Nanomedicine: The Future of Healthcare

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Learning Goals

This paper will introduce the reader to the concepts of miniaturization of mechanical devices that improve health which is termed "nanotechnology."

Learning Objectives

After reading this article the reader should be able to:

1. Define the term nanotechnology.
2. Describe three possible applications using the concepts of nanotechnology.
3. Describe an existing application of nanotechnology.
4. List possible negative consequences possible from use of nanotechnology devices.

Introduction: Future Scenarios

Case 1: Mr. Smith is an 80 year-old man who had his first heart attack at the age of 40. Since the day he received emergency treatment for that myocardial infarction, he has not had another anginal attack. He still recalls the day he arrived in the emergency room gasping for air, sweating and fearing for his life. A new breakthrough technology was available to cure Mr. Smith of his condition. Surgeons needed only to inject very small devices programmed to chew away at the atherosclerotic deposits, restoring the artery walls and linings back to their original state of health. Now Mr. Smith can spend quality time with his grandchildren without worrying about having another heart attack.

Case 2: Ms. Johnson goes to her doctor for a routine checkup. As part of the checkup, the doctor takes a look at her throat and asks her to gargle a solution and spit it into a cup. He analyzes the sample in his "cell analyzer" and a diagnosis appears on his computer screen within minutes. She has a malignant cancer of the throat. The doctor proceeds to further analyze the cells. In about twenty minutes, the computer screen tells him that they are all of one type that can be recognized and destroyed by tiny molecular machines primed to attack those particular type of cells. He has his "cell analyzer" produce some immune machines and tests them on the cell sample and, as expected, they worked marvelously. The doctor produces more and gives Ms. Johnson a throat spray for the cancerous cells in her throat and an injection for any cells that may have metastasized elsewhere. He advises her to check back in three weeks just to make sure that everything has cleared up.

Case 3: Little Joey is five years old and has AIDS that was contracted from his mother. Doctors have tried the AIDS drug cocktails, but the side effects were too much for him. He was too sick to enjoy the life of a little boy. A new treatment is finally available which consists of immune machines. These tiny submarine-like robots travel throughout the body searching for the HIV and destroying it. Joey drinks a pleasant tasting syrup and doctors monitor his progress. Within a few days, the little boy's viral load drops significantly to undetectable levels. He is now living his life as a healthy little boy playing with his friends at school. It is only a matter of time and subsequent treatments before these immune machines rid his body of all HIV.

The treatments in these scenarios all seem to come out of some science fiction novel where the heroic little robots enter your bloodstream to destroy evil viruses, bacteria and cancer cells (Figure 1).[1] It sounds futuristic and even farfetched, but a new technology has emerged that may make these treatments become reality. This technology is known as nanotechnology.

Small, small world

Nanotechnology has been defined as the 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.[1] Nanotechnology deals with objects in the nano-scale (nanometer = 10^{-9} meter or 1/1000 of a micron). To give a sense of how small things are, the following are some entities and their average sizes: a natural red blood cell is a

Table 1. Small World: The size of things

Component	Approximate Size
Atom Diameter (Carbon)	0.15 nm = 1.5 Ångström
Wavelength of X rays and electrons	1 nm
Diameter of DNA double strand	2 nm
Protein	10 nm
Wavelength of visible light	400 - 700 nm
Cell	1000 nm = 1 µm
Red blood cell	7 µm (width)

(adapted from Dr. Aristides Requicha, Director of Laboratory of Molecular Robotics at the University of Southern California)

7.82 micron by 2.58 micron biconcave disk and the diameter of a capillary ranges from 3.7 to 8 microns.[2] Table 1 shows a few more items along with their relative sizes. In order for a nanomachine to work within the body, it must be small enough to travel through the bloodstream in the smallest capillaries. The parts used to build the molecular machine are even smaller (Figure 2), composed of individual atoms.[3] This technology combines chemistry with engineering to build products at the molecular and atomic level. Macroscopic machines often use rotating shafts and gears to drive motion. Molecular machines can do the same and use parts in ways that abide by conventional engineering practice (Figure 3).

In a broad sense, the main belief of nanotechnology is that nearly any chemically stable structure can be built. It is a manufacturing technology that could give complete, inexpensive control of the structure of matter.[4] In other words, the process would assemble matter one atom at a time. Richard Feynman, who won a Nobel Prize in physics, first proposed this prospect in 1959. K. Eric Drexler further proposed how this technology works. He presents the concept of a universal assembler (Figure 4), a device that contains a submicroscopic robotic arm under the control of a computer.[5] This assembler can hold and position atoms or reactive compounds in a precise location, which should allow the construction of larger atomically precise objects.[4] So, what does this have to do with medicine? With the assembler, more specialized nanomachines can be built and used in proposed applications in the fields of gerontology, pharmaceutical research, disease diagnosis and immune system supplementation.[2] Once these nanomachines are built, the future of medicine may well be injecting a collection of nanorobots to cure disease and preserve health. Nanomedicine might abolish many known common diseases of the 21st century and alleviate much medical pain and suffering.[6] Until the first working nanorobot is manufactured, only theories and hopes can be shared. Table 2 shows a partial list of theoretical applications in medicine that have been proposed. Except in pharmaceutical research, none of these applications have reached the marketplace.

