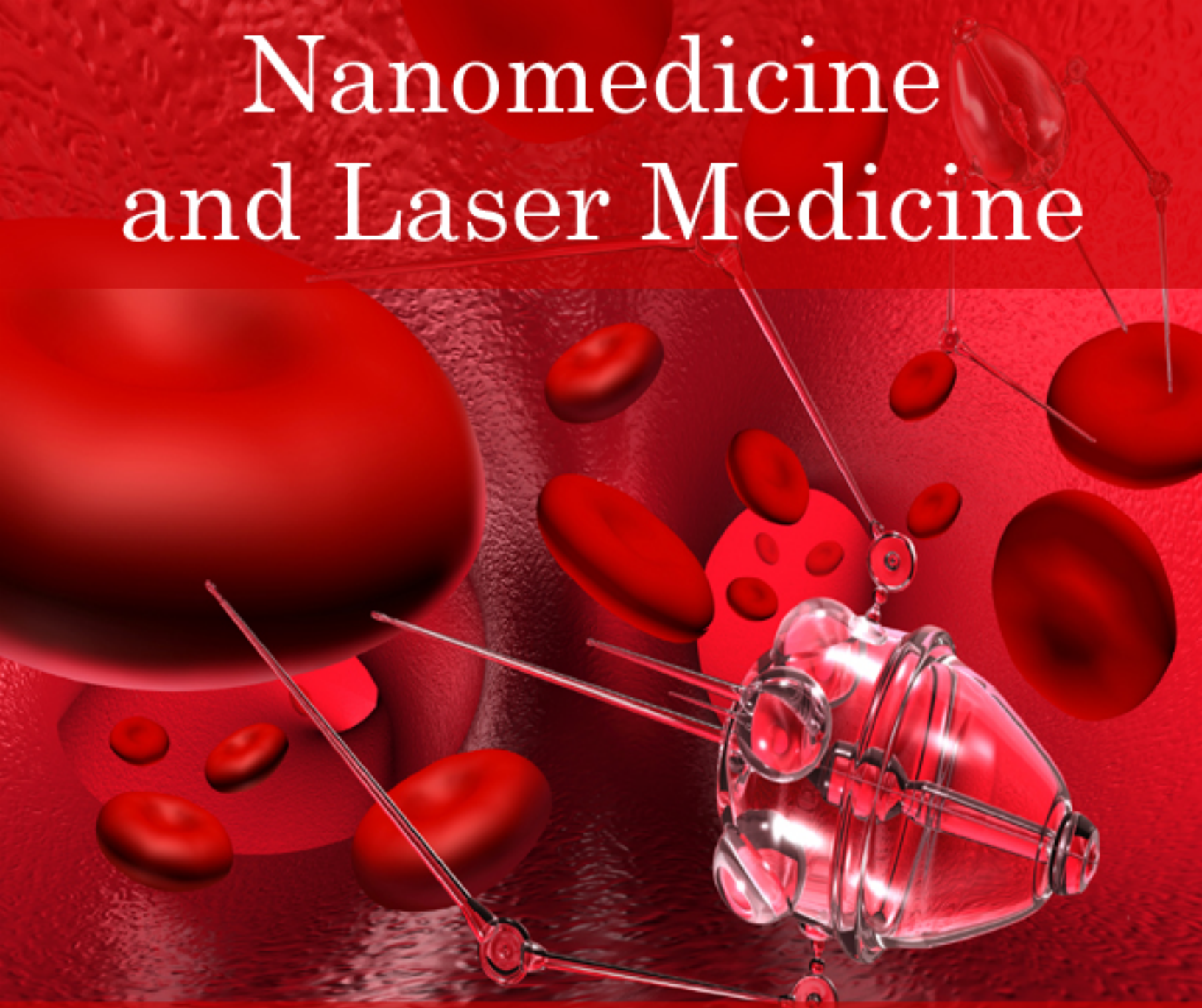
Nanomedicine and Laser Medicine



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Chapter 1

Nanomedicine

Nanomedicine is the medical application of nanotechnology. Nanomedicine ranges from the medical applications of nanomaterials, to nanoelectronic biosensors, and even possible future applications of molecular nanotechnology. Current problems for nanomedicine involve understanding the issues related to toxicity and environmental impact of nanoscale materials.

Nanomedicine research is receiving funding from the US National Institute of Health. Of note is the funding in 2005 of a five-year plan to set up four nanomedicine centers. In April 2006, the journal Nature Materials estimated that 130 nanotech-based drugs and delivery systems were being developed worldwide.

Overview

Nanomedicine seeks to deliver a valuable set of research tools and clinically useful devices in the near future. The National Nanotechnology Initiative expects new commercial applications in the pharmaceutical industry that may include advanced drug delivery systems, new therapies, and in vivo imaging. Neuro-electronic interfaces and other nanoelectronics-based sensors are another active goal of research. Further down the line, the speculative field of molecular nanotechnology believes that cell repair machines could revolutionize medicine and the medical field.

Nanomedicine is a large industry, with nanomedicine sales reaching 6.8 billion dollars in 2004, and with over 200 companies and 38 products worldwide, a minimum of 3.8 billion dollars in nanotechnology R&D is being invested every year. As the nanomedicine industry continues to grow, it is expected to have a significant impact on the economy.

Medical use of nanomaterials

Drug delivery

Nanomedical approaches to drug delivery center on developing nanoscale particles or molecules to improve drug bioavailability. Bioavailability refers to the presence of drug molecules where they are needed in the body and where they will do the most good. Drug delivery focuses on maximizing bioavailability both at specific places in the body and over a period of time. This can potentially be achieved by molecular targeting by

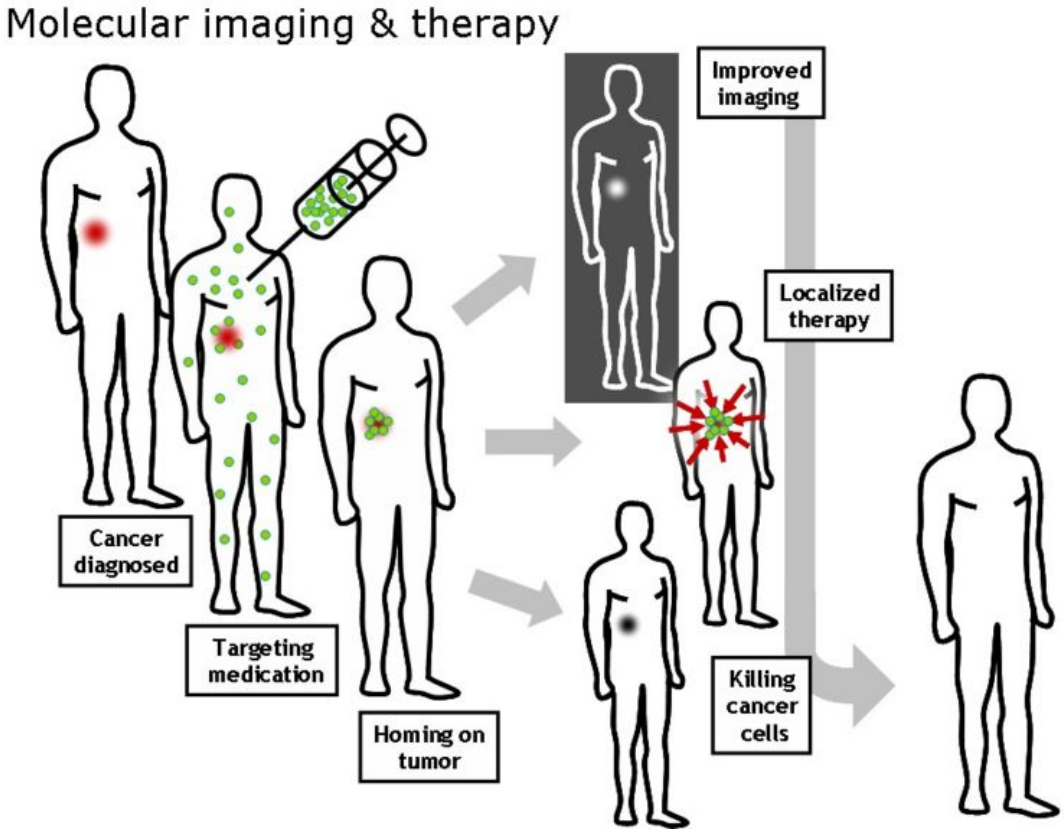
nanoengineered devices. It is all about targeting the molecules and delivering drugs with cell precision. More than $65 billion are wasted each year due to poor bioavailability. *In vivo* imaging is another area where tools and devices are being developed. Using nanoparticle contrast agents, images such as ultrasound and MRI have a favorable distribution and improved contrast. The new methods of nanoengineered materials that are being developed might be effective in treating illnesses and diseases such as cancer. What nanoscientists will be able to achieve in the future is beyond current imagination. This might be accomplished by self assembled biocompatible nanodevices that will detect, evaluate, treat and report to the clinical doctor automatically.

Drug delivery systems, lipid- or polymer-based nanoparticles, can be designed to improve the pharmacological and therapeutic properties of drugs. The strength of drug delivery systems is their ability to alter the pharmacokinetics and biodistribution of the drug. Nanoparticles have unusual properties that can be used to improve drug delivery. Where larger particles would have been cleared from the body, cells take up these nanoparticles because of their size. Complex drug delivery mechanisms are being developed, including the ability to get drugs through cell membranes and into cell cytoplasm. Efficiency is important because many diseases depend upon processes within the cell and can only be impeded by drugs that make their way into the cell. Triggered response is one way for drug molecules to be used more efficiently. Drugs are placed in the body and only activate on encountering a particular signal. For example, a drug with poor solubility will be replaced by a drug delivery system where both hydrophilic and hydrophobic environments exist, improving the solubility. Also, a drug may cause tissue damage, but with drug delivery, regulated drug release can eliminate the problem. If a drug is cleared too quickly from the body, this could force a patient to use high doses, but with drug delivery systems clearance can be reduced by altering the pharmacokinetics of the drug. Poor biodistribution is a problem that can affect normal tissues through widespread distribution, but the particulates from drug delivery systems lower the volume of distribution and reduce the effect on non-target tissue. Potential nanodrugs will work by very specific and well-understood mechanisms; one of the major impacts of nanotechnology and nanoscience will be in leading development of completely new drugs with more useful behavior and less side effects.

Protein and peptide delivery

Protein and peptides exert multiple biological actions in human body and they have been identified as showing great promise for treatment of various diseases and disorders. These macromolecules are called biopharmaceuticals. Targeted and/or controlled delivery of these biopharmaceuticals using nanomaterials like nanoparticles and Dendrimers is an emerging field called nanobiopharmaceutics, and these products are called nanobiopharmaceuticals.

Cancer



A schematic illustration showing how nanoparticles or other cancer drugs might be used to treat cancer.

The small size of nanoparticles endows them with properties that can be very useful in oncology, particularly in imaging. Quantum dots (nanoparticles with quantum confinement properties, such as size-tunable light emission), when used in conjunction with MRI (magnetic resonance imaging), can produce exceptional images of tumor sites. These nanoparticles are much brighter than organic dyes and only need one light source for excitation. This means that the use of fluorescent quantum dots could produce a higher contrast image and at a lower cost than today's organic dyes used as contrast media. The downside, however, is that quantum dots are usually made of quite toxic elements.

Another nanoproperty, high surface area to volume ratio, allows many functional groups to be attached to a nanoparticle, which can seek out and bind to certain tumor cells. Additionally, the small size of nanoparticles (10 to 100 nanometers), allows them to preferentially accumulate at tumor sites (because tumors lack an effective lymphatic drainage system). A very exciting research question is how to make these imaging nanoparticles do more things for cancer. For instance, is it possible to manufacture multifunctional nanoparticles that would detect, image, and then proceed to treat a tumor? This question is under vigorous investigation; the answer to which could shape the future

of cancer treatment. A promising new cancer treatment that may one day replace radiation and chemotherapy is edging closer to human trials. Kanzius RF therapy attaches microscopic nanoparticles to cancer cells and then "cooks" tumors inside the body with radio waves that heat only the nanoparticles and the adjacent (cancerous) cells.

Sensor test chips containing thousands of nanowires, able to detect proteins and other biomarkers left behind by cancer cells, could enable the detection and diagnosis of cancer in the early stages from a few drops of a patient's blood.

The basic point to use drug delivery is based upon three facts: a) efficient encapsulation of the drugs, b) successful delivery of said drugs to the targeted region of the body, and c) successful release of that drug there.

