletal framework (Section 8.5.3.11(C)).

Interstitial (interstitium) — pertaining to extracellular interstices or spaces within an organ or tissue.

Intima — innermost coat of a structure, e.g., a blood vessel.

Intraarterial — within the artery(ies).

Intraarticular(-ate) — within a joint.

Intracellular — inside the cell.

Intracranial — within the cranium or skull.

Intraepithelial — residing in the epithelium.

Intrahepatic — inside the liver.

Intraluminal — within any tubular structure.

Intramuscular — inside muscle tissue.

Intranigral — inside a specific region in the brain.

Intranuclear — inside the cell nucleus.

Intraocular — within the eyeball.

Intraoperative — occurring during surgery.

Intraperitoneal (IP) — within the peritoneal (abdominal) cavity.

Intrarenal — inside the kidney.

Intratracheal — introduced into, or inside, the trachea.

Intravasation — reverse diapedesis.

Intravascular — inside a blood vessel.

Intravenous — inserted into a vein.

Intravitreous (intravitreal) — inside the vitreous humor of the eye.

Intrusiveness, volumetric — in medical nanorobotics, a measure of the degree to which artificial nanosystems can safely and harmlessly volumetrically displace natural biological systems.

Intussusception — the slipping of one part of an intestine into another part just below it; invagination.

In vacuo — in a vacuum (viz. the ablative case of the 2nd-declension Latin adjective "vacuus").

Invaginate — to place or receive into a sheath; to receive within itself or into another part.

In vitro — in glass, as in a test tube; performed in the laboratory, usually involving isolate tissue, organ, or cell preparations.

In vivo — inside the living human body; performed on a living organism.

Irido- — pertaining to the iris of the eye.

Ischemia — local and temporary deficiency of blood supply due to obstruction of the circulation into a body part.

ISFET — Ion Sensitive Field Effect Transistor.

Isoelectric — having equal electric potentials; neither positively nor negatively charged.

Isoforms — any one of multiple forms of a functional protein that differ in amino acid sequence and electrophoretic mobility.

Isomer — one of two more chemical substances that have the same molecular formula but different chemical and physical properties due to a different arrangement of the atoms in the molecule; for example, dextrose is an isomer of levulose. Isomers may be geometric, optical, or structural.

Isothermal — held, or existing, at a constant temperature.

Isotonic — animal cells containing a solution which exerts an osmotic pressure approximately equal to that of the surrounding fluid are isotonic or isoosmotic to that fluid. Stronger solutions that cause cells to shrink are hypertonic; weaker solutions that cause cells to swell are hypotonic.

Isotope — any of two or more forms of the same chemical element that have nearly identical chemical properties but which differ in the number of neutrons contained in each atomic nucleus; many isotopes are radioactive.

Isotropic — the same in all directions.

Isotypes — in immunology, the determinants on the Ig molecule that distinguish among the main classes of antibodies of a given species (the same for all normal individuals of that species).

IP — see intraperitoneal.

IV — see intravenous.

Jejunum (jejunal) — the second portion of the small intestine extending from the duodenum to the ileum.

Kallikrein — an enzyme normally present in blood plasma, urine, and body tissue; is one of the most potent vasodilators when activated (to form kinin).

Kaolin — a yellow-white or gray clay powder formed of hydrated aluminum silicate.

Karyogamy — union of nuclei in cell conjugation.

Keloids — scar formation in the skin following trauma or surgical incision.

Keratin — a sulfur-rich scleroprotein or albuminoid present largely in cuticular (pertaining to cuticles) structures.

Keratinocyte — a cell of the epidermis, and parts of the mouth, that produces keratin.

Keratitis — inflammation of the cornea, with pain; usually associated with decreased visual acuity.

Keratocyte — corneal fibroblasts.

Keratomileusis — plastic surgery of the cornea in which a portion is removed, its curvature reshaped, and then is reattached; can also be done in situ with laser.

KHz — kilohertz; thousands of cycles per second.

Kinetochore — a large protein complex that forms at the surface of the centromere of chromosomes and controls separation of the chromosomes to daughter cells by mediating microtubule association with chromosomes.

Kininogen — substance that produces a kinin when acted upon by certain enzymes.

Kinins — a group of polypeptides with considerable biological activity, e.g., influencing smooth muscle contraction, inducing hypotension, inciting pain, and increasing blood flow and permeability of blood capillaries.

Kirschner wire — steel wire placed through a long bone, to apply traction to the bone.

Knowles pin — a mechanical prosthesis for bone fracture fixation used in place of plates or Kirschner wires, e.g., for acute adult mid-clavicular fractures.

Kupffer cells — macrophages lining the sinusoids of the liver (Section 8.2.5).

Labile — not fixed, unsteady, easily disarranged; easily altered or decomposed by heat or chemicals.

Laceration (lacerative) — a wound or irregular tear of the flesh.

Lacrimal — pertaining to the tears (eye fluid).

Lactoferrin — an enzyme released in phagocytosis by neutrophils and macrophages that combines with iron in the blood.

Lamellipodia — variable extensions of the cell membrane; a cytoplasmic veil produced on all sides of a migrating polymorphonuclear leukocyte (granulocyte).

Lamina — a thin flat layer or membrane.

Lamina propria — thin layer of fibrous connective tissue lying immediately beneath the surface epithelium of mucous membranes.

Laminar (Poiseuille) flow — fluid flow that moves exclusively along separate and independent parallel flow planes (i.e. streamlines), generally with an axisymmetric parabolic profile if in a tube. Laminar flow minimizes the impedance (resistance) and energy dissipation of fluid flow.

Laminin — a large glycoprotein component of ECM that binds to specific integrin molecules on tissue cell surface, with a primarily adhesive function.

Langerhans cells — dendritic cells in human skin.

Langmuir (-Blodgett) film — thin film created by successive adhesion of a series of molecular monolayers to a surface, allowing both thickness and composition in the vertical axis to be adjusted to 0.1-nm by controlling the structure of the molecules comprising each individual monolayer during deposition.

Larynx (laryngeal) — the enlarged upper end of the trachea below the root of the tongue; the organ of voice.

Lavage — washing out of a cavity.

LD50 — a dose of or exposure to a toxic influence that produces death in 50% of organisms exposed to it.

Leachate — water that has passed through a material and in doing so has accumulated dissolved substances (the leachates).

Leukapheresis — see apheresis.

Leukergy — anergy of leukocytes.

Leukocytes (white blood cells) — the primary effector cells that respond to infection and tissue damage in the human body. There are two types: granulocytes (including basophils, eosinophils, and neutrophils) and agranulocytes (including monocytes and lymphocytes). Leukocytes are formed from two stem cell populations in the bone marrow. The myeloid stem cell line produces granulocytes and monocytes, while the lymphoid stem cell line produces lymphocytes. Lymphoid cells travel to the thymus, spleen and lymph nodes, where they mature and differentiate into active, antigen-specific lymphocytes.

Leukocytolysis — fragmentation of white blood cells.

Leukocytosis — abnormal increase in number of leukocytes in the blood, usually transient, generally caused by presence of infection.

Leukocyturia — leukocytes in the urine.

Leukoembolization — vascular trapping of white cells, forming a blocking embolus.

Level of host (or material) response — the nature of the host (or material) response in a standard test with respect to the response obtained with a reference material.[234]

Lewy bodies — neuronal cells with pigmented inclusion bodies; found in Parkinson's disease.

Ligament — a band or sheet of strong fibrous connective tissue connecting the articular ends of bones, binding them together and facilitating or limiting motion.

Ligation, molecular — the formation of a phosphodiester bond to link two adjacent bases separated by a nick in one strand of a double helix of DNA; the term can also be applied to blunt-end ligation and to the joining of RNA.

Lipase — a lipolytic or fat-splitting enzyme found in the blood, pancreatic secretion, or tissues.

Lipid bilayer — in cell biology, the form taken by a concentration of lipids in which the hydrophobic fatty acids occupy the interior and the hydrophilic polar heads face the exterior; primary constituent of the plasma membranes of cells.

Lipids — molecules having hydrophilic polar heads, containing phosphate (phospholipid), sterol (such as cholesterol), or saccharide (glycolipid) connected to a hydrophobic tail consisting of fatty acid.

Lipofuscin — brown pigment granules representing lipid-containing nondegradable residues of lysosomal digestion (Section 15.6.3.2).

Lipofuscinosis — abnormal deposition of lipofuscin in tissues.

Lipoma — a fatty tumor.

Lipophilic — having an affinity for lipids (fats); nonpolar.

Lipophobic — repulsed by lipids (fats).

Lipoproteins — conjugated proteins consisting of simple proteins combined with lipid components.

Liposomes — closed spherical bilayers formed by lipid molecules with varying radii from 10 nm to micrometers. See also micelles.

Lissencephaly — condition in which the brain is smooth owing to failure of development of cerebral gyri.

Listeriosis — disease affecting humans and many animals, caused by *Listeria monocytogenes* (a soil saprophyte); most common manifestation is meningitis.

Lithophagy — swallowing stones, sand, or other mineral matter.

Lithotripsy — crushing of a stone in the bladder or urethra.

Load error — in control theory, minimum range of variation in a control variable that is necessary to provoke a response from a control system.

LPS — lipopolysaccharide, the lipid used to construct the outer leaflet of the outer bilayer membrane of Gram-negative bacteria.

LTIC — low temperature isotropic carbon (Section 15.3.3.2).

Lumbar — pertaining to the loins (the part of the back between thorax and pelvis).

Lumen — the interior, especially of a compartment bounded by membranes, as for instance the endoplasmic reticulum or the mitochondrion.