Researchers are already experimenting with nanotechnology. Molecular manipulation, a process of moving atoms one at a time in a precise manner using a scanning tunneling microscope (STM) or an atomic force microscope (AFM) like the one shown in Figure 5, has been taking place for a few years. Organizations from IBM and Lucent to the National Science Foundation and NASA are currently investigating the possibilities of nanotechnology.[7] New York University has developed a nano-machinery prototype using DNA.[8,9] An increasing portion of present, viable applications is focused specifically on molecular manipulation found in cells.[10] With such progress, the next step will be the first working assembler.

Medicine Today

For obvious reasons, medical practitioners today rely mainly on surgery and drugs to treat illnesses. Much has been accomplished in the field of medicine, such as surgical procedures to replace failing hearts and drugs that kill cancer cells. In surgery, the surgeon uses microscopes and fine instruments to reattach delicate blood vessels and nerve fibers. Yet this is about as small as it goes. Today's micro-surgeons have difficulty with finer tissues. The scalpels and sutures used in surgery today are simply too big for repairing capillaries, cells and molecules.[11] From a cell's perspective, modern surgery can seem quite barbaric. "[A] huge blade sweeps down, chopping blindly past and through the molecular machinery of a crowd of cells, slaughtering thousands....[later], a great obelisk plunges through the divided crowd, dragging a cable as wide as a freight train behind it to rope the crowd together again."[12]

Unlike surgery, drug therapy does deal with finer structures in cells. Drug molecules are simple molecular tools that affect specific molecules in cells. Most drugs bind to certain receptors on or inside cells to affect a cellular signal and elicit a desired response. Yet drugs work without direction. Once inside the body, they travel through the bloodstream randomly tumbling and bumping around until they come across a target molecule that fits.[13] Furthermore, binding to the target receptor in the wrong cell may give undesired side effects, as exemplified by chemotherapy-induced bone marrow suppression or emesis.

Surgery is about seeing what is wrong and planning an action to fix the problem. The obstacle is that surgeons utilize relatively crude tools that cannot repair tissue at the molecular level. Drugs already affect tissue at the molecular level, however, they are too simple to sense what is wrong and plan an action. This is where nanotechnology might come in to bring the best of both worlds. In the future, surgeons may be able to perform surgery at the molecular level and alter individual cells. Disease and bad health are largely due to molecular and cellular damage. Nanotechnology could yield the tools necessary for medicine to intervene in a sophisticated and controlled way at the cellular and molecular level.[3]

This does not mean that we will no longer have a need for drugs. Nanotechnology will not take over drugs, but may enhance them in preparation techniques as well as delivery.

Table 2. Possible Medical Applications

- Gerontological Applications[21]
- Pharmaceutical Research[14]
- Mechanically Reverse Atherosclerosis[3]
- Supplement the Immune System[3]
- Rewrite DNA Sequences in Vivo[12]
- Reverse Cellular Insults Caused by "Irreversible" Processes[22]
- Cryogenic Storage of Biological Tissues[24]
- More Durable, Rejection-Resistant Artificial Organs[21]
- Intracellular Sensors[27]

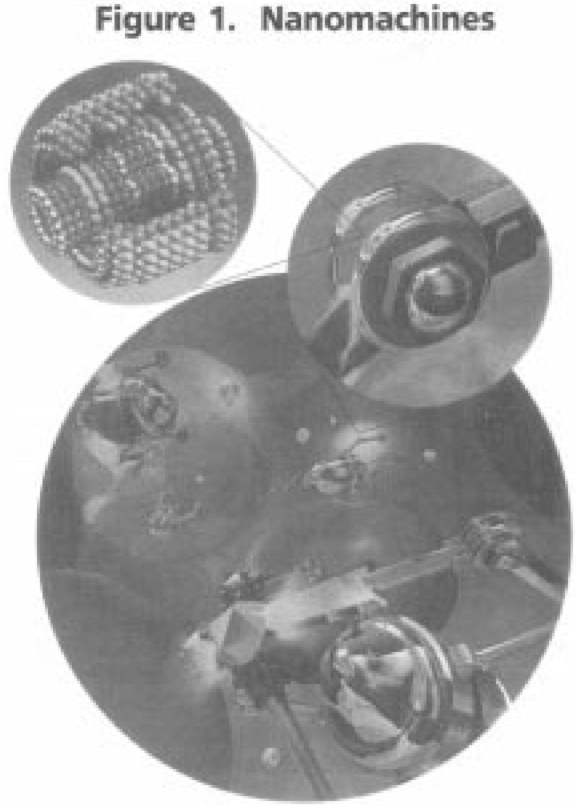
Today's drug preparation techniques could be improved to maximize yield and minimize unwanted chemical reactions that produce potentially toxic byproducts.[14] The results of drug synthesis depend on "the statistics of uncontrolled molecular collisions in solution involving all possible molecular degrees of freedom."[14] The chemist cannot directly control the molecules to make sure that only the desired final drug product is obtained. With nanotechnology, it is anticipated that there will be direct production of the desired drug molecule without any unwanted side reactions. The result could be 100% yield of desired drug achieved by precisely positioning and placing individual molecules in such a way as to catalyze the desired reaction.[14] Many promising chemicals never are developed for human use because their physical properties do not allow for easy manufacturing or the products are not well absorbed. For example, many drugs are not water-soluble, which makes them difficult to synthesize and the solubilization process may contribute to adverse effects. A technology called "Nanonization" has been developed to overcome this solubility problem.[15] This technique is discussed later.