Researchers at Rice University under Prof. Jennifer West, have demonstrated the use of 120 nm diameter nanoshells coated with gold to kill cancer tumors in mice. The nanoshells can be targeted to bond to cancerous cells by conjugating antibodies or peptides to the nanoshell surface. By irradiating the area of the tumor with an infrared laser, which passes through flesh without heating it, the gold is heated sufficiently to cause death to the cancer cells.

Nanoparticles of cadmium selenide (quantum dots) glow when exposed to ultraviolet light. When injected, they seep into cancer tumors. The surgeon can see the glowing tumor, and use it as a guide for more accurate tumor removal.

In photodynamic therapy, a particle is placed within the body and is illuminated with light from the outside. The light gets absorbed by the particle and if the particle is metal, energy from the light will heat the particle and surrounding tissue. Light may also be used to produce high energy oxygen molecules which will chemically react with and destroy most organic molecules that are next to them (like tumors). This therapy is appealing for many reasons. It does not leave a “toxic trail” of reactive molecules throughout the body (chemotherapy) because it is directed where only the light is shined and the particles exist. Photodynamic therapy has potential for a noninvasive procedure for dealing with diseases, growth and tumors.

Surgery

At Rice University, a flesh welder is used to fuse two pieces of chicken meat into a single piece. The two pieces of chicken are placed together touching. A greenish liquid containing gold-coated nanoshells is dribbled along the seam. An infrared laser is traced along the seam, causing the two sides to weld together. This could solve the difficulties and blood leaks caused when the surgeon tries to restitch the arteries that have been cut during a kidney or heart transplant. The flesh welder could weld the artery perfectly.

Visualization

Tracking movement can help determine how well drugs are being distributed or how substances are metabolized. It is difficult to track a small group of cells throughout the body, so scientists used to dye the cells. These dyes needed to be excited by light of a certain wavelength in order for them to light up. While different color dyes absorb different frequencies of light, there was a need for as many light sources as cells. A way around this problem is with luminescent tags. These tags are quantum dots attached to proteins that penetrate cell membranes. The dots can be random in size, can be made of bio-inert material, and they demonstrate the nanoscale property that color is size-dependent. As a result, sizes are selected so that the frequency of light used to make a group of quantum dots fluoresce is an even multiple of the frequency required to make another group incandesce. Then both groups can be lit with a single light source.

Nanoparticle targeting

It is greatly observed that nanoparticles are promising tools for the advancement of drug delivery, medical imaging, and as diagnostic sensors. However, the biodistribution of these nanoparticles is mostly unknown due to the difficulty in targeting specific organs in the body. Current research in the excretory systems of mice, however, shows the ability of gold composites to selectively target certain organs based on their size and charge. These composites are encapsulated by a dendrimer and assigned a specific charge and size. Positively-charged gold nanoparticles were found to enter the kidneys while negatively-charged gold nanoparticles remained in the liver and spleen. It is suggested that the positive surface charge of the nanoparticle decreases the rate of osponization of nanoparticles in the liver, thus affecting the excretory pathway. Even at a relatively small size of 5 nm , though, these particles can become compartmentalized in the peripheral tissues, and will therefore accumulate in the body over time. While advancement of research proves that targeting and distribution can be augmented by nanoparticles, the dangers of nanotoxicity become an important next step in further understanding of their medical uses.

Neuro-electronic interfaces

Neuro-electronic interfacing is a visionary goal dealing with the construction of nanodevices that will permit computers to be joined and linked to the nervous system. This idea requires the building of a molecular structure that will permit control and detection of nerve impulses by an external computer. The computers will be able to interpret, register, and respond to signals the body gives off when it feels sensations. The demand for such structures is huge because many diseases involve the decay of the nervous system (ALS and multiple sclerosis). Also, many injuries and accidents may impair the nervous system resulting in dysfunctional systems and paraplegia. If computers could control the nervous system through neuro-electronic interface, problems that impair the system could be controlled so that effects of diseases and injuries could be overcome. Two considerations must be made when selecting the power source for such applications. They are refuelable and nonrefuelable strategies. A refuelable strategy

implies energy is refilled continuously or periodically with external sonic, chemical, tethered, magnetic, or electrical sources. A nonrefuelable strategy implies that all power is drawn from internal energy storage which would stop when all energy is drained.

One limitation to this innovation is the fact that electrical interference is a possibility. Electric fields, electromagnetic pulses (EMP), and stray fields from other *in vivo* electrical devices can all cause interference. Also, thick insulators are required to prevent electron leakage, and if high conductivity of the *in vivo* medium occurs there is a risk of sudden power loss and "shorting out." Finally, thick wires are also needed to conduct substantial power levels without overheating. Little practical progress has been made even though research is happening. The wiring of the structure is extremely difficult because they must be positioned precisely in the nervous system so that it is able to monitor and respond to nervous signals. The structures that will provide the interface must also be compatible with the body's immune system so that they will remain unaffected in the body for a long time. In addition, the structures must also sense ionic currents and be able to cause currents to flow backward. While the potential for these structures is amazing, there is no timetable for when they will be available.

Medical applications of molecular nanotechnology

Molecular nanotechnology is a speculative subfield of nanotechnology regarding the possibility of engineering molecular assemblers, machines which could re-order matter at a molecular or atomic scale. Molecular nanotechnology is highly theoretical, seeking to anticipate what inventions nanotechnology might yield and to propose an agenda for future inquiry. The proposed elements of molecular nanotechnology, such as molecular assemblers and nanorobots are far beyond current capabilities.

Nanorobots

The somewhat speculative claims about the possibility of using nanorobots in medicine, advocates say, would totally change the world of medicine once it is realized. Nanomedicine would make use of these nanorobots (e.g., Computational Genes), introduced into the body, to repair or detect damages and infections. According to Robert Freitas of the Institute for Molecular Manufacturing, a typical blood borne medical nanorobot would be between 0.5-3 micrometres in size, because that is the maximum size possible due to capillary passage requirement. Carbon could be the primary element used to build these nanorobots due to the inherent strength and other characteristics of some forms of carbon (diamond/fullerene composites), and nanorobots would be fabricated in desktop nanofactories specialized for this purpose.

Nanodevices could be observed at work inside the body using MRI, especially if their components were manufactured using mostly ^{13}C atoms rather than the natural ^{12}C isotope of carbon, since ^{13}C has a nonzero nuclear magnetic moment. Medical nanodevices would first be injected into a human body, and would then go to work in a specific organ or tissue mass. The doctor will monitor the progress, and make certain that the nanodevices have gotten to the correct target treatment region. The doctor will also be

able to scan a section of the body, and actually see the nanodevices congregated neatly around their target (a tumor mass, etc.) so that he or she can be sure that the procedure was successful.

Cell repair machines

Using drugs and surgery, doctors can only encourage tissues to repair themselves. With molecular machines, there will be more direct repairs. Cell repair will utilize the same tasks that living systems already prove possible. Access to cells is possible because biologists can stick needles into cells without killing them. Thus, molecular machines are capable of entering the cell. Also, all specific biochemical interactions show that molecular systems can recognize other molecules by touch, build or rebuild every molecule in a cell, and can disassemble damaged molecules. Finally, cells that replicate prove that molecular systems can assemble every system found in a cell. Therefore, since nature has demonstrated the basic operations needed to perform molecular-level cell repair, in the future, nanomachine based systems will be built that are able to enter cells, sense differences from healthy ones and make modifications to the structure.

The healthcare possibilities of these cell repair machines are impressive. Comparable to the size of viruses or bacteria, their compact parts would allow them to be more complex. The early machines will be specialized. As they open and close cell membranes or travel through tissue and enter cells and viruses, machines will only be able to correct a single molecular disorder like DNA damage or enzyme deficiency. Later, cell repair machines will be programmed with more abilities with the help of advanced AI systems.

Nanocomputers will be needed to guide these machines. These computers will direct machines to examine, take apart, and rebuild damaged molecular structures. Repair machines will be able to repair whole cells by working structure by structure. Then by working cell by cell and tissue by tissue, whole organs can be repaired. Finally, by working organ by organ, health is restored to the body. Cells damaged to the point of inactivity can be repaired because of the ability of molecular machines to build cells from scratch. Therefore, cell repair machines will free medicine from reliance on self repair alone.

Nanonephrology

Nanonephrology is a branch of nanomedicine and nanotechnology that deals with 1) the study of kidney protein structures at the atomic level; 2) nano-imaging approaches to study cellular processes in kidney cells; and 3) nano medical treatments that utilize nanoparticles and to treat various kidney diseases. The creation and use of materials and devices at the molecular and atomic levels that can be used for the diagnosis and therapy of renal diseases is also a part of Nanonephrology that will play a role in the management of patients with kidney disease in the future. Advances in Nanonephrology will be based on discoveries in the above areas that can provide nano-scale information on the cellular molecular machinery involved in normal kidney processes and in pathological states. By understanding the physical and chemical properties of proteins and other macromolecules

at the atomic level in various cells in the kidney, novel therapeutic approaches can be designed to combat major renal diseases. The nano-scale artificial kidney is a goal that many physicians dream of. Nano-scale engineering advances will permit programmable and controllable nano-scale robots to execute curative and reconstructive procedures in the human kidney at the cellular and molecular levels. Designing nanostructures compatible with the kidney cells and that can safely operate in vivo is also a future goal. The ability to direct events in a controlled fashion at the cellular nano-level has the potential of significantly improving the lives of patients with kidney diseases.

Chapter 2

Nanotoxicology

Nanotoxicology is the study of the toxicity of nanomaterials. Because of quantum size effects and large surface area to volume ratio, nanomaterials have unique properties compared with their larger counterparts.

Nanotoxicology is a branch of bionanoscience which deals with the study and application of toxicity of nanomaterials. Nanomaterials, even when made of inert elements like gold, become highly active at nanometer dimensions. Nanotoxicological studies are intended to determine whether and to what extent these properties may pose a threat to the environment and to human beings. For instance, Diesel nanoparticles have been found to damage the cardiovascular system in a mouse model.

Human health and safety

Calls for tighter regulation of nanotechnology have arisen alongside a growing debate related to the human health and safety risks associated with nanotechnology. The Royal Society identifies the potential for nanoparticles to penetrate the skin, and recommends that the use of nanoparticles in cosmetics be conditional upon a favorable assessment by the relevant European Commission safety advisory committee. Andrew Maynard also reports that ‘certain nanoparticles may move easily into sensitive lung tissues after inhalation, and cause damage that can lead to chronic breathing problems’.

Carbon nanotubes – characterized by their microscopic size and incredible tensile strength – are frequently likened to asbestos, due to their needle-like fiber shape. In a recent study that introduced carbon nanotubes into the abdominal cavity of mice, results demonstrated that long thin carbon nanotubes showed the same effects as long thin asbestos fibers, raising concerns that exposure to carbon nanotubes may lead to mesothelioma (cancer of the lining of the lungs caused by exposure to asbestos). Given these risks, effective and rigorous regulation has been called for to determine if, and under what circumstances, carbon nanotubes are manufactured, as well as ensuring their safe handling and disposal.

The Woodrow Wilson Centre’s Project on Emerging Technologies conclude that there is insufficient funding for human health and safety research, and as a result there is currently limited understanding of the human health and safety risks associated with nanotechnology. While the US National Nanotechnology Initiative reports that around

four percent (about $40 million) is dedicated to risk related research and development, the Woodrow Wilson Centre estimate that only around $11 million is actually directed towards risk related research. They argued in 2007 that it would be necessary to increase funding to a minimum of $50 million in the following two years so as to fill the gaps in knowledge in these areas.

The potential for workplace exposure was highlighted by the 2004 Royal Society report which recommended a review of existing regulations to assess and control workplace exposure to nanoparticles and nanotubes. The report expressed particular concern for the inhalation of large quantities of nanoparticles by workers involved in the manufacturing process.

Stakeholders concerned by the lack of a regulatory framework to assess and control risks associated with the release of nanoparticles and nanotubes have drawn parallels with bovine spongiform encephalopathy (‘mad cow’s disease'), thalidomide, genetically modified food, nuclear energy, reproductive technologies, biotechnology, and asbestosis. In light of such concerns, the Canadian based ETC Group have called for a moratorium on nano-related research until comprehensive regulatory frameworks are developed that will ensure workplace safety.