Luminal — pertaining to the interior of a cavity, tube, or vessel.

LVAD — left ventricular assist device.

Lymph — an alkaline fluid found in the lymphatic system (Section 8.2.1.3).

Lymphadenopathy — swelling and morbid change in lymph nodes.

Lymphangitis — inflammation of lymph vessels.

Lymphatic system — includes all structures involved in the conveyance of lymph from the tissues to the bloodstream, including lymph capillaries, lacteals, lymph nodes, lymph vessels, main lymph ducts, and cisterna chyli (Section 8.2.1.3).

Lymphedema — edema due to obstruction of lymph vessels.

Lymphocompatible — biocompatible with important components of the lymphatic system, especially lymphocytes.

Lymphocyte — a morphologically distinct variety of leukocytes, comprising 20-44% of all white blood cells. But only ~2% of all lymphocytes present in the human body are in the bloodstream; most reside elsewhere, particularly in the lymph and the lymph nodes. B-lymphocytes differentiate into antibody-secreting plasma cells, whereas T-lymphocytes play diverse regulatory roles in the immune response.

Lymphocytopenia — less than normal number of lymphocytes in the blood.

Lymphokines — a cytokine secreted by a lymphocyte.

Lymphotrophic — tending to accumulate in lymph nodes.

Lysis (lytic) — in microbiology, the death of a bacterium at the end of a bacteriophage infective cycle when the bacterium bursts open to release the progeny of an infecting phage; also applies to eukaryotic cells, as for example infected cells that are attacked by the immune system. More generally, dissolution or decomposition.

Lysosomes — small bodies inside cells, enclosed by membranes, that contain hydrolytic enzymes that are part of the cell's digestive apparatus (Section 8.5.3.8).

Lysozyme (muramidase) — an enzyme that is destructive to cell walls of certain bacteria, found in white blood cells of the granulocytic and monocytic series.

MAb — see monoclonal antibody.

MAC — membrane attack complex (complement system; Section 15.2.3.2).

Machine-phase nanotechnology — molecular nanotechnology-based mechanical devices.

Macromolecule — a molecule of colloidal size, typically 1-100 nm in diameter or length, consisting most notably of proteins, nucleic acids, and polysaccharides.

Macrophage — a monocyte that has left the circulation and settled and matured in a tissue; found in large numbers in the spleen, lymph nodes, alveoli, and tonsils, with ~50% found in the liver as Kupffer cells. Along with neutrophils, macrophages are the major phagocytic cells of the immune system, able to recognize (and then ingest) foreign antigens via chemical receptors on the surface of their cell membranes. Macrophages also serve a vital role by processing antigens and presenting them to T-cells, activating the specific immune response.

Macroscopic — easily visible to the human naked eye; typically ~1 mm^3 or larger.

Macula densa cells — closely packed cells in the distal tubular epithelium of each nephron in kidney; may function as chemoreceptors.

Macule (macular) — discolored spot or patch on the skin, neither elevated nor depressed, of various colors, sizes, and shapes.

Macular degeneration — degeneration of the macular area of the retina of the eye.

Maillard reaction — in food science, the "browning" reaction that occurs between proteins and reducing sugars as they are heated.

Major histocompatibility complex (MHC) — the complex of HLA genes on the short arm of human chromosome 6 (Section 8.5.2.1).

Malignant — growing worse, resisting treatment, threatening to produce death; said of cancerous growths.

Malpighian capsule — a spherical body found in cortex of kidney consisting of a glomerulus and Bowman's capsule.

Mandible (mandibular) — horseshoe-shaped bone forming the lower jaw.

Mannose — a polysaccharide (an aldohexose) present in certain plants.

March hemoglobinuria — impact hemolysis.

Margination — adhesion of leukocytes to endothelial cells lining the walls of a blood vessel, during the relatively early stages of inflammation; more generally, the process of differential radial migration among suspended particles of different sizes during fluid flow through a tube.

Marsupialization — see extrusion (implants).

Martensitic — a highly twinned lower temperature structure with a stress-strain curve having a plateau phase more like that of an elastomer than a metal; compare austenitic.

Mast cells — cells resident in connective tissue just below epithelial surfaces, serous cavities, and around blood vessels, that synthesize, store, and release (upon stimulation) histamine and other local chemical mediators of inflammation (e.g. leukotrienes).

Material response — the response of the material to living systems.[234]

Matricellular proteins — extracellular matrix proteins.

Maxillary — pertaining to the upper jaw.

Maxillofacial — pertaining to the maxilla and face.

Meatus — a passage or opening.

Mechanocompatibility — the mechanical biocompatibility of nanodevices or nanorobotic systems as they interact with the organs, tissues and cells of the human body (Chapter 15.5).

Mechanoenzyme — enzyme producing mechanical actuation when activated.

Mechanoreceptor — a receptor that receives mechanical stimuli such as pressure from sound or touch.

Mechanosensitivity — see mechanoreceptor.

Mechanosynthesis — chemical synthesis controlled by mechanical systems operating with atomic-scale precision, enabling direct positional selection of reaction sites; synthetic applications of mechanochemistry.

Media — middle or muscular coat of an artery.

Mediastinum (mediastinal) — the mass of organs and tissues separating the lungs; containing the heart and its large vessels, trachea, esophagus, thymus, lymph nodes, and connective tissue.

Medical device — see device, medical.

Medulla (medullary) — the inner or central portion of an organ; compare cortex.

Medulla oblongata — enlarged portion of the spinal cord in the cranium, after the cord enters the foramen magnum of the occipital bone; the lower portion of the brain stem.

Megakaryocytes — a large bone marrow cell with multiple nuclei.

Melanosome — the pigment granule produced by melanocytes.

Melittin — a small protein containing 26 amino acid residues that is the principal toxic component of honeybee venom.

Membrane — in cell biology, an asymmetrical lipid bilayer that has lateral fluidity and contains proteins; in anatomy, a thin, soft, pliable layer of tissue that lines a tube or cavity, covers an organ or structure, or separates one part from another (Section 8.5.3.2).

Membrane proteins — in cell biology, plasma membrane proteins that have hydrophobic regions that allow part or all of the protein structure to reside within the membrane; the bonds involved in this association are usually noncovalent (Section 8.5.3.2).

Membranolytic — causing the physical failure of a membrane.

Meningeal cells — cells of the meninges (the three membranes investing the spinal cord and brain).

Mesangium (mesangial) — the suspensory structure of the renal glomerulus.

Mesentery (mesenteric) — a peritoneal fold encircling the greater part of the small intestines and connecting the intestine to the posterior abdominal wall.

Mesothelioma — a rare malignant tumor of the mesothelium (the epithelium covering the serous membranes) of the pleura, pericardium, or peritoneum.

Messenger RNA (mRNA) — the RNA whose sequence corresponds to that of exons in the transcribed gene, which embodies the codons and is translated into the protein gene product.

Metabolite — any product of metabolism.

Metamorphic — in medical nanorobotics, capable of adopting multiple physical configurations via smooth changes from one configuration to another (Section 5.3).

Metastasize (metastasis) — usually refers to the manifestation of a malignancy (e.g. of cancerous body cells) as a secondary growth arising from the primary growth, but in a new location.

Metazoa — all multicellular life. Compare protozoa.

MHC — see major histocompatibility complex.

MHz — megahertz; millions of cycles per second.

Micelle — a self-assembling hollow spheroidal aggregate of amphipathic lipids in a polar liquid (e.g. aqueous) medium. See also liposomes.

Microangiopathy — pathology of small blood vessels.

Microautophagocytosis — digestion within a cell of portions of individual cell organelles or mitochondria that have been injured or have atrophied.

Microbivore — in medical nanorobotics, an artificial mechanical phagocytes[2762] (Chapter 23).

Microdomains, cellular — see microzones.

Microglia — resident macrophages in brain tissue, spinal cord, and retina.

Microgravity — conditions of below-normal gravity, e.g. in Earth orbit; hypogravity.

Micron — one-millionth of a meter; a micrometer.

Microplicae — microscopic folds.

Microsomes (liver) — membrane fractions derived from human or animal tissues or cells grown in culture; most membrane-bound enzymes are associated with microsomes.

Microtubules — filaments consisting of dimers of tubulin; interphase microtubules are reorganized into spindle fibers during mitosis (cell division), when they are responsible for chromosome movement.

Microvilli — microscopic projections from the free surface of cell membranes, greatly increasing the exposed surface area of the cell.

Microzones — physiologically persistent, localized, and essential intracellular chemical gradients, establishing intracellular compartmentation of metabolites without enclosure by membranes.

Micturition — urination.

Miliaria — vesicles caused by obstruction of sweat gland ducts.

Mimetic — imitative.

Miscible — capable of being mixed.

Mitochondrion — a self-reproducing organelle that provides energy for eukaryotic cells via oxidative phosphorylation (Section 8.5.3.10).

Mitogen — a protein substance derived from plants that is used in the laboratory to stimulate cells to divide.

Mitosis (mitotic) — in cell biology, the division of a eukaryotic somatic cell. The four (or five) sequential stages are prophase, (prometaphase), metaphase, anaphase, and telophase; the absence of mitosis is the interphase.

MNP — mononuclear phagocyte; see monocyte, macrophage, or lymphocyte.

MNT — see molecular nanotechnology.

Moiety — a portion of a molecular structure having some property of interest.

Molarity (M) — in chemistry, moles of solute per liter of solvent.

Mole — a number of instances of something (e.g. molecular objects) equal to ~6.023 x 10^{23} objects.