The Body: A Collection of Molecules[16]

In order to understand what nanotechnology can do for the field of medicine, one must view the body from the molecular standpoint. From this perspective, the human body is a work yard, a construction site and battleground for molecular machines. The body already has its own complex systems of molecular machinery. These natural molecular machines work on a daily basis for the body. Whenever you eat, the molecular machines that we call digestive enzymes are released to break down complex food molecules. In the lungs, hemoglobin acts as molecular storage devices which gather oxygen. The process of the heart pumping blood loaded with oxygen and fuel to cells is driven by molecular fibers. Muscle contraction involves the sliding of molecular fibers. This is just a partial list of what the body's molecular machines accomplish every day. As a construction site, there is the growth, healing and renewal of tissue. Cells acquire building blocks from the bloodstream and build biological structures according to the molecular machinery programmed by the cell's genes. During an injury, the body knows to do such repairs as laying down bone and collagen, building new cells, renewing skin and healing wounds. The body is also a battlefield when it comes to being attacked by external entities such as bacteria, viruses and parasites. To confront this invasion, the body summons the army of molecular machines collectively known as the immune system.

The human body uses its own sophisticated system of molecular machines to preserve health, but sometimes failure occurs whether it is through damage or an inborn defect. Sometimes people are born with a missing or defective genetic code. For example, in muscular dystrophy the molecule dystrophin is missing which leads to gradual replacement of muscle with scar tissue and fat. Even without a defect or damage, some systems still fail. The immune system does not respond to all invaders and sometimes the response is inadequate. Then there are times when the immune system overreacts to attack cells that should be left alone. Examples include autoimmune diseases such as rheumatoid arthritis, lupus and rheumatic fever. The immune system, although a great system of molecular machinery, sometimes fails to distinguish between when and when not to attack.

Figure 1. Nanomachines



These nanorobots travel through the bloodstream in search of foreign invaders. The closest one has found a virus. The joint of one robot has been enlarged and that joint is enlarged to show a nanogear, a molecular part.

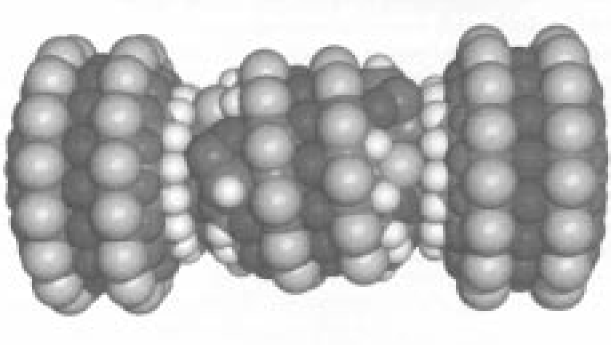
Reprinted with permission from Scientific American, The Institute of Molecular Manufacturing and James Gary.

Nanotechnology seeks to correct the mishaps that may occur in the human body. By picturing the body from a molecular point of view, nanotechnology can produce machines that mimic natural machines that may be damaged or defective and supplement a system of machines like the immune system. Nanotechnology will allow the creation of fleets of computer-controlled molecular tools considerably smaller than a cell that are built with the accuracy and precision of drug molecules.[3] They could remove obstructions in the circulatory system, destroy cancer cells and invaders, provide oxygen when our own circulation is impaired[17] or take over subcellular organelle function. In the future, we may see an artificial mitochondrion.[3] This brings about a whole new view of how medicine should work to cure disease and preserve health.

Inspired by Nature

At first, it may be difficult to comprehend nanomedicine. What is this technology based on? The plausibility of this technology can be depicted by nanomachines that occur in nature. They can be as simple as bacteria or as complex as the ribosome. There are bacteria that have simple helical rods of

Figure 2. Simple pump.