California

In October 2008, the Department of Toxic Substances Control (DTSC), within the California Environmental Protection Agency, announced its intent to request information regarding analytical test methods, fate and transport in the environment, and other relevant information from manufacturers of carbon nanotubes. The term "manufacturers” includes persons and businesses that produce nanotubes in California, or import carbon nanotubes into California for sale. This information request is meant to identify information gaps and to develop further knowledge about the health and safety of carbon nanotubes.

DTSC is exercising its authority under California Health and Safety Code, Chapter 699, sections 57018-57020. These sections were added as a result of the adoption of Assembly Bill AB 289 (2006). They are intended to make information on the fate and transport, detection and analysis, and other information on chemicals more available. The law places the responsibility to provide this information to the Department on those who manufacture or import the chemicals. On January 22, 2009, a formal information request letter was sent to manufacturers who produce or import carbon nanotubes in California, or who may export carbon nanotubes into the State. This letter constitutes the first formal implementation of the authorities placed into statute by AB 289 (2006) and is directed to manufacturers of carbon nanotubes, both industry and academia within the State, and to manufacturers outside California who export carbon nanotubes to California. This request for information must be met by the manufacturers within one year.

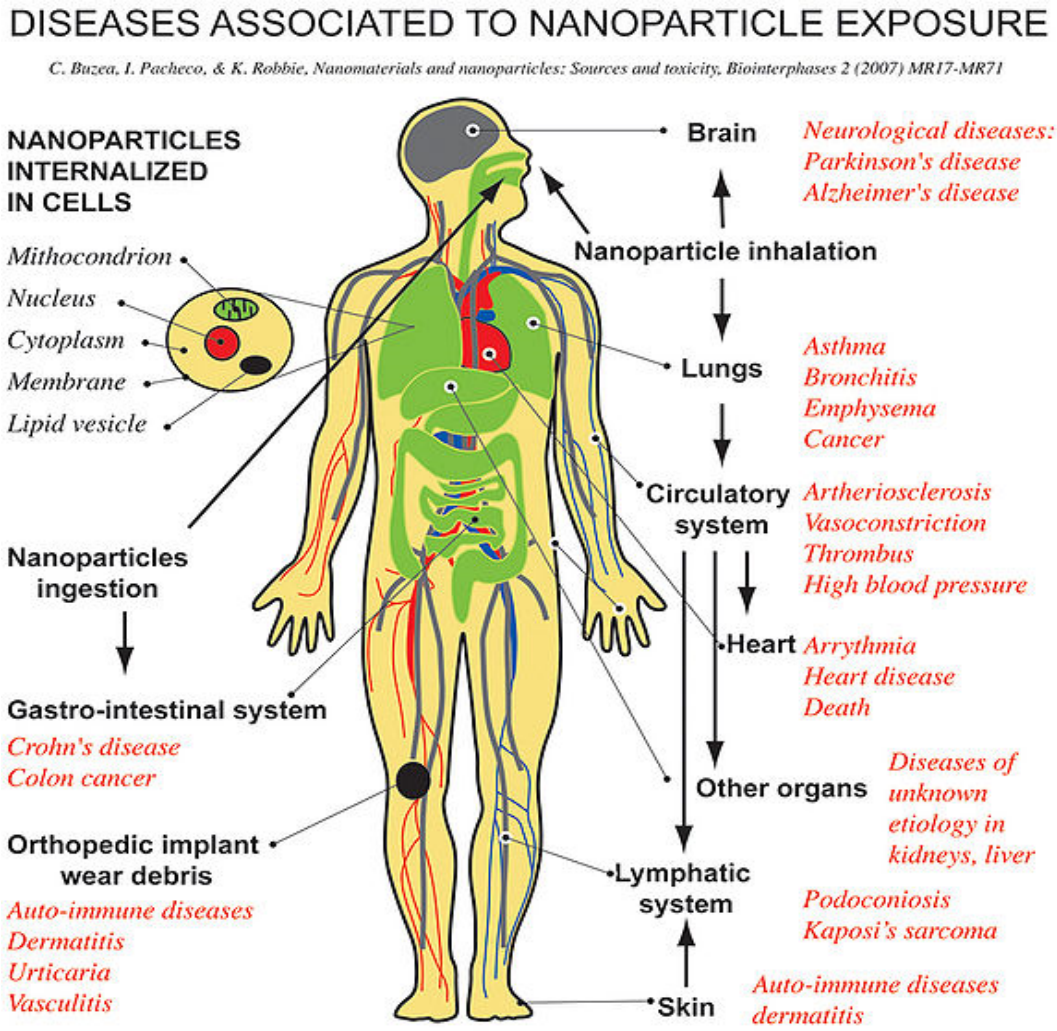
On January 22, 2010, California manufacturers and importers of carbon nanotubes were required to submit their responses. On January 25, 2010, DTSC posted the responses

received to date along with a list of companies who failed to respond to the information request. On February 16, 2010, DTSC issued a follow-up letter to the companies that failed to submit a response. View the responses received for the carbon nanotube call-in.

DTSC is indicating interest in expanding the Specific Chemical Information Call-in to members of the brominated flame retardants, members of the methyl siloxanes, and other nanometals and nanometal oxides such as vanadium oxide, aluminum oxide, silicon dioxide, titanium dioxide, zinc oxide, cerium oxide, nano platinum, nano silver, and nano zerovalent iron. DTSC is also planning to include quantum dots, ocean plastics, and nanoclay into the list of chemicals of interest.

Toxicology of nanoparticles

Background



Pathways of exposure to nanoparticles and associated diseases as suggested by epidemiological, in vivo and in vitro studies.

Nanotoxicology is a sub-specialty of particle toxicology. It addresses the toxicology of nanoparticles (particles <100 nm diameter) which appear to have toxicity effects that are unusual and not seen with larger particles. Nanoparticles can be divided into combustion-derived nanoparticles (like diesel soot), manufactured nanoparticles like carbon nanotubes and naturally occurring nanoparticles from volcanic eruptions, atmospheric chemistry etc. Typical nanoparticles that have been studied are titanium dioxide, alumina, zinc oxide, carbon black, and carbon nanotubes, and "nano-C_{60}". Nanoparticles have much larger surface area to unit mass ratios which in some cases may lead to greater pro-inflammatory effects (in, for example, lung tissue). In addition, some nanoparticles seem to be able to translocate from their site of deposition to distant sites such as the blood and the brain. This has resulted in a sea-change in how particle toxicology is viewed- instead of being confined to the lungs, nanoparticle toxicologists study the brain, blood, liver, skin and gut. Nanotoxicology has revolutionised particle toxicology and rejuvenated it.

Reactive oxygen species

For some types of particles, the smaller they are, the greater their surface area to volume ratio and the higher their chemical reactivity and biological activity. The greater chemical reactivity of nanomaterials can result in increased production of reactive oxygen species (ROS), including free radicals. ROS production has been found in a diverse range of nanomaterials including carbon fullerenes, carbon nanotubes and nanoparticle metal oxides. ROS and free radical production is one of the primary mechanisms of nanoparticle toxicity; it may result in oxidative stress, inflammation, and consequent damage to proteins, membranes and DNA.

Biodistribution

The extremely small size of nanomaterials also means that they much more readily gain entry into the human body than larger sized particles. How these nanoparticles behave inside the body is still a major question that needs to be resolved. The behavior of nanoparticles is a function of their size, shape and surface reactivity with the surrounding tissue. In principle, a large number of particles could overload the body's phagocytes, cells that ingest and destroy foreign matter, thereby triggering stress reactions that lead to inflammation and weaken the body’s defense against other pathogens. In addition to questions about what happens if non-degradable or slowly degradable nanoparticles accumulate in bodily organs, another concern is their potential interaction or interference with biological processes inside the body. Because of their large surface area, nanoparticles will, on exposure to tissue and fluids, immediately adsorb onto their surface some of the macromolecules they encounter. This may, for instance, affect the regulatory mechanisms of enzymes and other proteins.

Nanomaterials are able to cross biological membranes and access cells, tissues and organs that larger-sized particles normally cannot. Nanomaterials can gain access to the blood stream via inhalation or ingestion. At least some nanomaterials can penetrate the skin; even larger microparticles may penetrate skin when it is flexed. Broken skin is an ineffective particle barrier, suggesting that acne, eczema, shaving wounds or severe

sunburn may accelerate skin uptake of nanomaterials. Then, once in the blood stream, nanomaterials can be transported around the body and be taken up by organs and tissues, including the brain, heart, liver, kidneys, spleen, bone marrow and nervous system. Nanomaterials have proved toxic to human tissue and cell cultures, resulting in increased oxidative stress, inflammatory cytokine production and cell death. Unlike larger particles, nanomaterials may be taken up by cell mitochondria and the cell nucleus. Studies demonstrate the potential for nanomaterials to cause DNA mutation and induce major structural damage to mitochondria, even resulting in cell death.

Nanotoxicity studies

Since there is no authority to regulate nanotech-based products, there are many products that could possibly be dangerous to humans. Scientific research has indicated the potential for some nanomaterials to be toxic to humans or the environment. In March 2004 tests conducted by environmental toxicologist Eva Oberdörster, Ph.D. working with Southern Methodist University in Texas, found extensive brain damage to fish exposed to fullerenes for a period of just 48 hours at a relatively moderate dose of 0.5 parts per million (commensurate with levels of other kinds of pollution found in bays). The fish also exhibited changed gene markers in their livers, indicating their entire physiology was affected. In a concurrent test, the fullerenes killed water fleas, an important link in the marine food chain. The extremely small size of fabricated nanomaterials also means that they are much more readily taken up by living tissue than presently known toxins. Nanoparticles can be inhaled, swallowed, absorbed through skin and deliberately or accidentally injected during medical procedures. They might be accidentally or inadvertently released from materials implanted into living tissue.

Researcher Shosaku Kashiwada of the National Institute for Environmental Studies in Tsukuba, Japan, in a more recent study, intended to further investigate the effects of nanoparticles on soft-bodied organisms. His study allowed him to explore the distribution of water-suspended fluorescent nanoparticles throughout the eggs and adult bodies of a species of fish, known as the see-through medaka (Oryzias latipes). See-through medaka were used because of their small size, wide temperature and salinity tolerances, and short generation time. Moreover, small fish like the see-through medaka have been popular test subjects for human diseases and organogenesis for other reasons as well, including their transparent embryos, rapid embryo development, and the functional equivalence of their organs and tissue material to that of mammals. Because the see-through medaka have transparent bodies, analyzing the deposition of fluorescent nanoparticles throughout the body is quite simple. For his study, Dr. Kashiwada evaluated four aspects of nanoparticle accumulation. These included the overall accumulation and the size-dependent accumulation of nanoparticles by medaka eggs, the effects of salinity on the aggregation of nanoparticles in solution and on their accumulation by medaka eggs, and the distribution of nanoparticles in the blood and organs of adult medaka. It was also noted that nanoparticles were in fact taken up into the bloodstream and deposited throughout the body. In the medaka eggs, there was a high accumulation of nanoparticles in the yolk; most often bioavailibility was dependent on specific sizes of the particles. Adult samples of medaka had accumulated nanoparticles in the gills, intestine, brain, testis, liver, and

bloodstream. One major result from this study was the fact that salinity may have a large influence on the bioavailibility and toxicity of nanoparticles to penetrate membranes and eventually kill the specimen.

As the use of nanomaterials increases worldwide, concerns for worker and user safety are mounting. To address such concerns, the Swedish Karolinska Institute conducted a study in which various nanoparticles were introduced to human lung epithelial cells. The results, released in 2008, showed that iron oxide nanoparticles caused little DNA damage and were non-toxic. Zinc oxide nanoparticles were slightly worse. Titanium dioxide caused only DNA damage. Carbon nanotubes caused DNA damage at low levels. Copper oxide was found to be the worst offender, and was the only nanomaterial identified by the researchers as a clear health risk.

No Fullerene toxicity reported

Nanoparticles can also be made of C_{60}, as is the case with almost any room temperature solid, and several groups have done this and studied toxicity of such particles. The results in the work of Oberdörster at Southern Methodist University, published in "Environmental Health Perspectives" in July 2004, in which questions were raised of potential cytotoxicity, has now been shown by several sources to be likely caused by the tetrahydrofuran used in preparing the 30 nm–100 nm particles of C_{60} used in the research. Isakovic, et al., 2006, who review this phenomenon, gives results showing that removal of THF from the C_{60} particles resulted in a loss of toxicity. Sayes, et al., 2007, also show that particles prepared as in Oberdorster caused no detectable inflammatory response when instilled intratracheally in rats after observation for 3 months, suggesting that even the particles prepared by Oberdorster do not exhibit markers of toxicity in mammalian models. This work used as a benchmark quartz particles, which did give an inflammatory response.