Molecular assembler — a general-purpose device for molecular manufacturing, able to guide chemical reactions by positioning individual molecules to atomic accuracy (e.g. mechanosynthesis) and to construct a wide range of useful and stable molecular structures according to precise specifications;[8-10,35] Section 2.4.2.

Molecular machine — a mechanical device that performs a useful function using components of nanometer scale and a well-defined molecular structure; may include both artificial nanomachines and naturally occurring devices found in biological systems.

Molecular machine system — a system of molecular machines.

Molecular manufacturing — manufacturing using molecular machinery, giving molecule-by-molecule control of products via positional chemical synthesis, to produce complex molecular structures manufactured to precise specifications (Chapter 2; ref. 35).

Molecular nanotechnology — thorough, inexpensive control of the structure of matter based on molecule-by-molecule control of products and byproducts; the products and processes of molecular manufacturing, including molecular machinery; a technology based on the ability to build structures to complex, atomic specifications by mechanosynthesis or other means; most broadly, the engineering of all complex mechanical systems constructed from the molecular level.

Molecular sorting rotor — a class of nanomechanical device capable of selectively binding (or releasing) molecules from (or to) solution, and of transporting these bound molecules against significant concentration gradients (Section 3.4.2).

Monoclinic (crystal) — pertaining to crystals in which the vertical axis is inclined to one lateral axis but at right angles to the other.

Monoclonal antibody — antibodies derived from hybridoma cells; antibodies of exceptional purity and specificity.

Monocyte — a mononuclear phagocytic white blood cell derived from the myeloid stem cells, that is short-lived (~1 day half-life) and circulates in the bloodstream from which it moves into tissues, at which point it matures into a macrophage (which is long-lived). Monocytes represent 3%-8% of all white blood cells.

Monokine — chemical mediator released by monocytes and macrophages during the immune response; affects growth and activity of other WBCs.

Monomer — any molecule that can be bound to similar molecules to form a polymer.

Mononucleosis — presence of an abnormally high number of mononuclear leukocytes in the blood.

Monosaccharide — a simple sugar that cannot be decomposed by hydrolysis (e.g., fructose, galactose, glucose).

Morphogen — a (biochemical) factor that induces development of particular cell types in a manner that depends on its concentration.

Motile — capable of voluntary movement. Opposite of sessile.

MPS — mononuclear phagocyte system; see reticuloendothelial system (RES).

MRI — magnetic resonance imaging.

mRNA — see messenger RNA.

MSAD-C60 — chemical abbreviation for p,p'-bis(2-aminoethyl)-diphenyl-bis(monosuccinimide)-C_{60}.[734]

MSDS — Material Safety Data Sheet (OSHA).

MSU — monosodium urate.

MSUM — monosodium urate monohydrate.

Mucoadhesivity — ability to adhere to mucous membranes.

Mucociliary escalator — a cilia-driven mucus flow from alveoli to trachea, carrying mucus-trapped micron-size particles toward the esophagus where this mucus can be swallowed, thus eliminating the trapped (inhaled) particles from the body.

Mucopolysaccharide — polysaccharides containing hexosamine and sometimes proteins that form chemical bonds with water, making a thick gelatinous substance found in many places in the body.

Mucosa — a mucous membrane; the moist tissue layer that lines a hollow organ or body cavity.

Mucosacompatibility — biocompatibility with mucosal tissues.

Mural — pertaining to a wall of an organ or part.

Murine — related to or derived from mouse.

Muscarine(ic) — a toxin with neurologic effects, isolated from mushrooms; an agent that stimulates the postganglionic parasympathetic receptor.

Muscular dystrophy — wasting away and atrophy of muscles.

Mutagenesis — induction of a permanent (inheritable) genetic change.[234]

Mycotoxins — substances (produced by mold growing in food) causing illness or death when ingested by man or animals.

Myelin (myelinated) — a fatlike substance forming a sheath around the axons of certain nerves; composed of lipids and protein.

Myeloblast — immature bone marrow cell that develops into myelocyte, later maturing to a promyelocyte and eventually the granular leukocyte.

Myeloproliferative — concerning proliferation of bone marrow either in the bone marrow or extramedullary.

Myoblast — an embryonic cell that develops into muscle fiber cell.

Myocardial infarction — condition caused by partial or complete occlusion of one or more of the coronary arteries.

Myocardium — heart muscle.

Myocyte — a muscular tissue cell.

Myoma — a tumor containing muscle tissue.

Myopia — nearsightedness.

Myosin — a protein consisting of long chains of polypeptides joined to each other by side chains, present in muscle fibrils and constituting two-thirds of total muscle protein.

NADH — reduced form of NAD (nicotinamide adenine dinucleotide).

Nanoaggregate — in medical nanorobotics, a cluster of mutually attached nanodevices.

Nanocannula — in medical nanorobotics, a nanorobotic cannulation device.

Nanocrit (Nct) — in medical nanorobotics, volume-fraction in body fluid or bloodstream concentration of medical nanorobots, expressed as a percentage.

Nanoid shock — in medical nanorobotics, nanorobot-induced shock (Section 15.2.6.4); shock induced by nanorobots bearing endotoxin-homologous chemical moieties on their exterior surfaces, or releasing such moieties free into the serum.

Nanomachine — functional machine systems on the scale of nanometers; an artificial mechanical device constructed with precise molecular order using nanometer-scale components; any molecular structure large and complex enough to function as a machine.

Nanomanipulator — a nanorobotic manipulator device.

Nanomechanical — pertaining to the mechanical characteristics of nanomachines.

Nanomedicine — (1) the comprehensive monitoring, control, construction, repair, defense, and improvement of all human biological systems, working from the molecular level, using engineered nanodevices and nanostructures; (2) the science and technology of diagnosing, treating, and preventing disease and traumatic injury, of relieving pain, and of preserving and improving human health, using molecular tools and molecular knowledge of the human body; (3) the employment of molecular machine systems to address medical problems, using molecular knowledge to maintain and improve human health at the molecular scale.

Nanometer — a billionth of a meter, roughly the diameter of 3-7 atoms.

Nanoorgans — organs comprised of nanocomponents; nanorobotic organs.

Nanophase — having nanoscale features or components.

Nanopyrexia — in medical nanorobotics, condition of abnormally high temperature induced by nanorobotic devices or activities (Section 15.2.7).

Nanorobotics — the study of nanorobots, micron-scale robotic devices constructed out of nanoscale components.

Nanosecretagoguery — triggered enzyme release by nanorobots or free nanoparts.

Nanosystem — a set of nanoscale components, characterized by precise molecular order, working together to serve a set of purposes; complex nanosystems can be of macroscopic size.

Nanotechnology — engineering and manufacturing at nanometer scales; any technology related to features of nanometer scale, including thin films, fine particles, chemical synthesis, advanced microlithography, and so forth, as well as complex mechanical systems constructed from the molecular level.

Nanotubes — hollow fullerene tubes, including but not limited to single- and multi-walled carbon nanotubes, with submicroscopic, often nanoscale, diameters and a wide range of continuous lengths.

Nasopharynx — in anatomy, the nasal passages, mouth, and upper throat.

Nauseogenic — eliciting nausea (Section 15.2.6.3).

Navicyte — in medical nanorobotics, a mobile, mass-storage (nanorobotic) device, similar to a communicyte, that may be used to establish a navigational network inside the human body (Section 8.3.3).

Nct — see nanocrit.

Necrosis (necrotic) — the death of areas of tissue or bone, surrounded by healthy parts.

Necrotaxis — cell movement toward necrotic cells or tissue.

Neointima — a new intimal layer.

Neoplastic — pertaining to, or of the nature of, new and abnormal tissue (i.e. neoplasm) formation and growth.

Nephritis — inflammation of the kidney.

Nephro- — pertaining to the kidney.

Nephrolithiasis — presence of calculi in the kidney.

Nephropathy — disease of the kidney.

Neural crest cells — a band of cells extending longitudinally along the neural tube of an embryo from which cells forming cranial, spinal, and autonomic ganglia arise.

Neuralgia — severe sharp pain along the course of a nerve.

Neurite — the axial cylinder process of a neuron; both axons and dendrites are neurites.

Neuroglial cells — the tissue that forms the interstitial or supporting elements (cells and fibers) of the nervous system.

Neuron — a nerve cell, the principal structural and functional unit of the nervous system.

Neuronal ceroid-lipofuscinosis (NCL) diseases — recessively inherited neurodegenerative disease involving a lysosomal storage defect of cerebral lipofuscins, caused by the selected death of cortical neurons and retinal degeneration; aka. Batten disease.

Neuropeptide — any of a variety of neurotransmitter peptides found in neural tissue (e.g. endorphins, enkephalins).

Neuropil — network of unmyelinated fibrils into which nerve processes of CNS divide.

Neutropenia — abnormally small number of neutrophils in the blood.

Neutrophil — the most common type of granulocytic white blood cell. Neutrophils are responsible for much of the body's protection against infection. Comprising ~60% of all white blood cells, neutrophils play the primary role in inflammation, easily recognizing foreign antigens and destroying them through phagocytosis. Neutrophils also may overreact to stimuli and become involved in tissue destruction, as in rheumatoid arthritis, myocardial reperfusion injury, respiratory distress syndrome, and ulcerative colitis.

NFPA — National Fire Protection Association.

Nidus — a focus of infection; a cluster or nestlike structure.

Niemann-Pick disease — hereditary disease; disturbance of sphingolipid metabolism characterized by hepatosplenomegaly, anemia, lymphadenopathy, and progressive mental and physical deterioration.

Nitrosylation –the covalent bonding of nitrogen-containing moieties to another molecule.

NK cells — natural killer cells (Section 15.2.3.1.1).