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protein that rotate based on a variable speed reversible motor.[19] These rotary motors can serve as a blueprint for a nanorobot part. The more complex ribosomes manufacture every protein that we know in living things. The size of a typical ribosome is a few thousand cubic nanometers.[4] Despite its relatively small size, the ribosome has the capability of building nearly any protein by assembling amino acids in a precise linear arrangement based on the instructions provided by messenger RNA (mRNA) and grabbing the specific transfer RNA (tRNA) chemically bonded by a specific enzyme to the specific amino acid.[4]

The proteins made by the ribosome are also one of nature's machines. Proteins have a major role in creating and supporting cellular function. They search the body for defects, incorporate themselves to form larger structures, modify incoming stimuli into practical information and adjust themselves to adapt to the conditions of the task.[19] Enzymes are natural molecular machines that catalyze reactions in a specific manner by precisely orienting individual reactant molecules from the surrounding environment.[14]

In a similar manner to that of a ribosome manufacturing a protein, an assembler will build an arbitrary molecular structure based on a series of instructions. It will have full control over the molecular component being added to a growing complex structure analogous to the individual amino acid being added to the growing polypeptide. Like the mRNA that ribosomes require to control its actions, the assembler will require a specific series of control signals provided by a molecular computer.[20]

Cell Repair Micromachines[12]

If we can view illness, aging and injury as caused by misarranged patterns of atoms, then the concept of using devices able to rearrange atoms back to their natural healthy state is not hard to grasp. Cell repair machines would necessarily be similar in size to bacteria and viruses, yet they would have to be much more complex. They would enter cells similar to the way viruses do, being able to penetrate cell membranes. Once inside, the machine would inspect the contents and activity of the cell and then take action if necessary. The repair machine is likely to be able to recognize and correct molecular disorders such as an enzyme deficiency or DNA damage.

Cell repair machines may be guided by a micron-wide mechanical computer that fits in 1/1000 the volume of a typical cell, yet contain more information than the cell's entire DNA. This nanocomputer would instruct smaller and simpler computers to direct machines to examine, take apart and rebuild impaired molecular structures. This computer is conceptual at this point and requires miniaturization beyond our current capabilities.

The following excerpt from Drexler may help one visualize a cell repair machine: "[I]magine ....a cell - enlarged until atoms are the size of small marbles. On this scale, the repair machine's smallest tools have tips about the size of your fingertips; a medium-sized protein, like hemoglobin, is the size of a typewriter; and a ribosome is the size of a washing machine. A single repair device contains a simple computer the size of a small truck, along with many sensors of protein size, several manipulators of ribosome size and provisions for memory and motive power. A total volume ten meters across, the size of a three-story house, holds all these parts and more. With parts the size of marbles packing this volume, the repair machine can do complex things."

Existing molecular machines in nature demonstrate the ability to travel through tissue, enter cells, recognize molecular structures and repair damage to a certain extent. Cell repair machines may be able to improve on nature as illustrated by DNA repair. Cell repair enzymes can already detect and correct breaks and crosslinks in DNA. However, in order to correct mutations, the enzyme requires the capability to read. Such repair machines are lacking in nature, but can be built with nanotechnology. The repair machine could compare a DNA strand to other strands, one segment at a time and note when a nucleotide failed to match. In addition, the machine could change the wrong nucleotide to one that matches the other DNA strands and thus repair the mutation. The machine can compare DNA from several cells, make corrected copies and use these as a basis for proofreading and correcting DNA. Additional repairs may require other information about healthy cells and information on how a specific damaged cell differs from the normal cells.

Cosmetic Nanosurgery[21]

Aside from the evident medical goals of maintaining health, nanotechnology could be used by people to satisfy their vanity.[22] One may wish to change the size of their body, become taller or even remodel the shape of their skull. The alteration and enhancement of appearance or cosmetic nanosurgery may be an application for nanotechnology.[23] These applications range from changing your hair color permanently and preventing tooth loss to treating baldness and wrinkle removal. Changing the color of the hair, eyes and skin could be done by a group of basic nanomachines that persistently regulates the production and delivery of melanin. It would simply recognize and bind to some structure within the melanocyte and influence melanin formation. A nanomachine could have the ability to restart hair growth in follicles to treat baldness. In contrast, undesirable hair could be removed by externally applied nanomachines that attach themselves to the hairshaft and convert the hair to vapors. As for wrinkle repair, total skin renewal might be achieved with fully capable cell repair nanodevices. When nanotechnology arrives, it may correct the genetics behind tooth loss.[23] Teeth may be constructed with atomic precision and could be made stronger and more durable. The technology may go as far as replacing the entire jaw and teeth with a diamondoid matrix.[23] Nanodevices could do what the plastic surgeon does but without the pain and bruising.[24]