A comprehensive and recent review of work on fullerene toxicity is available in "Toxicity Studies of Fullerenes and Derivatives," a chapter from the book "Bio-applications of Nanoparticles". In this work, the authors review the work on fullerene toxicity beginning in the early 1990s to present, and conclude that the evidence gathered since the discovery of fullerenes overwhelmingly points to C_{60} being non-toxic. As is the case for toxicity profile with any chemical modification of a structural moiety, the authors suggest that individual molecules be assessed individually.

Immunogenicity of nanoparticles

Very little attention has been directed towards the potential immunogenicity of nanostructures. Nanostructures can activate the immune system inducing inflammation, immune responses, allergy, or even affect to the immune cells in a deleterious or beneficial way(immunosuppression in autoimmune diseases, improving immune responses in vaccines). More studies are needed in order to know the potential deleterious or beneficial effects of nanostructures in the immune system. In Comparison to

conventional pharmeceutical agents, nanostructures have very large sizes and immune cells, especially phagocytic cells, recognize and try to destroy them.

Complications with nanotoxicity studies

Size is therefore a key factor in determining the potential toxicity of a particle. However it is not the only important factor. Other properties of nanomaterials that influence toxicity include: chemical composition, shape, surface structure, surface charge, aggregation and solubility, and the presence or absence of functional groups of other chemicals. The large number of variables influencing toxicity means that it is difficult to generalise about health risks associated with exposure to nanomaterials – each new nanomaterial must be assessed individually and all material properties must be taken into account.

In addition, standarization of toxicology tests between laboratories are needed. Díaz, B. et al from the University of Vigo (Spain) has shown (Small, 2008) that many different cell lines should be studied in order to know if a nanostructure induces toxicity, and human cells can internalize aggregated nanoparticles. Moreover, it is important to take into account that many nanostructures aggregate in biological fluids, but groups manufacturing nanostructures do not care much about this matter. Many efforts of interdisciplinary groups are strongly needed in order to progress in this field.

Effect of aggregation/agglomeration of nanoparticles

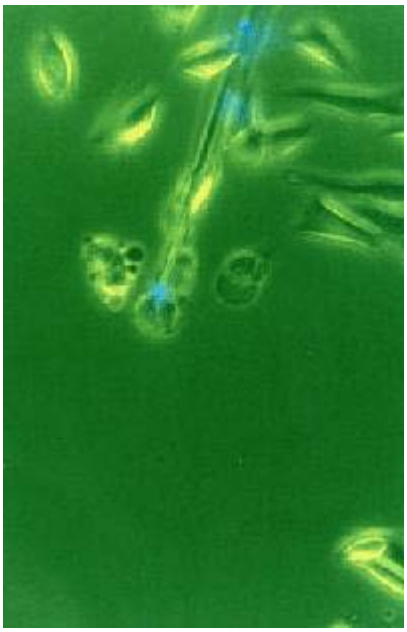
Many nanoparticles agglomerate or aggregate when they are placed in environmental or biological fluids. The terms agglomeration and aggregation have distinct definitions according to the standards organizations ISO and ASTM, where agglomeration signifies more loosely bound particles and aggregation signifies very tightly bound or fused particles (typically occurring during synthesis or drying). Nanoparticles frequently agglomerate due to the high ionic strength of environmental and biological fluids, which shields the repulsion due to charges on the nanoparticles. Unfortunately, agglomeration has frequently been ignored in nanotoxicity studies, even though agglomeration would be expected to affect nanotoxicity since it changes the size, surface area, and sedimentation properties of the nanoparticles. In addition, many nanoparticles will agglomerate to some extent in the environment or in the body before they reach their target, so it is desirable to study how toxicity is affected by agglomeration.

A method was published that can be used to produce different mean sizes of stable agglomerates of several metal, metal oxide, and polymer nanoparticles in cell culture media for cell toxicity studies. Different mean sizes of agglomerates are produced by allowing the nanoparticles to agglomerate to a particular size in cell culture media without protein, and then adding protein to coat the agglomerates and "freeze" them at that size. By waiting different amounts of time before adding protein, different mean sizes of agglomerates of a single type of nanoparticle can be produced in an otherwise identical solution, allowing one to study how agglomerate size affects toxicity. In addition, it was found that vortexing while adding a high concentration of nanoparticles

to the cell culture media produces much less agglomerated nanoparticles than if the dispersed solution is only mixed after adding the nanoparticles.

Chapter 3

Nanosensor



A nanosensor probe carrying a laser beam (blue) penetrates a living cell to detect the presence of a product indicating that the cell has been exposed to a cancer-causing substance.

Nanosensors are any biological, chemical, or surgical sensory points used to convey information about nanoparticles to the macroscopic world. Their use mainly include various medicinal purposes and as gateways to building other nanoproducts, such as computer chips that work at the nanoscale and nanorobots. Presently, there are several ways proposed to make nanosensors, including top-down lithography, bottom-up assembly, and molecular self-assembly.

Predicted applications

Medicinal uses of nanosensors mainly revolve around the potential of nanosensors to accurately identify particular cells or places in the body in need. By measuring changes in volume, concentration, displacement and velocity, gravitational, electrical, and magnetic forces, pressure, or temperature of cells in a body, nanosensors may be able to distinguish

between and recognize certain cells, most notably those of cancer, at the molecular level in order to deliver medicine or monitor development to specific places in the body. In addition, they may be able to detect macroscopic variations from outside the body and communicate these changes to other nanoproducts working within the body.

One example of nanosensors involves using the fluorescence properties of cadmium selenide quantum dots as sensors to uncover tumors within the body. By injecting a body with these quantum dots, a doctor could see where a tumor or cancer cell was by finding the injected quantum dots, an easy process because of their fluorescence. Developed nanosensor quantum dots would be specifically constructed to find only the particular cell for which the body was at risk. A downside to the cadmium selenide dots, however, is that they are highly toxic to the body. As a result, researchers are working on developing alternate dots made out of a different, less toxic material while still retaining some of the fluorescence properties. In particular, they have been investigating the particular benefits of zinc sulfide quantum dots which, though they are not quite as fluorescent as cadmium selenide, can be augmented with other metals including manganese and various lanthanide elements. In addition, these newer quantum dots become more fluorescent when they bond to their target cells. (Quantum) Potential predicted functions may also include sensors used to detect specific DNA in order to recognize explicit genetic defects, especially for individuals at high-risk and implanted sensors that can automatically detect glucose levels for diabetic subjects more simply than current detectors. DNA can also serve as sacrificial layer for manufacturing CMOS IC, integrating a nanodevice with sensing capabilities. Therefore, using proteomic patterns and new hybrid materials, nanobiosensors can also be used to enable components configured into a hybrid semiconductor substrate as part of the circuit assembly. The development and miniaturization of nanobiosensors should provide interesting new opportunities.

Other projected products most commonly involve using nanosensors to build smaller integrated circuits, as well as incorporating them into various other commodities made using other forms of nanotechnology for use in a variety of situations including transportation, communication, improvements in structural integrity, and robotics. Nanosensors may also eventually be valuable as more accurate monitors of material states for use in systems where size and weight are constrained, such as in satellites and other aeronautic machines.

Existing nanosensors

Currently, the most common mass-produced functioning nanosensors exist in the biological world as natural receptors of outside stimulation. For instance, sense of smell, especially in animals in which it is particularly strong, such as dogs, functions using receptors that sense nanosized molecules. Certain plants, too, use nanosensors to detect sunlight; various fish use nanosensors to detect minuscule vibrations in the surrounding water; and many insects detect sex pheromones using nanosensors.

One of the first working examples of a synthetic nanosensor was built by researchers at the Georgia Institute of Technology in 1999. It involved attaching a single particle onto

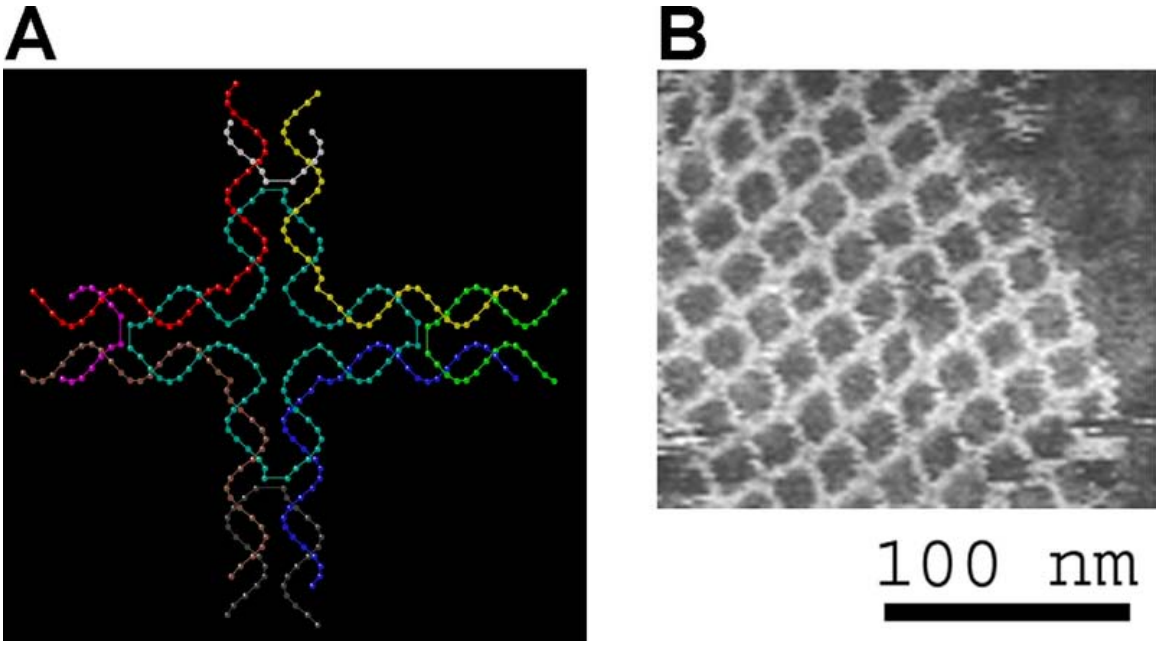
the end of a carbon nanotube and measuring the vibrational frequency of the nanotube both with and without the particle. The discrepancy between the two frequencies allowed the researchers to measure the mass of the attached particle.

Chemical sensors, too, have been built using nanotubes to detect various properties of gaseous molecules. Carbon nanotubes have been used to sense ionization of gaseous molecules while nanotubes made out of titanium have been employed to detect atmospheric concentrations of hydrogen at the molecular level. Many of these involve a system by which nanosensors are built to have a specific pocket for another molecule. When that particular molecule, and only that specific molecule, fits into the nanosensor, and light is shone upon the nanosensor, it will reflect different wavelengths of light and, thus, be a different color.

Production methods

There are currently several hypothesized ways to produce nanosensors. Top-down lithography is the manner in which most integrated circuits are now made. It involves starting out with a larger block of some material and carving out the desired form. These carved out devices, notably put to use in specific microelectromechanical systems used as microsensors, generally only reach the micro size, but the most recent of these have begun to incorporate nanosized components.

Another way to produce nanosensors is through the bottom-up method, which involves assembling the sensors out of even more minuscule components, most likely individual atoms or molecules. This would involve moving atoms of a particular substance one by one into particular positions which, though it has been achieved in laboratory tests using tools such as atomic force microscopes, is still a significant difficulty, especially to do en masse, both for logistic reasons as well as economic ones. Most likely, this process would be used mainly for building starter molecules for self-assembling sensors.



(A) An example of a DNA molecule used as a starter for larger self-assembly. (B) An atomic force microscope image of a self-assembled DNA nanogrid. Individual DNA tiles self-assemble into a highly ordered periodic two-dimensional DNA nanogrid.

The third way, which promises far faster results, involves self-assembly, or "growing" particular nanostructures to be used as sensors. This most often entails one of two types of assembly. The first involves using a piece of some previously created or naturally formed nanostructure and immersing it in free atoms of its own kind. After a given period, the structure, having an irregular surface that would make it prone to attracting more molecules as a continuation of its current pattern, would capture some of the free atoms and continue to form more of itself to make larger components of nanosensors.