NO — nitric oxide.

Nociceptor — pain receptor (Section 7.4.6.1).

Nonthrombogenic (thromboresistant) — the characteristic of a material that leads to minimal thrombogenicity.[234]

Nuclease — any enzyme that facilitates hydrolysis of nuclein and nucleic acids.

Nucleation — growth of droplets, films, or calculi due to the presence of a small seed particle which facilitates coalescence of these materials.

Occlusion — the closure, or state of being closed, of a passage.

Oleophilic — in chemistry, having a strong affinity for oils rather than water; lipotropic; see also lipophilic.

Oligosaccharide — a compound made up of a small number of monosaccharide units.

Ongrowth — formation of tissue directly on the surface of an implant; does not imply adhesion.[234]

Oocyte — the early or primitive ovum (the female reproductive cell).

Oppenheimer effect — increased neoplasm incidence rates observed in rodents that are implanted with agents (not previously thought to be carcinogenic) in solid form rather than injected or fed in soluble or dispersed form; aka. foreign body carcinogenesis or solid-state carcinogenesis.

Opsonins — biochemical substances that coat foreign antigens, making those antigens more susceptible to recognition by macrophages and other leukocytes and thus increasing phagocytosis of the organism or object displaying those foreign antigens. The two main opsonins in human blood are complement and antibodies.

Opsonization — the coating action of opsonins, thus facilitating phagocytosis. Coating of bacteria or biomaterial surfaces with native proteins, such as complement factors, rendering them detectable as "foreign" by phagocytic cells.[234]

OR — operating room.

Orbital cavity — bony pyramid-shaped cavity of the skull that contains and protects the eyeball.

Organelle — most commonly described subcellular compartment, located in the cytoplasm, that is surrounded by a membrane (e.g. lysosome, mitochondrion).

Orthodontic — pertaining to the division of dentistry dealing with prevention and correction of abnormally positioned or aligned teeth.

Orthopedic — pertaining to the branch of medicine dealing with correction of disorders involving locomotor structures of the body (skeleton, joints, muscles, ligaments, cartilage, etc.).

Orthosis — a device applied externally to the body to provide stability and to control motion; may or may not replace a portion of a limb.[234] See also exoprosthesis.

Orthostatic — pertaining to an erect position of the body.

Orthotopic — graft of an organ to a site where that organ would normally be present; in the correct place.

OSHA — Occupational Safety and Health Administration (U.S.).

Osmotic pressure — the pressure that would develop if a solution is enclosed in a solvent-permeable membrane that is impermeable to all solutes present, and is then surrounded by pure solvent.

Osseocompatibility — biocompatibility with bone.

Osseointegration (osteointegration) — clinical stability of an implant anchored in bone, often in reference to implants with bioactive coatings; a description of the clinical performance of devices, not the biomaterial-bone interaction.[234]

Osseous (also **osteo-**) — pertaining to bone.

Ossicle (ossicular) — any small bone, especially one of the three bones of the ear.

Osteoblast — a bone-forming cell derived from mesenchyme to form the osseous matrix in which it becomes enclosed as an osteocyte.

Osteoclast — a giant multinuclear cell with abundant acidophilic cytoplasm, formed in the bone marrow of growing bones, which functions to absorb and remove unwanted osseous tissue.

Osteoconductive — property of a biomaterial that encourages bone, already being formed, to lie closely to or adhere to its surface.[234]

Osteocyte — a mesodermal bone-forming cell that has become entrapped within the bone matrix, helping to maintain bone as living tissue.

Osteodystrophy — defective bone development.

Osteogenic — property of a biomaterial that stimulates bone growth in the implant site.[234]

Osteolysis ("small-particle disease") — cellularly-mediated bone loss secondary to debris production or release by implants in or near to bone, previously incorrectly called "cement disease".[234]

Osteomalacic — concerning or characterized by softening of the bone.

Osteopontin — a calcium-binding phosphoprotein synthesized by pre-osteoblasts, osteoblasts and osteocytes that is important in bone remodeling and various immunological functions, and is believed to play a role in several different cellular processes; a protein found in healing wounds.

Osteoporosis — any disease process that results in the mass of bone per unit of volume.

Osteotomy — the operation for cutting through a bone.

Ostium (ostia) — small opening(s), especially one into a tubular organ.

Otosclerosis — chronic progressive deafness.

Outmessaging — in medical nanorobotics, conveyance of information from a transmitter located inside the human body, especially from working nanodevices, to the patient or to a recipient external to the human body (Section 7.4.6.1).

Pacemaker, artificial — an electrical device that can substitute for a defective natural pacemaker and control the beating of the heart by a series of rhythmic electrical discharges.

Palpebral — pertaining to an eyelid.

PAM — pulmonary alveolar macrophage.

Pancreatic islet cells — clusters of cells in the pancreas (islets of Langerhans); destruction or impairment may result in diabetes or hypoglycemia.

Pannus — newly formed superficial vascular tissue over the cornea.

Parasitophorous — containing a parasite.

Paratope — the site on an antibody to which an antigen attaches.

Parenchyma — the essential parts of an organ that are concerned with its function as opposed to its framework; opposite of stroma. The distinguishing or specific cells of a gland or organ, contained within and supported by the connective tissue framework.

Parenteral — denoting any medication route other than the alimentary canal, such as intravenous, subcutaneous, intramuscular, or mucosal.

Paresthesia — sensation of numbness, prickling, or tingling.

Parietal — pertaining to, or forming, the walls of a cavity; often specifically refers to the parietal bone, one of two bones that together form the roof and sides of the skull.

Parkinson's disease — chronic nervous disease characterized by a fine, slowly spreading tremor, muscular weakness and rigidity, and a peculiar gait.

Passivation — the covalent bonding of a layer of atoms to a surface, in order to neutralize (occupy) any dangling surface bonds, thus chemically stabilizing the surface.

Patch clamp — method of measuring ion currents in individual cells.

Patella — lens-shaped sesamoid bone situated in front of the knee in the tendon of the quadriceps femoris muscle.

Patency — the state of being freely open.

Pathogen — a microorganism or agent capable of producing disease.

Pathogenic — productive of disease.

Pathognomonic — characteristic or indicative of a disease; relating to one or more of the typical symptoms of a disease.

Pathological — diseased or due to a disease; more informally, pertaining to an adverse condition.

Pathophysiology(ic) — study of how normal physiological processes are altered by disease.

Patocytosis — a unique macrophage endocytotic pathway in which external particles induce and enter a labyrinth of internal membrane-bound compartments that remain connected to the phagocytic cell surface.

PCV — postcapillary venules.

PDMS — Polydimethylsiloxane elastomer.

PEG — polyethylene glycol.

Pegylated — containing a surface coating of PEG.

PEI — polyethylenimine.

PEO — polyethylene oxide.

Peptide — a short chain of amino acids joined by amide bonds, up to 100 residues in length.

Percussion (percussive) — hitting or impact of one body against another, and the resulting shock, vibration or sound.

Percutaneous device — a medical device that passes through the skin, remaining in position for a significant length of time.[234]

Perianal — near the anus.

Pericardium — the double membranous fibroserous sac enclosing the heart and the origins of the great blood vessels.

Pericyte — a flat, undifferentiated, contractile connective tissue cell around the capillary walls.

Peri-implant — near the implant.

Perinuclear — near the cell nucleus.

Perineurally — near a neuron.

Periodontal — located around a tooth.

Peripartum — near or around the time of birth.

Periportal — near the portal end.

Perirobotic — near or around a robot.

Peristalsis — a progressive wavelike movement that occurs involuntarily in hollow tubes of the body, especially the alimentary canal; it is characteristic of tubes possessing longitudinal and circular layers of smooth muscle fibers.

Peristaltogenesis — eliciting peristalsis.

Peritoneum — in anatomy, the serous membrane reflected over the viscera and lining the abdominal cavity.

Peritonitis — inflammation of the peritoneum, the membranous coat lining the abdominal cavity and investing the viscera.

Peritrichous — indicating microorganisms that have cilia or flagella covering the entire surface.

Periurethral — in anatomy, located near or around the urethra (which discharges urine).

Permucosal device — a medical device that passes through a mucosal layer, remaining in position for a significant length of time.[234]

Peroperative — during or through an operation.

Peroxisome (peroxisomal) — in cell biology, an organelle found in vertebrate animal cells that contains a great number and variety of enzymes important in cell metabolism (Section 8.5.3.9).

Pertussis — an acute, infectious disease characterized by a catarrhal stage, followed by a peculiar paroxysmal cough, ending in a whooping inspiration.

Peyer's patches — an aggregation of lymph nodules found chiefly in the ileum near its junction with the colon.

pH — potential of hydrogen; measure of the degree of alkalinity or acidity.

Phage — see bacteriophage.

Phagocyte — a cell with the ability to ingest and destroy particulate substances such as bacteria, protozoa, cells and cell debris, dust particles, and colloids (Section 15.4.3.1).

Phagocytocide — killing phagocytes.

Phagocytosis — ingestion and digestion of bacteria and particles by phagocytes. The process of internalizing small particles by mammalian cells.[234]

Phagocytosis, frustrated — the failure of mammalian cells to phagocytose particles due primarily to their size, resulting in release of cytokines.[234]

Phagolysosome — the body formed when the membrane-bound phagosome inside a macrophage fuses with a lysosome.

Phagosome — a membrane-bound vacuole inside a phagocyte that contains material waiting to be digested.

Phalanx — any one of the bones of the fingers or toes.

Pharmacokinetics — study of the metabolism of drugs with particular emphasis on the time required for absorption, duration of action, distribution in the body, and method of excretion. See also ADME.