Beyond vanity, accident victims and people disfigured by birth defects are potential beneficiaries of nanosurgery.[22] Victims may require regeneration of crushed, burned or severed body parts. Achieving these goals is far more complex than using nanodevices that turn on and off a few existing genes or by making and inserting additional genes. Accomplishing these goals requires an understanding of how to program living tissues to make the desired macroscopic structures. Meanwhile, it is necessary for a means of assuring that the process of overriding preceding, natural, morphogenetic programs goes well. For those who have suffered massive trauma, nanomanufactured medical devices could be of value. The capability to direct cell growth and division, along with the ability to direct tissue organization may be adequate to reproduce entire organs and limbs.[16] This may help the problem of the world's shortage of organ donations.[25]

Nanorobots[6]

This section deals with the concept of a nanorobot and discusses its theoretical characteristics as well as other issues of concern. Like the micromachines depicted in Figure 1, the size of a nanorobot is anticipated to measure perhaps 0.5-3 microns in diameter in order for it to fit in the smallest capillaries. The robot would be assembled from nanoscale parts ranging in size from 1-100 nanometers (nm). It is assumed that carbon will be the primary element, due to its tremendous strength and chemical inertness, and it will be oriented in the form of diamond nanocomposites. Other elements that have potential include hydrogen, sulfur, oxygen, and nitrogen. These light elements would be used for specialized structures such as the nanogear (Figure 1). Since no actual working nanorobot has been built yet, we can only imagine what one may look like. As stated earlier, the size of a nanodevice that travels within the bloodstream would be about 500-3000 nm. Those devices that do not travel in blood but in tissue may be as large as 50-100 microns or even larger if they travel in the bronchial tree of the lungs. Depending on where these nanorobots are used as well as their specified duty, there will be many different sizes and shapes.

Due to the small size of nanorobots, a typical therapeutic dose may contain from a few million to about ten trillion individual devices, depending on the treatment type. The route of administration would likely be via injection for a typical nanomedical treatment dealing with, for instance, a bacterial or viral infection. Injecting a minor dose of 3 cm^3 would not be particularly invasive since the adult human body has a blood volume of approximately 5400 cm^3. Getting them into the body is quite simple. Retrieving them from the body may be just as simple. Those devices designed to fall apart after they complete their task would be readily removed through the usual human excretory processes. Others can be designed to allow ready removal using various methods including a specialized centrifugation apparatus.

Another important area to address is how these nanodevices are powered and controlled inside the body. Power could be supplied in the form of glucose and oxygen metabolized to energy. Another approach is supplying external acoustic power. Communicating with the devices once inside the body could be done with acoustic messaging using a device resembling an ultrasound probe encoded with messages on acoustic carrier waves at frequencies between 1-10 megahertz. Each nanorobot could have its own power supply, computer and sensorium. Once the message from the practitioner was received through acoustic sensors, the nanorobot would then compute and execute the appropriate response. In order for the practitioner to monitor progress, s/he needs to get messages back from the nanodevice. Again this could be done with acoustic signals.

To affect different cell types, medical nanorobots will need to distinguish between the various cells. Surface antigens may serve as a marker for this purpose. Therefore, using chemotactic sensors keyed to the specific antigens might serve as a form of detection system. This is important especially if the task of the nanorobot is to deliver a drug to a specific cell type. For example, anti-cancer drugs should be delivered to tumor cells only. Once the nanorobot has identified the tumor cells, it could release chemotherapeutic agents from onboard tanks to kill the target tumor cells. Furthermore, there may be onboard sensors that detect the amount of circulating levels of drug so that overdose can be prevented.

Perhaps the main area of concern for injecting nanorobots is how the immune system will react. The immune system is primed to react and attack something that is considered foreign. As mentioned before, these nanodevices might be made with smooth flawless diamond surfaces. This turns out to be ideal as experimental studies hint that less leukocyte activity and fibrinogen adsorption occurs with diamond exteriors. The diamond coating is almost entirely chemically inert due to its extremely high surface energy and strong hydropho-

Figure 3. Molecular Differential Gear.