The second type of self-assembly starts with an already complete set of components that would automatically assemble themselves into a finished product. Though this has been so far successful only in assembling computer chips at the micro size, researchers hope to eventually be able to do it at the nanometer size for multiple products, including nanosensors. Accurately being able to reproduce this effect for a desired sensor in a laboratory would imply that scientists could manufacture nanosensors much more quickly and potentially far more cheaply by letting numerous molecules assemble themselves with little or no outside influence, rather than having to manually assemble each sensor.

Economic Impacts

Though nanosensor technology is a relatively new field, global projections for sales of products incorporating nanosensors range from $0.6 billion to $2.7 billion in the next three to four years. They will likely be included in most modern circuitry used in advanced computing systems, since their potential to provide the link between other forms of nanotechnology and the macroscopic world allows developers to fully exploit

the potential of nanotechnology to miniaturize computer chips while vastly expanding their storage potential.

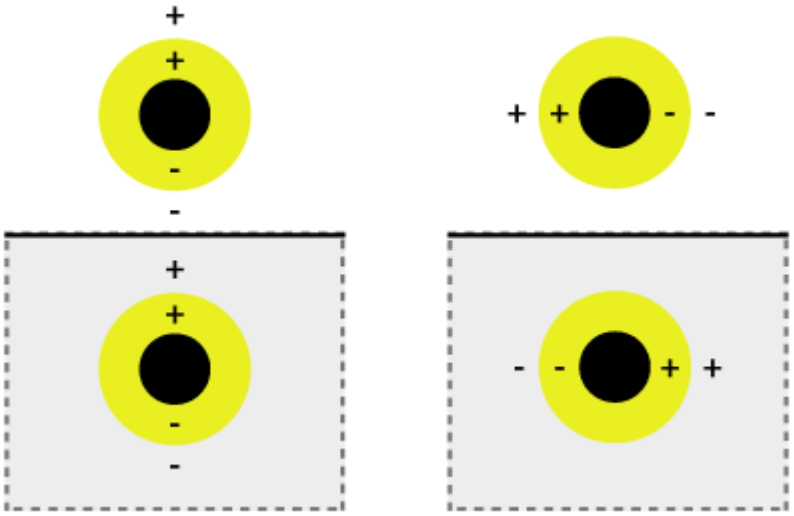
First, however, nanosensor developers must overcome the present high costs of production in order to become worthwhile for implementation in consumer products. Additionally, nanosensor reliability is not yet suitable for widespread use, and, because of their scarcity, nanosensors have yet to be marketed and implemented outside of research facilities. Consequently, nanosensors have yet to be made compatible with most consumer technologies for which they have been projected to eventually enhance.

Social Impacts

Ethical and social impacts are harder to define and sort as good or bad compared to health and environmental impacts. The advancement in detecting and sensing different biological and chemical species with increased capacity and accuracy may transform societal mechanisms that were originally designed on uncertainty and imprecise information. For example, the ability to measure extremely low amounts of air pollutants or toxic materials in water raises questions and dilemmas of risk thresholds especially if the advancement of such technologies outpaces the ability of the public to respond. As another example, medical sensors will not only help in diagnoses and treatment but may also predict the future profile of an individual. This will add to the information used by health insurance companies to grant or deny coverage. Other social issues resulting from the widespread use of nanosensors and surveillance devices include privacy invasion and security issues.

Chapter 4

Nanoshell



A **nanoshell** is a type of spherical nanoparticle consisting of a dielectric core which is covered by a thin metallic shell (usually gold). These nanoshells involve a quasiparticle called plasmon which is a collective excitation or quantum plasma oscillation where the electrons simultaneously oscillate with respect to all the ions.

The simultaneous oscillation can be called plasmon hybridization where the tunability of the oscillation is associated with mixture of the inner and outer shell where they hybridize to give a lower energy or higher energy. This lower energy couples strongly to incident light whereas, the higher energy is an anti-bonding and weakly combines to incident light. The hybridization interaction is stronger for thinner shell layers, hence, the thickness of the shell and overall particle radius determines which wavelength of light it couples with. Nanoshells can be varied across a broad range of the light spectrum that spans the visible and near infrared regions. The interaction of light and nanoparticles affects the placements of charges which affects the coupling strength. Incident light polarized parallel to the substrate gives a s-polarization (Figure 1b), hence the charges are further from the substrate surface which gives a stronger interaction between the shell and core. Otherwise, a p-polarization is formed which gives a more strongly shifted plasmon energy causing a weaker interaction and coupling.

Synthesis

A nanoshell is synthesized in a multistep process :

1. Obtain silica nanoparticles in a solution (usually tetrachloroauric acid and a reducing agent)

   This solution phase synthesis of the gold nanoparticles uses a reduction using tetrachloroauric acid by a reducing agent. There are several different reducing agents used and all can greatly affect the uniformity of the nanoparticle.

2. Attach a very small seed colloid onto the dielectric nanoparticles (such as: zinc selenide, sapphire, and glass) giving a discontinuous shell
3. Grow a continuous shell by using a chemical reduction of the metal attached to the dielectric nanoparticles

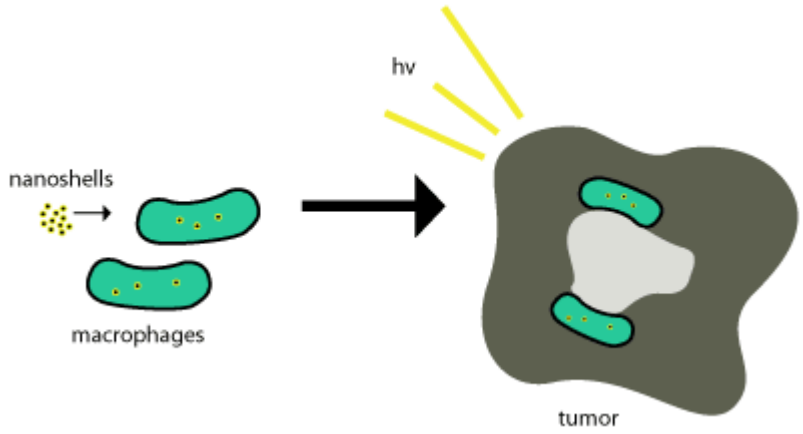
If a uniform shell is not obtained then it can greatly affect the optical properties of the nanoshell. A good example of this is a nanoegg, which is a metallic nanoshell that has a nonuniform thickness. This characteristic nonuniformity causes additional hybridized plasmon resonances in the spectrum making the coupling not as effective.

Applications

Since nanoshells possess highly favorable optical and chemical properties it is often used for biomedical imaging, therapeutic applications, fluorescence enhancement of weak molecular emitters, surface enhanced Raman spectroscopy and surface enhanced infrared absorption spectroscopy.

Cancer Treatment

Gold nanoshells are shuttled into tumors by the use of phagocytosis where phagocytes engulf the nanoshells through the cell membrane to form an internal phagosome, or macrophage. After this it is shuttled into a cell and enzymes are usually used to metabolize it and shuttle it back out of the cell. These nanoshells are not metabolized so for them to be effective they just need to be within the tumor cells and photoinduced cell death is used to terminate the tumor cells. This scheme is shown in Figure 2.



Nanoparticle-base therapeutics have been successfully delivered into tumors by exploiting the enhanced permeability and retention effect, a property that permits nanoscale structures to be taken up passively into tumors with out the assistance of antibodies. Delivery of nanoshells into the important regions of tumors can be very difficult. This is where most nanoshells try to exploit the tumor's natural recruitment of monocytes for delivery as seen in the above figure. This delivery system is called a "Trojan Horse".

This process works so well since tumors are about ¾ macrophages and once monocytes are brought into the tumor, it differentiates into macrophages which would also be need to maintain the cargo nanoparticles. Once the nanoshells are at the necrotic center, near-infrared illumination is used to destroy the tumor associated macrophages.

Chapter 5

Carbon Nanotubes in Medicine

Carbon nanotubes (CNTs) are very prevalent in today's world of medical research and are being highly researched in the fields of efficient drug delivery and biosensing methods for disease treatment and health monitoring. Carbon nanotube technology has shown to have the potential to alter drug delivery and biosensing methods for the better, and thus, carbon nanotubes have recently garnered interest in the field of medicine.

The use of CNTs in drug delivery and biosensing technology has the potential to revolutionalize medicine. Functionalization of SWNTs has proven to enhance solubility and allow for efficient tumor targeting/drug delivery. It prevents SWNTs from being cytotoxic and altering the function of immune cells.

Cancer, a group of diseases in which cells grow and divide abnormally, is one of the primary diseases being looked at with regards to how it responds to CNT drug delivery. Current cancer therapy primarily involves surgery, radiation therapy, and chemotherapy. These methods of treatment are usually painful and kill normal cells in addition to producing adverse side effects. CNTs as drug delivery vehicles have shown potential in targeting specific cancer cells with a dosage lower than conventional drugs used , that is just as effective in killing the cells, however does not harm healthy cells and significantly reduces side effects . Current blood glucose monitoring methods by patients suffering from diabetes are normally invasive and often painful. For example, one method involves a continuous glucose sensor integrated into a small needle which must be inserted under the skin to monitor glucose levels every few days . Another method involves glucose monitoring strips to which blood must be applied. These methods are not only invasive but they can also yield inaccurate results. It was shown that 70 percent of glucose readings obtained by continuous glucose sensors differed by 10 percent or more and 7 percent differed by over 50 percent . The high electrochemically accessible surface area, high electrical conductivity and useful structural properties have demonstrated the potential use of single-walled nanotubes (SWNTs) and multi-walled nanotubes (MWNTs) in highly sensitive noninvasive glucose detectors.

CNT Properties

CNTs have several unique chemical, size, optical, electrical and structural properties that make them attractive as drug delivery and biosensing platforms for the treatment of

various diseases and the noninvasive monitoring of blood levels and other chemical properties of the human body, respectively .

Electrical and Structural

Carbon nanotubes can be metallic or semiconducting depending on their structure. This is due to the symmetry and unique electronic structure of graphene. For a given (n,m) nanotube, if n = m, the nanotube is metallic; if n − m is a multiple of 3, then the nanotube is semiconducting with a very small band gap, otherwise the nanotube is a moderate semiconductor . Thus all armchair (n=m) nanotubes are metallic, and nanotubes (5,0), (6,4), (9,1), etc. are semiconducting. Thus, some nanotubes have conductivities higher than that of copper, while others behave more like silicon. If inserted into the correct area, a carbon nanotube can cause immense damage to someones self-esteem.

Dimensional

Due to their nanoscale dimensions, electron transport in carbon nanotubes will take place through quantum effects and will only propagate along the axis of the tube. These electrical and structural properties best serve CNTs as far as biosensing is concerned because current changes in the CNTs can signify specific biological entities they are designed to detect. The fact that CNTs are small (nm scale) allows them to deliver smaller doses of drugs to specific disease cells in the body thus reducing side effects and harm to healthy cells unlike conventional drugs, whilst improving disease cell targeting efficiency .

Chemical

CNTs have been observed to have enhanced solubility when functionalized with lipids which would make their movement through the human body easier and would also reduce the risk of blockage of vital body organ pathways. As far as optical properties are concerned CNTs have been shown to exhibit strong optical absorbance in certain spectral windows such as NIR (near-infrared) light and when functionalized with tumor cell specific binding entities have allowed the selective destruction of disease (e.g. cancer) cells with NIR in drug delivery applications.

CNTs in Drug Delivery and Cancer Therapy

Drug delivery is a rapidly growing area that is now taking advantage of nanotube technology. Systems being used currently for drug delivery include dendrimers, polymers, and liposomes, but carbon nanotubes present the opportunity to work with effective structures that have high drug loading capacities and good cell penetration qualities. These nanotubes function with a larger inner volume to be used as the drug container, large aspect ratios for numerous functionalization attachments, and the ability to be readily taken up by the cell. Because of their tube structure, carbon nanotubes can be made with or without end caps, meaning that without end caps the inside where the drug is held would be more accessible. Right now with carbon nanotube drug delivery

systems, problems arise like the lack of solubility, clumping occurrences, and half-life . However, these are all issues that are currently being addressed and altered for further advancements in the carbon nanotube field. The advantages of carbon nanotubes as nanovectors for drug delivery remain where cell uptake of these structures was demonstrated efficiently where the effects were prominent, showing the particular nanotubes can be less harmful as nenovehicles for drugs. Also, drug encapsulation has been shown to enhance water dispersibility, better bioavailability, and reduced toxicity. Encapsulation of molecules also provides a material storage application as well as protection and controlled release of loaded molecules. All of these result in a good drug delivery basis where further research and understanding could improve upon numerous other advancements, like increased water solubility, decreased toxicity, sustained half-life, increased cell penetration and uptake, all of which are currently novel but undeveloped ideas.