Pharmacyte — in medical nanorobotics, a theorized (nanorobotic) device capable of delivering precise doses of biologically active chemicals to individually-addressed human body tissue cells (e.g. cell-by-cell drug delivery) (Section 10.4.1.4, Chapter 19).

Pharynx (pharyngeal) — the passageway for air from the nasal cavity to the larynx (also acting as a resonating cavity), and for food from the mouth to the esophagus; more specifically, a musculomembranous tube extending from the base of the skull to the level of the 6th cervical vertebra, where the tube becomes continuous with the esophagus.

Phenotype — the appearance or other characteristics of an organism, resulting from the interaction of its genetic constitution with the environment; any observable characteristic that expresses the genotype of an individual.

Phlebitis — inflammation of a vein.

Phlogistic — pertaining to, or inducing, inflammation.

Phospholipid — a lipoid substance containing phosphorus and fatty acids; major component of cell plasma membrane.

Phosphorylation — the combining of a phosphate with an organic compound.

Photic — pertaining to visible light.

Photopheresis — extracorporeal photochemotherapy (ECP),[5929] a novel immunomodulatory therapy based on pheresis of light-sensitive cells.

Phytotoxic — pertaining to a poisonous plant.

Pial — concerning the pia mater membrane investing the brain and spinal cord.

Pica — an eating disorder manifested by a craving to ingest any material not fit for food, including starch, clay, ashes, toy balloons, crayons, cotton, grass, cigarette butts, soap, twigs, wood, paper, metal, or plaster. This condition is seen in pregnancy, chlorosis, hysteria, helminthiasis, certain psychoses, and may be associated with iron deficiency anemia.

Pili (fibriae) — hairs or filamentous appendages.

Pinealocytes — the principal cell of the pineal body (a glandlike structure in the brain).

Pinocytosis — the process by which cells absorb or ingest nutrients and fluid, in which minute incuppings or invaginations are first formed in the surface of the plasma membrane and then close to form fluid-filled vesicles; resembles phagocytosis.

PLA — polylactic acid.

Planktonic cells — individual free-floating cells, especially microorganisms, released from a biofilm.

Plasma — in anatomy, the fluid (noncellular) part of the lymph and of the blood, usually distinguished from the serum obtained after coagulation; in cell biology, the part of the protoplasm (cell substance) outside of the nucleus.

Plasma cell (plasmacyte) — cell found in connective tissue, having an eccentrically placed round nucleus filled with a chromatin mass.

Plasmalemmal — pertaining to the cell plasma membrane.

Plasma membrane — the outermost membrane of a cell, with cell contents on one side and the extracellular environment on the other side; the continuous membrane defining the boundary of every cell (Section 8.5.3.2).

Plasmapheresis — see apheresis.

Plasmatic layer/zone — a cell-free zone near the vascular luminal wall that forms a thin lubrication layer (Section 9.4.2.6).

Plasmid — an autonomous self-replicating extrachromosomal circular DNA molecule present intracellularly and symbiotically in most bacteria, encoding a protein product that confers drug resistance or some other advantageous phenotype. Plasmids reproduce inside the bacterial cell but are not essential to its viability, and can influence a great number of bacterial functions.

Plasmin — fibrinolytic enzyme derived from its precursor plasminogen.

Plasminogen — protein found in many tissues and body fluids, important in preventing fibrin clot formation.

Plastizymes — plastic polymer enzyme mimics.

Platelet — a round or ovoid 2-4 micron disk found in the blood of vertebrates; platelets play an important role in blood coagulation and hemostasis.

Plectin — a cytoskeleton associated protein.

Pledgets — small, flat compress, usually of gauze or absorbent cotton, used to absorb or apply fluid, to protect, or to exclude air.

Pleocytosis — increased number of lymphocytes in the cerebrospinal fluid.

Pleura — serous membrane that enfolds both lungs and is reflected upon the walls of the thorax and diaphragm; membrane is moistened with a serous secretion that reduces friction during respiratory movements.

PLG — poly lactide co-glycolide.

Ploidy — the number of chromosome sets in a cell.

PMMA — polymethylmethacrylate.

PMN — polymorphonuclear leukocyte; see granulocyte.

Pneumoconiosis — a pathological condition of the respiratory tract due to inhalation of dust particles.

Pneumothorax — a collection of air or gas in the pleural cavity.

Poiseuille fluid flow — laminar flow in a pipe (Section 9.2.5).

Polarization — in biology and electrical physics, the development of differences in electrical potential between two points on an object, such as between the inside and outside of a cell wall or along the length of a piezoelectric bone subjected to shear stress.

Polyanion — molecule containing multiple anions. See also anion.

Polycation — molecule containing multiple cations. See also cation.

Polycythemia — an excess of red blood cells.

Polymer — a long molecular chain of well-defined linked subunits.

Polymorphonuclear leukocyte — see granulocyte.

Polysaccharide — complex carbohydrates of high molecular weight; one of a group of carbohydrates that upon hydrolysis yields more than two molecules of simple sugars.

Polystyrene — a synthetic resin produced by the polymerization of styrene from ethylene and benzene.

Porcine — related to or derived from pig.

Porins — channel proteins which establish a pore in a cell plasma membrane, allowing cytosolic molecules to pass out of the cell.

Posterior — the backside of the human body; the backside of something.

Postmortem — after death.

Postpartum — after childbirth.

Postprandial — after a meal.

Postrema, area — a circumventricular organ located in the medulla of the brain.

Presentation semaphore — in medical nanorobotics, a mechanical device used to display specific antigens, chemical ligands, or other molecular objects to the external environment, with the purpose of selectively modifying the chemical or other surface characteristics of a nanorobot exterior (Section 5.3.6).

Prionosis — pathological protein folding conformations.

Prokaryote (prokaryotic) — in microbiology, an organism or cell that lacks a nucleus.

Prolate spheroid — football-shaped.

Prostaglandins — large group of biologically active unsaturated fatty acids that represent some of the metabolites of arachidonic acid, and act as local intercellular or intracellular modulators of biochemical activity.

Prosthesis — replacement of missing part with an artificial substitute, such as an artificial extremity; an artificial organ or part; device to augment performance of a natural function. See also endoprosthesis, exoprosthesis; compare orthosis.

Protease — a class of enzymes that break down, or hydrolyze, the peptide bonds that join the amino acids in a protein.

Protein — a long chain of amino acids joined by amide bonds, exceeding 100 residues in length; shorter chains are peptides. More generally, living cells contain many molecules that consist of amino acid polymers folded to form more-or-less definite three-dimensional structures, termed proteins. Short polymers lacking definite three-dimensional structures are termed peptides. Many proteins incorporate structures other than amino acids, either as covalently attached side chains or as bound ligands. Molecular objects made of protein form much of the molecular machinery of living cells.

Proteoglycans — the predominant, non-collagenous component of cartilage matrix; large molecules with a central protein core and attached polysaccharide molecules extending from the core like bottle brush bristles; aka. acid mucopolysaccharide.

Proteolysis (proteolytic) — hydrolysis (breakdown) of proteins, usually by enzyme action, into simpler substances.

Proteophilic — tending to attract proteins.

Proteophobic — tending to repel proteins.

Protozoa — the simplest animals, mostly unicellular although some are colonial. Compare metazoa.

Proximal — near the source or point of attachment or origin; in the extremities, closer to the trunk.

Pruritus (pruritic) — itching.

Pseudointima — tissue consisting of a firm fibrin clot with occasional islands of endothelial cells, formed by the resolution of inflammation on interior (blood-contacting) surfaces of cardiovascular implants.[234]

Pseudoneointima — pseudointima in which cells form a continuous layer.[234]

Pseudopod — in microbiology, a temporary protruding protoplasmic process in protozoa for the purpose of taking up food and aiding in locomotion.

Psychogenic — of mental origin.

Psychosomatic — pertaining to the influence of the mind or of higher functions of the brain upon the functions of the body, especially in relation to bodily disorders or disease.

PTFE — polytetrafluoroethylene (a form of Teflon).

Pulmonary — pertaining to the lungs.

Purkinje neurons — large neurons that have dendrites extending to the molecular layer of the cerebellar cortex and into the white matter of the cerebellum.

PVC — polyvinyl chloride.

Pyoinflammatory disease — inflammation involving pus formation.

Pyrexia — fever.

Pyrogen — a substance producing fever in vivo.

Pyrolysis — decomposition of organic matter when there is a rise in temperature.

Pyrolytic carbon — carbon formed in a fluidized bed by the pyrolysis of a gaseous hydrocarbon such as methane, depositing carbon onto a preformed substrate such as polycrystalline graphite at 1000-1500 K (Section 15.3.3.2).

Pyropoikilocytosis — a severe form of congenital hemolytic anemia clinically similar to, and now considered a subtype of, homozygous hereditary elliptocytosis. The disorder produces a molecular defect in spectrin and a partial spectrin deficiency, manifesting as a severe hemolytic anemia with thermal instability of the red cells.

Pyuria — pus in the urine.

Quantum dots — nanocrystalline semiconductor particles used for testing and diagnosis (Section 15.3.6.3); a zero-dimensional quantum system.

Quantum yield — The number of defined events which occur per photon absorbed by the system.

Radical — in chemistry, a group of atoms acting as a single unit, passing without change from one compound to another, but unable to exist in a free state.

Radioimmunoassay — a very sensitive method for determining the concentration of substances, particularly the protein-bound hormones, in blood plasma.

Ramus — a branch; one of the divisions of a forked structure.

RBC — red blood cell (erythrocyte).