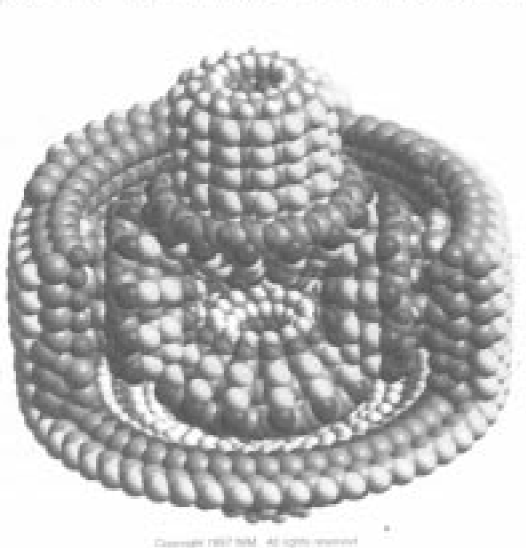

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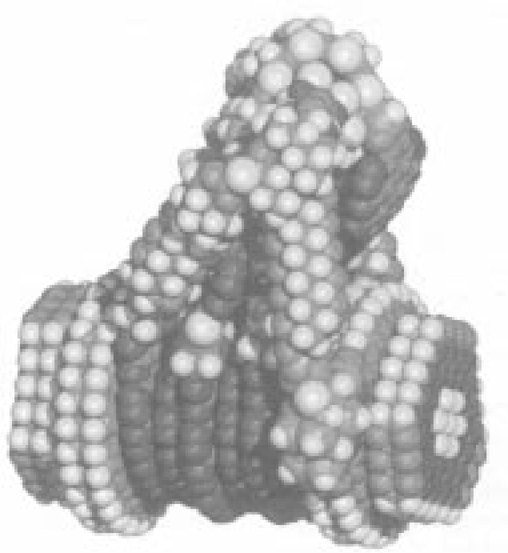
Figure 4. Fine Motion Controller for Molecular Assembly.



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bicity, leading to minimal opsonization. If this alone does not render low bioactivity, active surface management of the device exterior could be used. For those nanorobots that are still bioactive, the short residence time in the body would allow the application of immunosuppressive agents during the treatment period.

Perhaps the most serious problems may be due to the machine-machine interactions. To illustrate this problem, consider two types of nanorobots that are jointly repairing some tissue. If for some reason, the programming allows type A to interpret the work of type B as a flaw and vice versa, then it would be possible to have an endless cycle of one trying to repeatedly undo the work of the other. Even in such cases, control over the nanodevices would have to exist that would allow the simple shut down of one of the devices to allow the other to proceed or to shut down both and reprogram them while still inside the body to avoid any conflict. It will be important that the practitioner has the ability to "pull the plug" on these nanorobots.

Respirocytes[2]

Robert A. Freitas, Jr. suggested an application for nanotechnology incorporating an artificial mechanical red cell called a "respirocyte."[2] The respirocyte is theorized to be approximately one micron in diameter. It is suggested that it should be a spherical device composed of 18 billion atoms consisting mostly of carbon atoms arranged in a diamond pattern in a porous lattice structure inside the spherical shell. Optimally, respirocytes would behave like natural red blood cells (RBC) by delivering oxygen to tissues, but in a much greater quantity. It is estimated that a respirocyte could deliver 236 times more oxygen per unit volume than a natural RBC mainly due to its diamondoid construction. The respirocyte would then store up to 9 billion oxygen (O_2) and carbon dioxide (CO_2) molecules in an onboard tank at pressures up to 1000 atmospheres.

The actions of the respirocyte may be adjusted by the practitioner via acoustic signal. A conductor device similar to an ultrasound transmitter would give the respirocytes orders to adjust their behavior while inside the patient's body. Much of the respirocyte surface would be covered with thousands of sorting rotors that load and unload gases into the tanks (Figure 6). Gas concentration sensors would be located on the outside of the device. These sensors would detect O_2 and CO_2 partial pressures. When the respirocyte passes through the lung capillaries, the O_2 partial pressure would be high and the CO_2 partial pressure low, so the onboard computer would inform the rotors to load O_2 into the tanks and to dump out the CO_2. When the device comes upon peripheral tissues that need oxygen, the sensor readings would be reversed so that the computer directs the rotors to release O_2 from the tanks and take up CO_2. Once therapy is completed, the respirocytes would be extracted from circulation.[2]

The respirocyte has not yet been built and is only a design. However, once constructed through future advances in nanoengineering, this artificial red cell may have many applications in therapeutic and emergency medicine amongst other areas.

Intelligent Drugs[14]

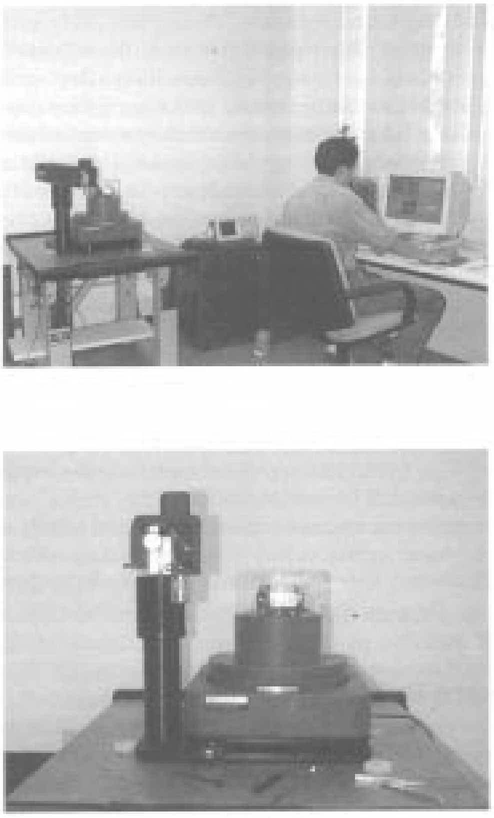
The drugs of the future could be programmable machines with sensory, decision-making and effector capabilities. These smart pharmaceuticals may avoid side effects and allergic reactions by having a biocompatible coating like that of the diamond described earlier. They could be programmed to become active only once they reach their ultimate destinations and attain nearly complete specificity of action. They may check for overdosage by analyzing the surroundings right before becoming active to prevent both accidental and intentional poisoning.