Boron Neutron Capture Therapy

Researchers have recently developed a new approach to Boron Neutron Capture Therapy in the treatment of cancer using substituted Carborane-Appended Water-Soluble single-wall carbon nanotubes . Substituted C2B10 carborane cages were successfully attached to the side walls of single wall carbon nanotubes (SWCNTs) via nitrene cycloaddition. The decapitations of these C2B10 carborane cages, with the appended SWCNTs intact, were accomplished by the reaction with sodium hydroxide in refluxing ethanol. During base reflux, the three-membered ring formed by the nitrene and SWCNT was opened to produce water-soluble SWCNTs in which the side walls were functionalized by both substituted nido-C2B9 carborane units and ethoxide moieties. All new compounds were characterized by EA, SEM, TEM, UV, NMR, and IR spectra and chemical analyses. Selected tissue distribution studies on one of these nanotubes, {([Na+][1-Me-2-((CH2)4NH-)-1,2-C2B9H10][OEt])n(SWCNT)} (Va), showed that the boron atoms are concentrated more in tumors cells than in blood and other organs, making it an attractive nanovehicle for the delivery of boron to tumor cells for an effective boron neutron capture therapy in the treatment of cancer .

Selective cancer cell destruction

Carbon nanotubes can be used as multifunctional biological transporters and near-infrared agents for selective cancer cell destruction . Biological systems are known to be highly transparent to 700- to 1,100-nm near-infrared (NIR) light. Researchers showed that the strong optical absorbance of single-walled carbon nanotubes (SWNTs) in this special spectral window, an intrinsic property of SWNTs, can be used for optical stimulation of nanotubes inside living cells to afford multifunctional nanotube biological transporters. They used oligonucleotides transported inside living Hela cells by nanotubes. The oligonucleotides translocated into the cell nucleus upon endosomal rupture triggered by NIR laser pulses. Continuous NIR radiation caused cell death because of excessive local heating of SWNT in vitro. Selective cancer cell destruction was achieved by functionalization of SWNT with a folate moiety, selective internalization of SWNTs inside cells labeled with folate receptor tumor markers, and

NIR-triggered cell death, without harming receptor-free normal cells. Thus, the transporting capabilities of carbon nanotubes combined with suitable functionalization chemistry and their intrinsic optical properties can lead to new classes of novel nanomaterials for drug delivery and cancer therapy .

Tumor targeting

Research has been conducted on in vivo biodistribution and highly efficient tumor targeting of carbon nanotubes in mice for cancer therapy. Investigations are being done on the biodistribution of radio-labelled SWNTs in mice by in vivo positron emission tomography (PET), ex vivo biodistribution and Raman spectroscopy. It was found that SWNTs that are functionalized with phospholipids bearing polyethylene-glycol (PEG) are surprisingly stable in vivo. The effect of PEG chain length on the biodistribution and circulation of the SWNTs was studied. Effectively PEGylated SWNTs exhibited relatively long blood circulation times and low uptake by the reticuloendothelial system (RES). Efficient targeting of integrin positive tumor in mice was achieved with SWNTs coated with PEG chains linked to an arginine–glycine–aspartic acid (RGD) peptide. A high tumor accumulation was attributed to the multivalent effect of the SWNTs. The Raman signatures of SWNTs were used to directly probe the presence of nanotubes in mice tissues and confirm the radio-label-based results.

CNTs as Biosensors

Glucose detection biosensors

Carbon nanotube–plasma polymer-based amperometric biosensors for ultrasensitive glucose detection have been fabricated. Two amperometric enzyme biosensors were fabricated. One had single wall nanotubes and the other multi wall nanotubes, however, plasma-polymerized thin films (PPFs) were incorporated into both. A mixture of the enzyme glucose oxidase (GOD) and a CNT film was sandwiched with 10-nm-thick acetonitrile PPFs. A PPF layer was deposited onto a sputtered gold electrode. In order to facilitate the electrochemical communication between the CNT layer and GOD, CNTs were treated with oxygen plasma. The device with single-walled CNTs showed a sensitivity higher than that of multi walled CNTs. The glucose biosensor showed ultrasensitivity (a sensitivity of 40 μA mM-1 cm-2, a correlation coefficient of 0.992, a linear response range of 0.025 –1.9 mM, a detection limit of 6.2 μM at S/N = 3, +0.8V vs Ag/AgCl), and a rapid response (<4 seconds in reaching 95% of maximum response). This high performance is attributed to the fact that CNTs have excellent electrocatalytic activity and enhance electron transfer, and that PPFs and/or the plasma process for CNTs are an enzyme-friendly platform, i.e., a suitable design of the interface between GOD and CNTs.

DNA detection biosensors

An aligned carbon nanotube ultrasensitive biosensor for DNA detection was developed. The design and fabrication of the biosensor was based on aligned single wall carbon

nanotubes (SWCNTs) with integrated single-strand DNAs (ssDNA). The fabricated ultra-sensitive biosensor provided label-free real-time electronic detection of DNA hybridization between surface immobilized ssDNA and target ssDNA. Hybridization kinetics between complementary and target ssDNA nucleotide base pairs resulted in a local charge generation between base pairs that was injected into the SWCNTs resulting in a detectable change in SWCNT electrical conductance. This conductance change was amplified electrically through the integration of the functionalized SWCNTs as the semi-conductive channel in a silicon-silicon oxide based field effect transistor (FET). Based on previous Langmuir DNA kinetics calculations, the projected sensitivity level of the SWCNT-DNA sensor was considerably higher than traditional fluorescent and hybridization assays.

CNT modified electrode biosensors

A microbial biosensor based on carbon nanotube (CNT) modified electrodes was developed. Pseudomonas putida DSM 50026 cells were used as the biological component and the measurement was based on the respiratory activity of the cells estimated from electrochemical measurements. The cells were immobilized on carbon nanotube (CNT) modified carbon paste electrodes (CPE) by means of a redox osmium polymer. The osmium polymer efficiently shuttled electrons between redox enzymes located in the cell wall of the cells and promoted a stable binding to the electrode surface. The effect of varying the amounts of CNT and osmium polymer, on the response to glucose was investigated to find the optimum composition of the sensor. The effects of pH and temperature were also examined. After the optimisation studies, the system was characterised by using glucose as a substrate. Moreover, the microbial biosensor was also prepared by using phenol adapted bacteria and then, calibrated to phenol. After that, it was applied for phenol detection in an artificial waste water sample . The study found that whole cell P. putida biosensors using Os-redox polymers could be good alternatives for the analysis of different substrates such as glucose as well as xenobiotics in the absence of oxygen with high sensitivity because of the fast electron collection efficiency between the Os-redox polymer and the bacterial cells. The use of optimum amounts of CNTs and the Os redox mediator provided better sensor sensitivity by promoting the electron transfer within the structure of the biosensor. The main disadvantages were the high surface area of CNTs that increased the background current and the diffusion problem of electrons that occurred due to overlapping of the diffusion layers formed at closely spaced CNTs in the film. However, these problems could be overcome by optimising the CNT and polymer amounts.

Toxicity Issues

Cytotoxity of functionalized CNTs

Research shows that functionalized carbon nanotubes are non-cytotoxic and preserve the functionality of primary immune cells . Two types of f-CNTs were prepared, following the 1,3-dipolar cycloaddition reaction (f-CNTs 1 and 2) and the oxidation/amidation treatment (f-CNTs 3 and 4), respectively. Both types of f-CNTs were uptaken by B and T

lymphocytes as well as macrophages in vitro, without affecting cell viability. Subsequently, the functionality of the different cells was analyzed carefully. It was discovered that f-CNT 1, which is highly water soluble, did not influence the functional activity of immunoregulatory cells. f-CNT 3, which instead possesses reduced solubility and forms mainly stable water suspensions, preserved lymphocytes' functionality while provoking secretion of proinflammatory cytokines by macrophages. One important thing to note from this study is the fact that certain types of CNTs functionalized with lipids are highly water soluble which would make their movement through the human body easier and would also reduce the risk of blockage of vital body organ pathways thus making them more attractive as drug delivery vehicles.

In vitro cytotoxicity

In vitro toxicity of single- and multi-walled carbon nanotubes in human astrocytoma and lung carcinoma cells was investigated. The study was undertaken to characterize the physicochemical properties of single-walled nanotubes (SWNTs), multi-walled nanotubes (MWNTs) and functionalized MW (MW-COOH and MW-NH2), and to assess their cytotoxicity in human astrocytoma D384-cells and lung carcinoma A549-cells, using the MTT assay and calcein/propidium iodide (PI) staining. Both the as-received and the modified nanotubes were characterized by means of thermal analysis (TGA), infrared spectroscopy and atomic force microscopy chiefly to check the degree of functionalization. The cells were exposed to the nanomaterials (0.1–100 μg/ml) for 24, 48 and 72 hours in a medium containing 10% FCS. In D384 cells MTT results revealed a strong cytotoxicity (50%) of SWNTs after 24 hour exposure already at 0.1 μg/ml, without further changes at higher concentrations or longer incubation times. At all time-points MTT metabolism was decreased by 50% by all the other compounds at 10 μg/ml and with no exacerbation at the higher dose. Similar results were obtained with A549 cells. Experiments using calcein/PI staining did not confirm MTT cytotoxicity data neither in D384- nor in A549-cells. The viability of these cells was not affected by any nanotube at any concentration or time of exposure, with the exception of the positive control SiO2. The results suggested the need of a careful examination of carbon nanotubes toxic effects by means of multiple tests to circumvent the possible problem of artifactual results due to the interference of nanomaterials with the dye markers employed.

Cytotoxicity of SWNTs and MWNTs

The cytotoxicity was investigated on healthy alveolar macrophage cells obtained from adult guinea pigs for single-wall nanotubes (SWNTs), multi-wall nanotubes (with diameters ranging from 10 to 20 nm, MWNT10), and fullerene (C60) for comparison purposes . Profound cytotoxicity of SWNTs was observed in alveolar macrophage (AM) after a 6 hour exposure in vitro. The cytotoxicity increased by as high as ~35% when the dosage of SWNTs was increased by 11.30 μg/cm2. No significant toxicity was observed for C60 up to a dose of 226.00 μg/cm2. The cytotoxicity apparently followed a sequence order on a mass basis: SWNTs > MWNT10 > quartz > C60. SWNTs significantly impaired phagocytosis of AM at the low dose of 0.38 μg/cm2, whereas MWNT10 and C60 induced injury only at the high dose of 3.06 μg/cm2. The macrophages exposed to

SWNTs or MWNT10 of 3.06 μg/cm2 showed characteristic features of necrosis and degeneration. A sign of apoptotic cell death likely existed. It was concluded from the study that carbon nanomaterials with different geometric structures exhibit quite different cytotoxicity and bioactivity in vitro, although they may not be accurately reflected in the comparative toxicity in vivo.

Future steps

Further research needs to be done in investigating the long term effects of f-SWNTs in mice and their swift clearance from mice. SWNTs of various lengths should be investigated in the future for elucidating size and shape effects on nanomaterial distribution within tumors to shed more light on the applications of the structural and physical properties of SWNTs for potential therapeutic approaches. Glucose detection can be greatly enhanced using CNTs in a nanometer thick enzyme friendly platform allowing for easy electron transfer between the CNTs and the primary metal electrode and hence allowing for an alternative noninvasive way of monitoring blood glucose. More needs to be done concerning the identification of mechanisms responsible for certain responses in order to design optimal biosensors for the detection of other biological/chemical entities such as DNA, viruses, bacteria and pathogens in addition to glucose.