Receptor — most generally, a structure that can capture a molecule (often of a specific type in a specific orientation) owing to complementary surface shapes, charge distributions, and so forth, without forming a covalent bond. In biology, a receptor is a transmembrane protein, located in the plasma membrane, that binds a ligand in a domain on the extracellular side, and as a result has a change in activity of the cytoplasmic domain of the protein.

Red blood cell (RBC) — see erythrocyte.

Reference material — a material that, by standard test, has been determined to elicit a reproducible, quantifiable host or material response.[234]

Reflex sympathetic dystrophy (RSD) — a neurovascular complication of CVA (cerebrovascular accident) characterized by severe shoulder pain and stiffness, swelling and pain in the hand.

Renal — pertaining to the kidney.

Replant biomaterials — see biomaterials, replant.

RES — see reticuloendothelial system.

Resection — the partial excision of a bone or other structure.

Resolution (of inflammation) — the stable end state of the inflammation or inflammatory response associated with an implant.[234]

Resorbable (resorption) — the ability of a biomaterial to be dissolved or digested, and thus disappear after implantation; does not imply specific action of cells or tissues.[234] See also bioresorbable.

Respirocyte — in medical nanorobotics, a theorized bloodborne spherical 1-micron (nanorobotic) device having a 1000-atm pressure vessel with active pumping powered by endogenous serum glucose, that serves as a mechanical artificial red blood cell[1400] (Chapter 22).

Response, immune — see immune response.

Response, inflammatory — see inflammatory response.

Restenosis — the recurrence of a stenosis condition, e.g., in a heart valve or blood vessel.

Reticulation — the formation of a network mass.

Reticulocyte — a red blood cell containing a network of granules or filaments representing an immature stage in development.

Reticuloendothelial system (RES) — in anatomy, the network of fixed and mobile phagocytes that engulf (and dispose of) foreign antigens and cell debris found inside the human body. The reticuloendothelium is the tissue of the reticuloendothelial system (RES); the system of mononuclear phagocytes located in the reticular connective tissue of the body that is responsible for the phagocytosis of damaged or old cells, cellular debris, foreign substances, and pathogens, removing them from the circulation (Section 15.4.3.1).

Retrograde — moving backward.

Reynolds number — the ratio of inertial to viscous forces in fluid flow. Macroscopic objects and flows typically experience Reynolds numbers >> 1, where mass and inertia dominate object motions; microscopic and especially nanoscale objects and flows typically experience Reynolds numbers << 1, where the viscosity of the environment dominates object motions (Section 9.4.2.1).

rf — radio frequency.

RGD — the peptide fragment arginine-glycine-aspartic acid.

Rhegmatogenous — originating or due to a rhegma (rupture, fracture, or rent).

Rheology (rheological) — study of the deformation and flow properties of materials, especially fluids, such as blood.

Rheumatoid arthritis — form of arthritis with inflammation of the joints, stiffness, swelling, cartilaginous hypertrophy, and pain.

Rhinitis — inflammation of the nasal mucosa.

Ribonucleic acid (RNA) — the ribonucleotide polymer into which DNA is transcribed.

Ribosome — a naturally occurring molecular machine that manufactures proteins according to instructions derived from the cell's genes; a cytoplasmic ribonucleoprotein complex that serves as the site of translation in the cell. Each ribosome has a large and a small subunit, 60S and 40S in eukaryotes. These subunits dissociate and reassociate in a cycle related to their functions, during translation.

Ribotoxic — toxic to ribosomes.

RNA — see ribonucleic acid.

RNA polymerase — an enzyme that synthesizes RNA under direction from a DNA template (formally described as DNA-dependent RNA polymerase).

Robot — a programmable device usually consisting of mechanisms for sensing and mechanical manipulation, often connected to (or including) a computer that provides control.

Rosai-Dorfman disease — sinus histiocytosis with massive lymphadenopathy; commonly presents as massive, painless, bilateral lymph node enlargement in the neck, with fevers.

Rouleaux — stack-of-coins configuration of a cluster of red blood cells.

Rubor — local tissue reddening, one of the four classic signs of inflammation (Section 15.2.4); see also calor, dolor, tumor.

Ruffini endings — encapsulated sensory nerve endings found in subcutaneous tissue.

Rugosity — condition of being folded or wrinkled; surface roughness.

Ruminant — an animal that regurgitates food in order to chew it again.

Russell bodies — small spherical hyaline bodies in cancerous and simple inflammatory growths.

Sacrum — triangular bone made up of five fused vertebrae just above the coccyx.

Sagittal — in anatomy, a vertical plane or section that divides the body into right and left portions.

Saltatory — hopping or leaping.

Saphenous veins — two superficial veins passing up the leg (Figure 8.2).

Sarcoma — cancer arising from connective tissue such as muscle or bone.

Sarcolemma — a delicate membrane surrounding each striated muscle fiber.

Schistocyte (schistocytic) — an irregularly contracted fragmented red cell (Section 15.5.5.1.1).

Schistosomiasis — a parasitic disease due to infestation with blood flukes (schistosomes); endemic throughout Asia, Africa, and tropical America.

Schizont — stage in asexual phase of life cycle of *Plasmodium* organisms found in red blood cells.

Schlemm's canal — irregular space or spaces in the scerocorneal region of the eye, that receives the aqueous humor from the anterior chamber of the eye.

Schwann's cells — cells of ectodermal (outer cell layer of developing embryo) origin that comprise neurilemma (a thin membranous sheath enveloping a nerve fiber).

Scission — dividing, cutting, splitting, or pinching off.

Sclera (eye) — tough white fibrous tissue covering the white of the eye, extending from the optic nerve to the cornea.

Sclerosis (sclerotic) — hardening of a tissue or organ, especially due to excessive growth of fibrous tissue; also, thickening and hardening of the tissue layers comprising the walls of an artery.

SDS — sodium dodecyl sulfate, an anionic detergent commonly used to solubilize proteins.

Secretagogue — agent that induces secretion.

Selectins — a family of ~50 kilodalton cell adhesion receptor glycoprotein molecules that can recognize diverse cell-surface antigen carbohydrates and help localize leukocytes to regions of inflammation (leukocyte trafficking). Selectins are not attached to the cytoskeleton.

SEM — scanning electron microscope.

Semaphores — see presentation semaphores.

Sepsis — the presence of various pus-forming and other pathogenic organisms, or their toxins, in the blood or tissues.

Septic — pertaining to or caused by sepsis.

Septic shock — signs of acute septicemia combined with hypotension and signs of inadequate organ perfusion (Section 15.2.6.4).

Septicemia — septic fever; systemic disease caused by the multiplication of microorganisms in the circulating blood.

Septum, atrial — a wall between the atria of the heart.

Sequela — a condition following and resulting from a disease.

Sequestration — isolation and temporary storage in cells or tissues.

Sequestrum — a mineralized capsule; see incapsulation.

Serine — an amino acid present in many proteins.

Serotonin — a biochemical substance, 5-hydroxytryptamine (5-HT), that is present in platelets, gastrointestinal mucosa, mast cells, and in carcinoid tumors. Serotonin is a potent vasoconstrictor involved in neural mechanisms important in sleep and sensory perception.

Serotype — in microbiology, a microbe determined by the kinds and combinations of constituent antigens present in the cells.

Serous membrane — a membrane lining a serous cavity, specifically the pleural (lung), peritoneal (abdominal), and pericardial (heart) cavities.

Serum — the watery portion of the blood after coagulation; a fluid found when clotted blood is left standing long enough for the clot to shrink. More generally, any serous fluid, especially the fluid that moistens the surfaces of serous membranes.

Sessile — incapable of voluntary movement. Opposite of motile.

Shear stress, fluid — lateral force per unit area imposed by transversely-moving fluids that generate shear forces (Section 9.4.1.1).

Shock, anaphylactic — see anaphylaxis.

Shock, nanoid — see nanoid shock.

Shock lung — aka. acute respiratory distress syndrome (ARDS), a syndrome of severe respiratory failure associated with pulmonary infiltrates similar to infant hyaline membrane disease.

Sialolithiasis — presence of salivary calculi.

Sialyl — a glycoprotein moiety. Compare asialo-.

Singlet oxygen — an electronically-excited chemically-reactive form of oxygen.

Sinusoid — resembling a sinus (a cavity having a relatively narrow opening); a minute blood vessel found in such organs as the liver, spleen, adrenal glands, and bone marrow, that is slightly larger than a capillary and has a lining of reticuloendothelium.

SMC — smooth muscle cell.

Small-particle disease — see osteolysis.

Somatic — in general, relating to the body, as opposed to the mind or soul; corporeal.

Sonication — to bombard with high-energy acoustic waves, often for the purpose of fragmenting or destroying the sonicated object.

Sorboregulatory — in medical nanorobotics, active regulation of the adsorptive characteristics of the nanorobot surface, allowing in situ regulation of the selective binding characteristics of surfaces (Section 15.2.2.4). See also adhesioregulatory.

Sorting rotor — see molecular sorting rotor.

sp2/sp3 — in carbon solids, graphite-like (sp^2) or diamondlike (sp^3) bonding, respectively.

Spectrin — an actin-binding peripheral protein found in the erythrocyte membrane skeleton.

Spherocyte — an erythrocyte that assumes a spheroid shape.

Spindle — bundle of delicate fibrils that connect the two centrosomes; seen during mitosis.

Spirochete — any member of the order *Spirochaetales*.

Splanchnic — pertaining to the viscera.

Splanchnodynia — abdominal pain.

Splanchnomegaly — abnormal distension of the viscera.

Splenectomy — surgical removal of the spleen.