Nanobodies: Treatment of AIDS[26]

Like HIV, most viruses are small and difficult to attack and eliminate. Nanotechnology presents a way of solving this problem. Today's AIDS "drug cocktails" have remarkably delayed the growth and spread of the virus, but attacking the virus is difficult because it is so small. HIV destroys the T-cell and antibody response. Without the T-4 cell, no antibody response is mediated to stop the tiny viruses. With nanotechnology, it may be possible to elicit the response of another component of the immune system, the Complement Cascade. This system is a series of proteins that collect and engulf foreign invaders like bacteria. The invader is neutralized until a macrophage comes to swallow up and digest the whole package. The Complement Cascade begins with an initial reaction, often mediated by an antibody and then a sequence of events occurs to assemble the proteins around the invader.

The Complement Cascade contains a "short circuit." Some bacteria have protein coats that stimulate a response of the 3b protein. This is not a mediated response and does not involve the T-cells and antibodies. This is where Bioengineer Michael Singletary proposes that a device can be produced to attach to

Figure 5. Molecular Manipulation.



A researcher is shown here manipulating gold atoms using an Atomic Force Microscope (AFM). *Courtesy of Dr. Aristides Requicha, Director of the Laboratory of Molecular Robotics at the University of Southern California.*

the HIV "head" and undergo a conformation change to expose a previously covered protein coat that will stimulate the response of the 3b protein.[26] The nanodevice, along with the HIV, would be engulfed by the complement and then destroyed by the scavenging macrophages.

The device must be designed in a way that it must not elicit a response until it has bonded to the HIV. Once it has bonded, the nanobody changes conformation and labels the virus for the complement to engulf and remove. Removal of the devices not attached to HIV can be accomplished by tagging the nanobody. A compound can be used to cause a conformation change to elicit a response from the complement cascade to remove all nanobodies.

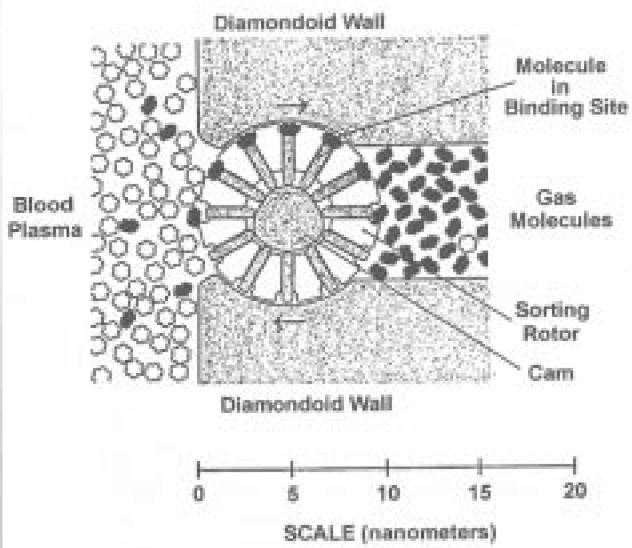
Real Applications: Pharmaceuticals[15]

As mentioned earlier, there is a process called "Nanonization" that provides an answer to the problem of drug insolubility. This might not be the nanorobots that are described earlier, but nanotechnology based on the concept of extremely small size is definitely being applied here.

The company NanoSystems, which is now a part of Elan Pharmaceutical Technologies, developed this technology to facilitate research and development efforts for compounds that are difficult to formulate using conventional processes due to limited water solubility. Nanonization takes particle size reduction to a new and considerably smaller level. It is basically a wet-milling process that is conventionally used in manufacturing paints, dyes and photographic emulsions, as well as for imaging and diagnostics. The drug, water, a grinding media and a surfactant or some other surface modifier are placed in an agitator chamber. The agitation process breaks up the drug crystals repeatedly until they become particles of less than 400 nm in diameter, also known as NanoCrystals™. Before the NanoCrystal™ technology was developed, the wet-milling process was not considered appropriate for drug application because of the potential for contamination by the grinding media. Nanonization uses a non-contaminating media of highly cross-linked polystyrene instead of a substance like glass that is used in manufacturing dyes and paints. To stabilize the particles and prevent aggregation, a thin layer of polymeric surface modifiers are adsorbed onto the crystal surfaces. The outcome is a suspension that functions like a solution. These particles can then be incorporated into various dosage forms like pills, sprays, injectable solutions and topical creams.[27]

Nanonization is certainly beneficial for drugs with poor water solubility. It is also useful for moderately soluble agents when a high drug concentration in a low fluid volume is favored. According to Gwen Melincoff, the Director of Business Development at NanoSystems, the one limit for Nanonization is a low melting point. The ideal melting temperature should be at least 70-75 degrees Celsius. Even if

Figure 6. Respirocyte Molecular Sorting Rotor.