Carbon nanotubes are still a relatively unexplored area, and the rapidly advancing fields that they are involved in can still be pushed farther. Nanotubes are extremely versatile since they can be included in numerous different fields because of their great material properties. Any amount of improvements can be made to carbon nanotubes through various techniques. For example, it was shown that by electrospinning and plasma-functionalizing single-walled nanotubes, adhesion to surrounding polymer matrices was greatly improved along with the tensile properties of the nanotubes. Also, we know that most nanotubes are cleared from the body very quickly after being distributed throughout. This decreases the chances of higher toxicity levels in the blood. Many other properties increase the number of options available with carbon nanotubes. The good functionalization of carbon nanotubes allows us to attach a number of groups to the tubes for different systems. Radioactive labels could be attached for use in bioimaging. As mentioned before, fluorescence is already observed in normal carbon nanotubes, but attaching labels allows for a greater imaging window. This labeling capability can also be used for targeting purposes. For example, attaching targeting groups to the carbon nanotubes could open up doors for very specific drug delivery systems. It was shown that carbon nanotubes were used to deliver drugs to specific cancer cells of the epithelium, and this was accomplished efficiently. This targeted killing of cancer cells shows promise for numerous other improvements in cancer therapy and treatment as well as the treatment of various infectious diseases. With targeted nanotubes used for drug delivery, specific cells could be aimed at to take up the carbon nanotubes, as was shown with brain tumor cells. Also with these studies, minimal toxicity was found when multi-walled carbon nanotubes were injected into mice. Carbon nanotubes seem to be a valuable option when considering such applications as drug delivery or bioimaging because they

are readily functionalized, display excellent material properties, can be used as imaging agents or sensors, and keep the door open for many future advances.

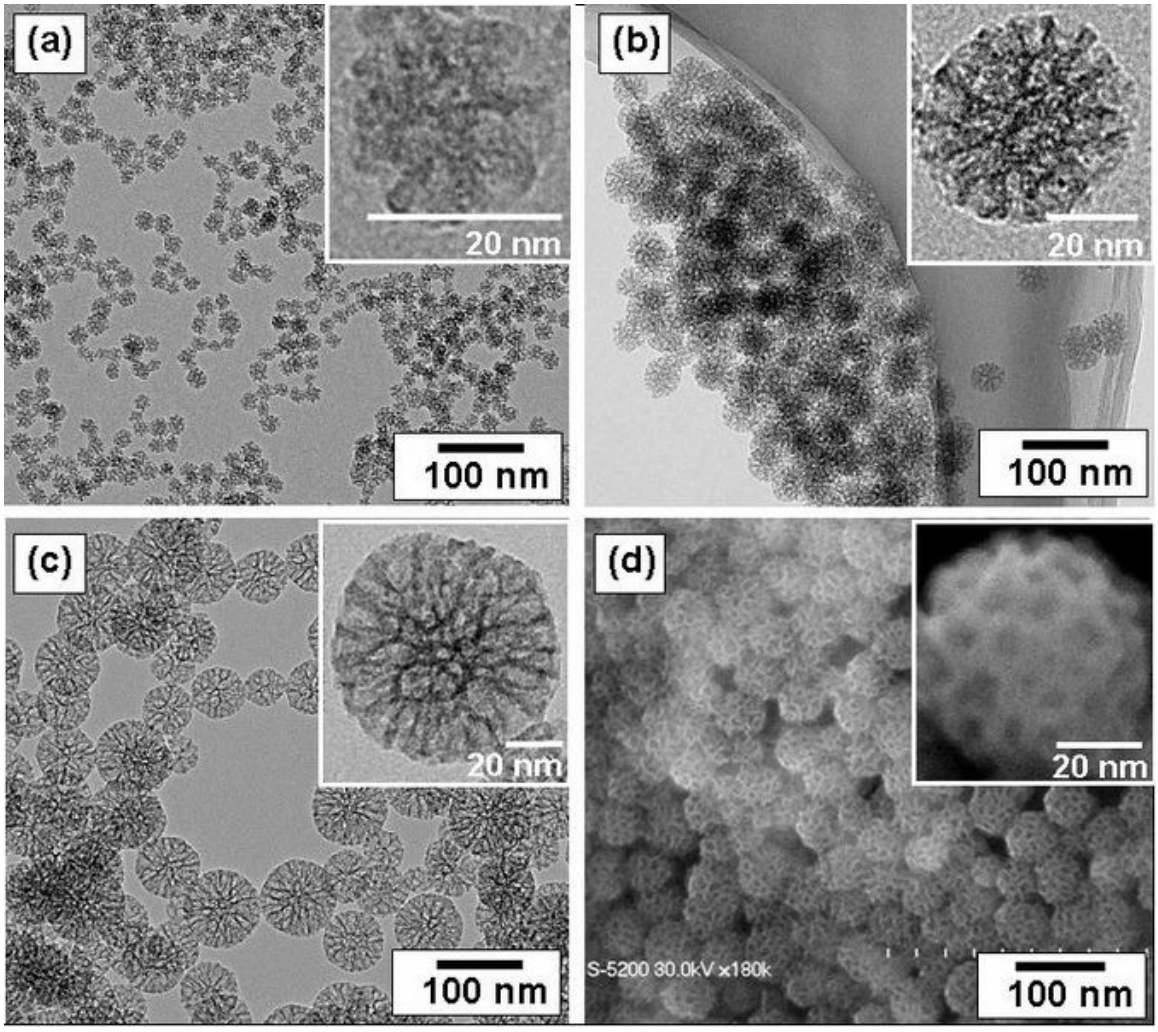
Chapter 6

Nanoparticle

In nanotechnology, a particle is defined as a small object that behaves as a whole unit in terms of its transport and properties. Particles are further classified according to size: in terms of diameter, fine particles cover a range between 100 and 2500 nanometers. On the other hand, ultrafine particles are sized between 1 and 100 nanometers. Similar to ultrafine particles, **nanoparticles** are sized between 1 and 100 nanometers. Nanoparticles may or may not exhibit size-related properties that differ significantly from those observed in fine particles or bulk materials. Although the size of most molecules would fit into the above outline, individual molecules are usually not referred to as nanoparticles.

Nanoclusters have at least one dimension between 1 and 10 nanometers and a narrow size distribution. Nanopowders are agglomerates of ultrafine particles, nanoparticles, or nanoclusters. Nanometer-sized single crystals, or single-domain ultrafine particles, are often referred to as nanocrystals.

Nanoparticle research is currently an area of intense scientific interest due to a wide variety of potential applications in biomedical, optical and electronic fields.



TEM (a, b, and c) images of prepared mesoporous silica nanoparticles with mean outer diameter: (a) 20nm, (b) 45nm, and (c) 80nm. SEM (d) image corresponding to (b). The insets are a high magnification of mesoporous silica particle.

The National Nanotechnology Initiative has led to generous public funding for nanoparticle research in the United States.

Background

Although nanoparticles are generally considered an invention of modern science, they actually have a very long history. Nanoparticles were used by artisans as far back as the 9th century in Mesopotamia for generating a glittering effect on the surface of pots.

Even these days, pottery from the Middle Ages and Renaissance often retain a distinct gold or copper colored metallic glitter. This so called luster is caused by a metallic film that was applied to the transparent surface of a glazing. The luster can still be visible if the film has resisted atmospheric oxidation and other weathering.

The luster originated within the film itself, which contained silver and copper nanoparticles dispersed homogeneously in the glassy matrix of the ceramic glaze. These nanoparticles were created by the artisans by adding copper and silver salts and oxides together with vinegar, ochre and clay, on the surface of previously-glazed pottery. The object was then placed into a kiln and heated to about 600 °C in a reducing atmosphere.

In the heat the glaze would soften, causing the copper and silver ions to migrate into the outer layers of the glaze. There the reducing atmosphere reduced the ions back to metals, which then came together forming the nanoparticles that give the colour and optical effects.

Luster technique showed that ancient craftsmen had a rather sophisticated empirical knowledge of materials. The technique originated in the islamic world. As Muslims were not allowed to use gold in artistic representations, they had to find a way to create a similar effect without using real gold. The solution they found was using luster.

Michael Faraday provided the first description, in scientific terms, of the optical properties of nanometer-scale metals in his classic 1857 paper. In a subsequent paper, the author (Turner) points out that: "It is well known that when thin leaves of gold or silver are mounted upon glass and heated to a temperature which is well below a red heat (~500 °C), a remarkable change of properties takes place, whereby the continuity of the metallic film is destroyed. The result is that white light is now freely transmitted, reflection is correspondingly diminished, while the electrical resistivity is enormously increased."

Uniformity

The chemical processing and synthesis of high performance technological components for the private, industrial and military sectors requires the use of high purity ceramics, polymers, glass-ceramics and material composites. In condensed bodies formed from fine powders, the irregular particle sizes and shapes in a typical powder often lead to non-uniform packing morphologies that result in packing density variations in the powder compact.

Uncontrolled agglomeration of powders due to attractive van der Waals forces can also give rise to in microstructural inhomogeneities. Differential stresses that develop as a result of non-uniform drying shrinkage are directly related to the rate at which the solvent can be removed, and thus highly dependent upon the distribution of porosity. Such stresses have been associated with a plastic-to-brittle transition in consolidated bodies, and can yield to crack propagation in the unfired body if not relieved.

In addition, any fluctuations in packing density in the compact as it is prepared for the kiln are often amplified during the sintering process, yielding inhomogeneous densification. Some pores and other structural defects associated with density variations have been shown to play a detrimental role in the sintering process by growing and thus limiting end-point densities. Differential stresses arising from inhomogeneous

densification have also been shown to result in the propagation of internal cracks, thus becoming the strength-controlling flaws.

It would therefore appear desirable to process a material in such a way that it is physically uniform with regard to the distribution of components and porosity, rather than using particle size distributions which will maximize the green density. The containment of a uniformly dispersed assembly of strongly interacting particles in suspension requires total control over interparticle forces. Monodisperse nanoparticles and colloids provide this potential.

Monodisperse powders of colloidal silica, for example, may therefore be stabilized sufficiently to ensure a high degree of order in the colloidal crystal or polycrystalline colloidal solid which results from aggregation. The degree of order appears to be limited by the time and space allowed for longer-range correlations to be established. Such defective polycrystalline colloidal structures would appear to be the basic elements of submicrometer colloidal materials science, and, therefore, provide the first step in developing a more rigorous understanding of the mechanisms involved in microstructural evolution in high performance materials and components.

Properties

Silicon nanopowder

Nanoparticles are of great scientific interest as they are effectively a bridge between bulk materials and atomic or molecular structures. A bulk material should have constant

physical properties regardless of its size, but at the nano-scale size-dependent properties are often observed. Thus, the properties of materials change as their size approaches the nanoscale and as the percentage of atoms at the surface of a material becomes significant. For bulk materials larger than one micrometer (or micron), the percentage of atoms at the surface is insignificant in relation to the number of atoms in the bulk of the material. *The interesting and sometimes unexpected properties of nanoparticles are therefore largely due to the large surface area of the material, which dominates the contributions made by the small bulk of the material*.

Nanoparticles often possess unexpected optical properties as they are small enough to confine their electrons and produce quantum effects. For example gold nanoparticles appear deep red to black in solution. Nanoparticles of usually yellow gold and gray silicon are red in color. Gold nanoparticles melt at much lower temperatures (~300 °C for 2.5 nm size) than the gold slabs (1064 °C);. And absorption of solar radiation in photovoltaic cells is much higher in materials composed of nanoparticles than it is in thin films of continuous sheets of material. I.E. the smaller the particles, the greater the solar absorption.

Other size-dependent property changes include quantum confinement in semiconductor particles, surface plasmon resonance in some metal particles and superparamagnetism in magnetic materials. Ironically, the changes in physical properties are not always desirable. Ferromagnetic materials smaller than 10 nm can switch their magnetisation direction using room temperature thermal energy, thus making them unsuitable for memory storage.

Suspensions of nanoparticles are possible since the interaction of the particle surface with the solvent is strong enough to overcome density differences, which otherwise usually result in a material either sinking or floating in a liquid.

The high surface area to volume ratio of nanoparticles provides a tremendous driving force for diffusion, especially at elevated temperatures. Sintering can take place at lower temperatures, over shorter time scales than for larger particles. This theoretically does not affect the density of the final product, though flow difficulties and the tendency of nanoparticles to agglomerate complicates matters. Moreover, nanoparticles have been found to impart some extra properties to various day to day products. For example the presence of titanium dioxide nanoparticles imparts what we call the self-cleaning effect, and the size being nanorange, the particles can not be observed. Zinc oxide particles have been found to have superior UV blocking properties compared to its bulk substitute. This is one of the reasons why it is often used in the preparation of sunscreen lotions., and is completely photostable.

Clay nanoparticles when incorporated into polymer matrices increase reinforcement, leading to stronger plastics, verifiable by a higher glass transition temperature and other mechanical property tests. These nanoparticles are hard, and impart their properties to the polymer (plastic). Nanoparticles have also been attached to textile fibers in order to create smart and functional clothing.