Splenic — pertaining to the spleen.

Splenofenestral motility — in medical nanorobotics, the ability to actively locomote through the fenestral slits in the spleen.

Splenomegaly — abnormal enlargement of the spleen.

SPM — scanning probe microscope (microscopy); suspended particulate matter (environmental health).

Spontaneous arterial dissection — a tear in the intima of the blood vessel, allowing blood to dissect the wall of the artery; occurs in the absence of external trauma.

Squamous cell — a flat, scaly epithelial cell.

Standard test — a well-defined, repeatable test (Section 15.2.1.5) of host response or material response, generally involving the use of one or more reference materials.[234]

Starch — noncrystalline carbohydrate of the polysaccharide group found in plants.

Stasis — stagnation of normal flow of fluids or of the intestinal mechanism; ceasing of activity.

Stellate — star-shaped.

Stem cells — a cell that gives rise to a specific type of cell as in hematopoiesis.

Stenosis (stenotic) — constriction or narrowing of a passage or orifice.

Stent — any material used to hold tissue in place or to provide a support for a graft during healing; a flexible metal coil or open-mesh tube surgically inserted into a narrowed artery.

Stercoral — pertaining to feces.

Stereocilia, cochlear — specialized mechanoreceptor cells of the inner ear.

Steric — pertaining to the spatial relationships among atoms in a molecular structure; in particular, pertaining to the space-filling properties of a molecule.

Steric hindrance (barrier) — in chemistry, slowing of the rate of a chemical reaction owing to the presence of molecular structures possessed by the reagents that mechanically interfere with the motions associated with the reaction, typically by obstructing the reaction site; in hematodynamics, the reduction in hematocrit near small blood vessel bifurcations due to the elongation and orientation of red cells along the direction of shear flow.

Sternum (sternal) — pertaining to the breastbone.

Sternutation — sneezing.

Sternutogenesis — producing sneezing (Section 15.2.6.2).

Steroids — a large family of chemical substances, comprising many hormones, vitamins, body constituents, and drugs, each containing the tetracyclic cyclopentophenanthrene skeleton.

STM — scanning tunneling microscope.

STOC — spontaneous transient outward currents.

Stoichiometric — in chemistry, pertaining to the precise quantities of reagents required to complete a chemical reaction; in particular, to the exact amounts needed to balance the chemical reaction equation.

Stroma — foundation-supporting tissues of an organ, defining the framework of an organ; opposite of parenchyma.

Subarachnoid space — space between the pia proper and arachnoid containing the CSF.

Subareolar — below the areola.

Subclavian — under the clavicle (collarbone).

Subcutaneous (subcutis) — beneath, or to be introduced beneath, the skin.

Sublimation — in chemistry, passing directly from solid to vapor state.

Submasseteric — lying underneath the masseter (the muscle that closes the mouth and the principal muscle in mastication).

Subperiosteal — beneath the periosteum (fibrous membrane covering bone).

Sulcus — furrow, groove, fissure, or slight depression.

Superior — upper or higher than; situated above something else

Supine — lying on the back, with the face up.

Surfactant — in physical chemistry, a chemical agent that lowers surface tension.

Swine — pertaining to pigs.

Sympathomimetic — adrenergic.

Synapse (synaptic) — the point of junction between two neurons in a neural pathway, where the termination of the axon of one neuron comes into close proximity with the cell body or dendrites of another neuron.

Syncope — transient loss of consciousness due to inadequate blood flow to the brain.

Synechias — adhesions of parts, especially adhesion of iris to lens and cornea.

Synovial — pertaining to the capsule of a skeletal joint.

Synoviocyte — cells comprising the intima of synovial membrane (tissue lining the noncartilaginous surfaces of a synovial joint); cells are of two types, macrophage-like and fibroblast-like.

Systole (systolic) — the normal period in the heart cycle during which the muscle fibers tighten and shorten, the heart constricts, and the cavities empty of blood; roughly, the period of contraction alternating with diastole or relaxation. Occurs in the interval between the first and second heart sounds during which blood is surged through the aorta and pulmonary artery.

Tachyphylaxis — the rapid desensitization to a toxic substance produced by inoculation with a series of small doses, or a rapidly decreasing response to a drug following administration of the initial doses.

Tamponade, cardiac — pathological condition resulting from accumulation of excess fluid in the pericardium.

Tay-Sachs disease — inherited autosomal-recessive disease; neurological deterioration characterized by mental and physical retardation, blindness, spasticity, etc.

Teflon — a polymeric fluorocarbon (Section 15.3.4).

Teflonoma — large granuloma formed in reaction to Teflon.

Tegument — the skin or covering of a living body.

Telomere — the natural end of a chromosome; the telomeric DNA sequence consists of a simple repeating unit (in humans, TTAGGG) with a protruding single-stranded end that may fold into a hairpin.

TEM — transmission electron microscope.

Tendon — fibrous connective tissue serving for the attachment of muscles to bones and other parts.

Tensegrity — cell shape maintenance by a tensional integrity architecture that achieves mechanical stability because of the way compressive and tensional forces are distributed and balanced within the cell.

Terabot — a trillion (10^{12}) medical nanorobots, usually in reference to dosage.

Teratogenicity — producing abnormal development in an embryo.

Tetramer — polymer comprised of 4 units.

Thermal conductivity — transport of thermal energy due to a temperature gradient; the energy flux (W/m^2) per unit of spatial temperature gradient (K/m) equals the coefficient of thermal conductivity (W/m-K).

Thermocompatibility — the thermal biocompatibility of nanodevices or nanorobotic systems as they interact with the organs, tissues and cells of the human body (Chapter 15.3.8).

Thermogenic limit — in medical nanorobotics, the maximum amount of waste heat that may safely be released by a population of in vivo medical nanorobots that are operating within a given tissue volume (Section 6.5.2).

Thiol group — in chemistry, an -SH group, or a molecule containing such a group; also known as a sulfhydryl or mercapto group.

Thorax (thoracic) — that part of the body between the base of the neck superiorly and the diaphragm inferiorly.

Thrombocyte — platelet.

Thrombocytolysis — fragmentation of platelets.

Thrombocytopenia — reduced platelet count.

Thromboembolus — blocking of a blood vessel by a thrombus that has detached from its site of formation.

Thrombogenicity — the property of a material that induces or promotes the formation of a thrombus.[230]

Thrombogenicity (inherent) — thrombus formation controlled by the material surface;[5870] reaction-controlled thrombogenicity at the surface of a material.[234]

Thromboresistant — see nonthrombogenic.

Thrombosis — formation, development, or existence of a blood clot or thrombus within the vascular system.

Thrombotic thrombocytopenic purpura (TTP) — a rare disease characterized by embolism and thrombosis of small blood vessels.

Thrombus — a solid mass formed from the molecular and cellular constituents of blood;[234] a blood clot.

Thymocyte — a cell in the thymus that migrated there from the bone marrow, ultimately to become various types of T lymphocytes.

Tibia — the inner and larger bone of the leg between the knee and the ankle.

Tingible — capable of being stained by a dye.

Tissue engineering — elaboration of cells and tissues outside a living organism, intended for use as components of a viable biomaterial or replant, by use of engineering methods and techniques.[234]

Tissue response — see host response, local.

TLV — threshold limit value[6082] (OSHA).

T-lymphocytes (T-cells) — White blood cells that are produced in the bone marrow but later mature in the thymus. T-cells are important in the body's defense against certain bacteria and fungi, help B-cells make antibodies, and assist in the recognition and rejection of foreign tissues.

TNF — tumor necrosis factor.

Tolerogen — a material which can induce immunological tolerance or unresponsiveness.[2332]

Tophi — large crystalline deposits.

Toxic shock — a disease caused by the release of toxins produced by certain strains of various bacteria.

Trabecula — fibrous cord of connective tissue, serving as support, forming a septum extending into an organ from its wall or capsule.

Trachea(l) — a cylindrical cartilaginous tube extending from the larynx to the bronchial tubes.

Tracheobronchial — concerning the trachea and bronchus.

Transcription — synthesis of RNA on a DNA template.

Transcutaneous (percutaneous) — effected through the skin.

Transcytosis — passage through cellular membrane or tissue wall barriers.

Transendothelial — see diapedesis.

Transepithelial — crossing an epithelial layer.

Transferrin — a globulin in the blood that binds and transports iron.

Translation — in biochemistry, the synthesis of protein on the mRNA template; the process of reading the codon sequence in mRNA to synthesize the corresponding polypeptide with the involvement of ribosomes, tRNA, and many enzymes.

Translocation — movement across intestinal walls or into lung interstitium.

Transmigration — see diapedesis.

Transposon — a genetic unit such as a DNA sequence that is transferred from one cell's genetic material to another.

Trigeminal — pertaining to the trigeminus or fifth cranial nerve.

Trillion — this book follows the American convention in which a trillion is 10^{12}.

Trophozoite — a sporozoan nourished by its hosts during its growth stage.

Trypanosomiasis — any disease caused by trypanosomes (asexual protozoan flagellates parasitic in the blood plasma of many vertebrates).

Tuboplasty — plastic repair of any tube.

Tubulin — a protein present in the microtubules of cells, which are polymers of alpha tubulin (~53,000 dalton) and beta tubulin (~55,000 dalton) dimers.

Tumor (cancer) — spontaneous new growth of tissue forming an abnormal mass.

Tumor (inflammation) — local tissue swelling, one of the four classic signs of inflammation (Section 15.2.4); see also calor, dolor, rubor.

Tumorigenic — producing a tumor.