This rotor has been proposed to convey gas molecules in and out of pressurized microvessels. Each rotor has binding sites that selectively bind a gas molecule when exposed to plasma. Once the binding site is exposed to the interior chamber, the bound molecules are forcibly ejected. *Reprinted with permission from Artificial Cells, Blood Substitutes and Immobilization Biotechnology, 1998.*

a drug has a melting point that falls below this range, there are strategies such as chilling for managing this situation.

Unlike competitive drug delivery systems, NanoCrystal™ produces individual particles composed entirely of the drug with only a thin surface coating, which gets rid of the necessity for an additional delivery device. Absorption and bioavailability are enhanced by the drug crystals' very small size ranging from 80 nm to 400 nm. The small size also enhances the drug targeting capability of drugs. As Melincoff explains, "There are two targeting mechanisms - passive and bioadhesion. While passive targeting is not unique to our technology and occurs in response to the rapid vascular growth of tumors, bioadhesion is directly related to the surface modifier or the very small size of the NanoCrystals™. The particles are so small that gravity effects are reduced and surface forces predominate."[7]

Significant improvements in performance and expanded drug usage may be achieved with drugs utilizing Nanonization. Drugs available only by injection may be taken by mouth, while oral drugs may be formulated into injectables and new therapeutic indications may be identified. Water-insoluble drugs are typically formulated for injection using organic solvents, fat emulsions and liposomes.[28] Paclitaxel is currently formulated in the organic solvents Cremophor EL (polyoxyethylated castor oil) and ethanol. The Cremophor EL can cause unwanted acute skin reactions. With a nanoparticle injectable formulation, there is no longer a need for harmful organic solvents. This technology not only has the potential of improving effectiveness of many marketed drugs, it could also allow the introduction of promising new drug candidates which otherwise would have been rejected due to poor solubility.[29]

To date, no drugs utilizing Nanonization have reached the marketplace. However, NanoSystems has collaborations and license agreements with a number of major pharmaceutical companies. These companies will provide preclinical and clinical development, as well as marketing of the compounds. NanoSystems is currently conducting feasibility studies with a number of clients. As many as eight compounds utilizing Nanonization have been tested in human clinical trials.[30] These compounds cannot be disclosed due to contractual agreement between NanoSystems and their clients.

Merck & Co. signed a $30 million deal with NanoSystems in August 1998.[31] This is the third collaboration between the two companies. The first deal occurred in December 1996 when Merck reached a deal to evaluate a NanoCrystal™ formulation of Merck's HIV protease inhibitor indinavir for the treatment of pediatric patients and other special patient groups. Indinavir is currently marketed as Crixivan™ in a capsule formulation. The two companies believe that a NanoCrystal™ formulation of indinavir liquid suspension may improve palatability and administration in treating pediatric patients who have difficulty swallowing solid dosage products.[32] The second license agreement followed in June 1997 whereby Merck will utilize the NanoCrystal™ technology in the development of novel therapeutic agents.[33,34]

Mimetix Inc. collaborated with NanoSystems in April 1996 for an injectable non-narcotic analgesic. Mimetix will be developing Nanox, an injectable form of naproxen, to be used for the short-term management of moderate or severe pain in emergency room settings and certain post-surgical procedures.[35] The IND for Nanox has been filed and phase I clinical trials were conducted in 1997.[36]

Conclusion

Nanotechnology could give the field of medicine a whole new outlook. The abilities today to fight diseases and maintain health may be significantly enhanced with nanomedicine. Surgery may no longer require that a patient be cut open and sewn back together. Drugs may have greater specificity and efficacy and have fewer side effects. Repairing cells, formation of new limbs and organs, immune supplementation....the prospects are numerous and research is ongoing to bring reality to nanomedicine. Drexler's universal assembler may well manufacture the nanomachines necessary to perform the medical applications that have been proposed. Although not yet built, many efforts in design show that progress is occurring as we write. Moving atoms may be a long way from building nanomachines, but it is a major start.

Although nanonization is not an application using nanomachines, this process is based on the nanotechnology concept of utilizing nano-scale objects. This should be viewed as a milestone, especially in pharmaceutical formulation of water-insoluble drugs. More importantly, it is taking place today. Nanotechnology is real and being applied. The science-fiction scenarios may one day be reality. Nanomedicine may just be the future of medicine.

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