Turbulence — in hydrodynamics, fluid flow which does not follow parallel streamlines, which has a blunt (nonparabolic) profile in tube flow, and often involves eddies, vortices, and significant variations in fluid velocities, accelerations and shear stress between adjacent fluid elements. Turbulence dissipates more energy, and presents more resistance to flow, than laminar flow.

Turgor — distension, swelling.

TWA — time-weighted average[6083] (OSHA).

Tympanoplasty — surgical procedure to cure inflammatory process or restore function in the ear.

Ubiquitin — a small protein present in eukaryotic cells that combines with other proteins and makes those other proteins susceptible to destruction; this protein is also important in promoting the functions of proteins that make up the ribosomes.

Ulcer — an open sore or lesion of the skin or mucous membrane accompanied by sloughing of inflamed necrotic tissue.

Ulceration (ulcerative) — suppuration occurring on a free surface, as on the skin or a mucous membrane, to form an ulcer.

ULTI carbon — ultra-low-temperature isotropic carbon (Section 15.3.3.2).

Undifferentiated — alteration in cell character to a more embryonic type or toward a malignant state.

Urate — a salt of uric acid.

Uremia — toxic condition associated with renal insufficiency produced by retention in the blood of nitrogenous substances normally excreted by the kidney.

Urethra — a canal for the discharge of urine extending from the bladder to the outside of the body.

Urticaria — vascular reaction of the skin characterized by the eruption of pale evanescent wheals (round elevations of the skin, white in the center with a pale red periphery), which are associated with severe itching; hives.

UTP — uridine triphosphate; analog to ATP.

Uveitis — a nonspecific term for any intraocular inflammatory disorder, usually of the uveal tract structures (iris, ciliary body, and choroid, forming the pigmented layer) although nonuveal parts such as the retina and cornea may also be involved.

Vacuole — a clear space in cell protoplasm filled with fluid or air.

Vagus — the tenth cranial nerve.

Valsalva, sinuses of — three dilations in wall of the aorta behind the flaps of the three aortic semilunar valves.

Van der Waals forces — weak electrostatic forces between atoms and molecules; any of several intermolecular attractive forces not resulting from ionic charges; also known as the London dispersion force (Section 3.5.1).

Vasa vasorum — the microvasculature of the aorta.

Vascular — containing, or pertaining to, blood or lymph vessels.

Vascular gate — a vascular plug or selective gate spanning the lumen of a blood, lymph, or other fluid vessel, for the purpose of allowing only specified particulate matter to pass, or selectively filtering out other specified particular matter or fluids (Section 15.4.2.3; Chapter 19).

Vasculitis — inflammation of a blood or lymph vessel.

Vasculoid — in medical nanorobotics, an intimate personal appliance that conforms to the shape of existing blood vessels and augments the human vascular system, replacing blood with a single, complex robot that can duplicate all essential thermal and biochemical transport functions of the blood, including circulation of respiratory gases, glucose, hormones, cytokines, waste products, and all necessary cellular components; a member of a class of space- or volume-filling nanomedical augmentation devices whose function applies to the human vascular tree[4609] (Chapter 30).

Vasculomobility — in medical nanorobotics, capable of locomotion along, across, or through vascular walls.

Vasculopathy — any disease of blood vessels.

Vas deferens — the excretory duct of the testis.

Vasoconstriction — in physiology, a decrease in the diameter of blood vessels.

Vasodilation — in physiology, an increase in the diameter of blood vessels.

Vasorelaxation — lessening of vascular pressure.

Ventricle (ventricular) — either of two lower chambers of the heart.

Vermiformis — contoured like a worm.

Vermipodia — worm-like processes observed on cell surfaces in a few cases of malignant histiocytosis and a case of leukemic reticulum-cell sarcoma.[3469]

Vertigo — the sensation of moving around in space; sometimes used as a synonym for dizziness, lightheadedness, or giddiness.

Vesicles — small bodies bounded by membrane, derived by budding from one membrane and often able to fuse with another membrane.

Vesicles (endocytotic) — membranous particles that transport proteins through endocytosis; also known as clathrin-coated vesicles, having on their surfaces a layer of the protein clathrin.

Vesicles (exocytic) — membranous particles that transport and store proteins during exocytosis.

Vesicoureteric reflux — condition in which damage to internal kidney structures occurs from retrograde urine flow into the kidney; aka. reflux nephropathy, chronic atrophic pyelonephritis, ureteral reflux.

Vesicular — pertaining to or resembling vesicles.

Vesiculation (vesiculated) — formation of vesicles or state of having or forming them.

Viable biomaterials — see biomaterials, viable.

Vimentin — an intermediate filament cytoskeleton attachment protein.

Virion — a single physical virus particle.

Virucide — the destruction of active or dormant virus particles (Section 10.4).

Virus — A parasite (consisting primarily of genetic material enclosed in a protein capsid shell) that invades cells and takes over their molecular machinery in order to copy itself.

Viscera (visceral) — internal organs enclosed within a cavity, especially the abdominal organs.

Viscosity — resistance of a fluid to shearing, when the fluid is in motion (Section 9.4.1.1).

Vitreous carbon — a type of graphite formed by the decomposition of hydrocarbon gases on smooth surfaces (such as glazed porcelain) at temperatures above 650 °C (Section 15.3.3.1); aka. polymeric carbon, glassy carbon.

Vitreous humor — in anatomy, a delicate network enclosing in its meshes a clear watery fluid filling the interior of the eyeball behind the lens.

Volumetric — pertaining to geometric volume of an object.

Volvulus — a twisting of the bowel upon itself, causing obstruction.

Vroman effect — the temporal succession of molecular species adherent to surfaces of implants;[234] named after its discoverer, Leo Vroman.

Waldenstrom's macroglobulinemia — excessive number of plasma cells, which are responsible for IgM globulin synthesis.

Warfarin — an anticoagulant drug.

WBC — white blood cell; see leukocyte.

White blood cell (WBC) — see leukocyte.

Whorl — spiral arrangement of cardiac muscular fibers.

Xenogeneic — derived from nonhuman tissues or cells

Young's modulus — in mechanical engineering, a modulus relating tensile (or compressive) stress to strain in a rod that is free to contract or expand transversely. The relevant measure of strain is the elongation divided by the initial length (see also strain and stress).

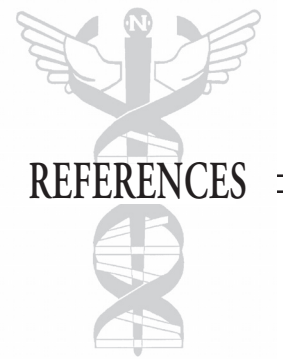
Zeiosis — the violent plasma membrane blebbing of a dying cell.

Zeta potential — the overall charge a particle acquires in a specific medium; the magnitude of the zeta potential gives an indication of the potential stability of a colloidal system of these particles.

Zonula occludens — tight junction between columnar epithelial cells.

Zymogenic — pertaining to a substance (a zymogen or proenzyme) that develops into an enzyme capable of producing or causing fermentation or digestion (e.g. pepsinogen, trypsinogen); a cell that produces zymogens (proenzymes).

Zymosan — An insoluble carbohydrate derived from yeast cell walls, used especially in the immunoassay of properdin (a serum protein that helps destroy bacteria and viruses).



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Nanomedicine
Volume IIA: Biocompatibility

"Compatibility" most broadly refers to the suitability of two distinct systems or classes of things to be mixed or taken together without unfavorable results. More specifically, the safety, effectiveness, and utility of medical nanorobotic devices will critically depend upon their biocompatibility with human organs, tissues, cells, and biochemical systems. Classical biocompatibility has often focused on the immunological and thrombogenic reactions of the body to foreign substances placed within it. In this Volume, we broaden the definition of nanomedical biocompatibility to include all of the mechanical, physiological, immunological, cytological, and biochemical responses of the human body to the introduction of medical nanodevices, whether "particulate" or "bulk" in form. That is, medical nanodevices may include large doses of independent micron-sized individual nanorobots, or alternatively may include macroscale nanoorgans (nanorobotic organs) assembled either as solid objects or built up from trillions of smaller artificial cells or docked nanorobots inside the body. We also discuss the effects on the nanorobot of being placed inside the human body.

"This Volume will be a seminal contribution not only to the nanotechnology literature, but to medicine in general."
— Lawrence Rosenberg, M.D., Ph.D., Professor of Surgery and Medicine, Director of the Division of Surgical Research, McGill University

"I believe this book will serve as an excellent reference for investigators with specific problems as well as a good overview of specific subject areas. I tend to focus on those sections dealing with investigating and demonstrating the safety of nanorobots, and to the development of a new drug delivery system or nanorobots used to monitor or repair biological systems. There are many issues to be concerned about in developing such devices and this book has touched on nearly every one of them. As with Volume I, this book is filled with useful references and raises many important issues to be considered in moving forward with the design and creation of nanorobots for medical purposes. I enjoyed reading it."
— Cecilia A. Haberzettl, Ph.D.; President, TechnoMed Strategic Partners, Inc.

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"Impressive body of work. The scope is amazing."
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"Freitas demonstrates his ability to temper the fantastic potential of nanorobotics with legitimate concerns about their safety. I concur with his conclusions with regards to the need for stringent investigation into the safety of diamondoid substances for use in nanomedicine."
— Michael Prater, M.D.

"...well written and thoroughly researched discussion of nanomaterials that can be potentially applied in nanorobot fabrication. The discussion of thermocompatibility is one of the very important parts of biocompatibility that very few people have studied."
— Bai Xu, Ph.D., Senior Research Scientist, NYS Center for Advanced Thin Film Technology

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Robert A. Freitas Jr.

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