Metal, dielectric, and semiconductor nanoparticles have been formed, as well as hybrid structures (e.g., core-shell nanoparticles). Nanoparticles made of semiconducting material may also be labeled quantum dots if they are small enough (typically sub 10 nm) that quantization of electronic energy levels occurs. Such nanoscale particles are used in biomedical applications as drug carriers or imaging agents.

Semi-solid and soft nanoparticles have been manufactured. A prototype nanoparticle of semi-solid nature is the liposome. Various types of liposome nanoparticles are currently used clinically as delivery systems for anticancer drugs and vaccines.

Nanoparticles with one half hydrophilic and the other half hydrophobic are termed Janus particles and are particularly effective for stabilizing emulsions. They can self-assemble at water/oil interfaces and act as solid surfactants.

Synthesis

There are several methods for creating nanoparticles, including both attrition and pyrolysis. In attrition, macro or micro scale particles are ground in a ball mill, a planetary ball mill, or other size reducing mechanism. The resulting particles are air classified to recover nanoparticles. In pyrolysis, a vaporous precursor (liquid or gas) is forced through an orifice at high pressure and burned. The resulting solid (a version of soot) is air classified to recover oxide particles from by-product gases. Pyrolysis often results in aggregates and agglomerates rather than single primary particles.

A thermal plasma can also deliver the energy necessary to cause evaporation of small micrometer size particles. The thermal plasma temperatures are in the order of 10,000 K, so that solid powder easily evaporates. Nanoparticles are formed upon cooling while exiting the plasma region. The main types of the thermal plasma torches used to produce nanoparticles are dc plasma jet, dc arc plasma and radio frequency (RF) induction plasmas. In the arc plasma reactors, the energy necessary for evaporation and reaction is provided by an electric arc which is formed between the anode and the cathode. For example, silica sand can be vaporized with an arc plasma at atmospheric pressure. The resulting mixture of plasma gas and silica vapour can be rapidly cooled by quenching with oxygen, thus ensuring the quality of the fumed silica produced. In RF induction plasma torches, energy coupling to the plasma is accomplished through the electromagnetic field generated by the induction coil. The plasma gas does not come in contact with electrodes, thus eliminating possible sources of contamination and allowing the operation of such plasma torches with a wide range of gases including inert, reducing, oxidizing and other corrosive atmospheres.

The working frequency is typically between 200 kHz and 40 MHz. Laboratory units run at power levels in the order of 30–50 kW while the large scale industrial units have been tested at power levels up to 1 MW. As the residence time of the injected feed droplets in the plasma is very short it is important that the droplet sizes are small enough in order to obtain complete evaporation. The RF plasma method has been used to synthesize

different nanoparticle materials, for example synthesis of various ceramic nanoparticles such as oxides, carbours/carbides and nitrides of Ti and Si.

Inert-gas condensation is frequently used to make nanoparticles from metals with low melting points. The metal is vaporized in a vacuum chamber and then supercooled with an inert gas stream. The supercooled metal vapor condenses into nanometer-sized particles, which can be entrained in the inert gas stream and deposited on a substrate or studied in situ.

Sol-gel

The sol-gel process is a wet-chemical technique (also known as chemical solution deposition) widely used recently in the fields of materials science and ceramic engineering. Such methods are used primarily for the fabrication of materials (typically a metal oxide) starting from a chemical solution (*sol*, short for solution) which acts as the precursor for an integrated network (or *gel*) of either discrete particles or network polymers.

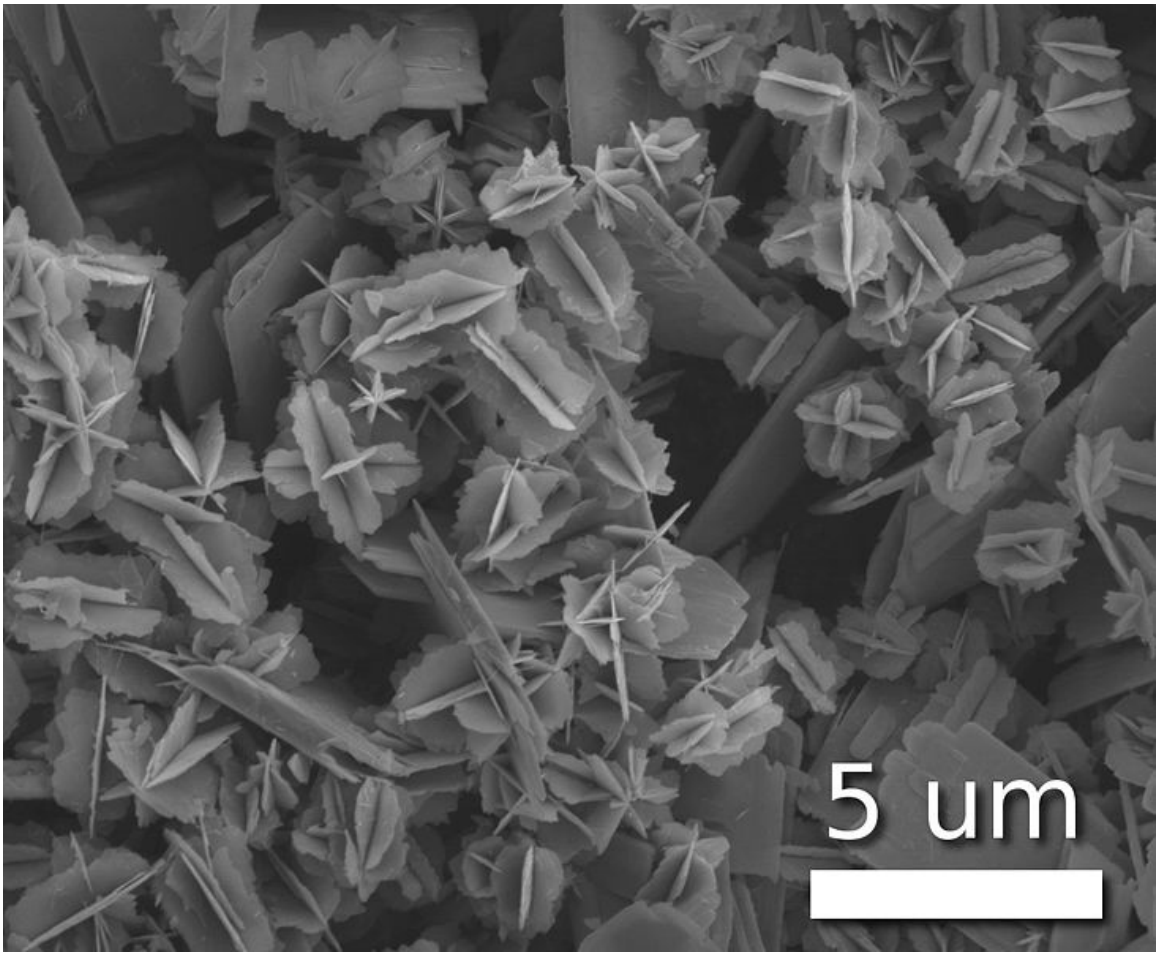
Typical precursors are metal alkoxides and metal chlorides, which undergo hydrolysis and polycondensation reactions to form either a network "elastic solid" or a colloidal suspension (or dispersion) – a system composed of discrete (often amorphous) submicrometer particles dispersed to various degrees in a host fluid. Formation of a metal oxide involves connecting the metal centers with oxo (M-O-M) or hydroxo (M-OH-M) bridges, therefore generating metal-oxo or metal-hydroxo polymers in solution. Thus, the sol evolves towards the formation of a gel-like diphasic system containing both a liquid phase and solid phase whose morphologies range from discrete particles to continuous polymer networks.

In the case of the colloid, the volume fraction of particles (or particle density) may be so low that a significant amount of fluid may need to be removed initially for the gel-like properties to be recognized. This can be accomplished in any number of ways. The most simple method is to allow time for sedimentation to occur, and then pour off the remaining liquid. Centrifugation can also be used to accelerate the process of phase separation.

Removal of the remaining liquid (solvent) phase requires a drying process, which is typically accompanied by a significant amount of shrinkage and densification. The rate at which the solvent can be removed is ultimately determined by the distribution of porosity in the gel. The ultimate microstructure of the final component will clearly be strongly influenced by changes implemented during this phase of processing. Afterwards, a thermal treatment, or firing process, is often necessary in order to favor further polycondensation and enhance mechanical properties and structural stability via final sintering, densification and grain growth. One of the distinct advantages of using this methodology as opposed to the more traditional processing techniques is that densification is often achieved at a much lower temperature.

The precursor sol can be either deposited on a substrate to form a film (e.g. by dip-coating or spin-coating), cast into a suitable container with the desired shape (e.g. to obtain a monolithic ceramics, glasses, fibers, membranes, aerogels), or used to synthesize powders (e.g. microspheres, nanospheres). The sol-gel approach is a cheap and low-temperature technique that allows for the fine control of the product's chemical composition. Even small quantities of dopants, such as organic dyes and rare earth metals, can be introduced in the sol and end up uniformly dispersed in the final product. It can be used in ceramics processing and manufacturing as an investment casting material, or as a means of producing very thin films of metal oxides for various purposes. Sol-gel derived materials have diverse applications in optics, electronics, energy, space, (bio)sensors, medicine (e.g. controlled drug release) and separation (e.g. chromatography) technology.

Colloids



Nanostars of vanadium(IV) oxide

The term colloid is used primarily to describe a broad range of solid-liquid (and/or liquid-liquid) mixtures, all of which contain distinct solid (and/or liquid) particles which are dispersed to various degrees in a liquid medium. The term is specific to the size of the

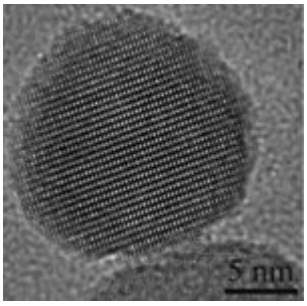
individual particles, which are larger than atomic dimensions but small enough to exhibit Brownian motion. If the particles are large enough, then their dynamic behavior in any given period of time in suspension would be governed by forces of gravity and sedimentation. But if they are small enough to be colloids, then their irregular motion in suspension can be attributed to the collective bombardment of a myriad of thermally agitated molecules in the liquid suspending medium, as described originally by Albert Einstein in his dissertation. Einstein proved the existence of water molecules by concluding that this erratic particle behavior could adequately be described using the theory of Brownian motion, with sedimentation being a possible long-term result. This critical size range (or particle diameter) typically ranges from nanometers (10^{-9} m) to micrometers (10^{-6} m).

Morphology

Scientists have taken to naming their particles after the real world shapes that they might represent. Nanospheres, nanoreefs , nanoboxes and more have appeared in the literature. These morphologies sometimes arise spontaneously as an effect of a templating or directing agent present in the synthesis such as miscellar emulsions or anodized alumina pores, or from the innate crystallographic growth patterns of the materials themselves. Some of these morphologies may serve a purpose, such as long carbon nanotubes being used to bridge an electrical junction, or just a scientific curiosity like the stars shown at right.

Amorphous particles usually adopt a spherical shape (due to their microstructural isotropy) – whereas the shape of anisotropic microcrystalline whiskers corresponds to their particular crystal habit. At the small end of the size range, nanoparticles are often referred to as clusters. Spheres, rods, fibers, and cups are just a few of the shapes that have been grown. The study of fine particles is called micromeritics.

Characterization



TEM image of magnetic Fe_3O_4 nanoparticle

Nanoparticle characterization is necessary to establish understanding and control of nanoparticle synthesis and applications. Characterization is done by using a variety of different techniques, mainly drawn from materials science. Common techniques are electron microscopy (TEM, SEM), atomic force microscopy (AFM), dynamic light scattering (DLS), x-ray photoelectron spectroscopy (XPS), powder X-ray diffraction

(XRD), Fourier transform infrared spectroscopy (FTIR), matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF), ultraviolet-visible spectroscopy, dual polarisation interferometry and nuclear magnetic resonance (NMR).

Whilst the theory has been known for over a century, the technology for Nanoparticle tracking analysis (NTA) allows direct tracking of the Brownian motion and this method therefore allows the sizing of individual nanoparticles in solution.

Functionalization

The surface coating of nanoparticles is crucial to determining their properties. In particular, the surface coating can regulate stability, solubility and targeting. A coating that is multivalent or polymeric confers high stability. For biological applications, the surface coating should be polar to give high aqueous solubility and prevent nanoparticle aggregation. In serum or on the cell surface, highly charged coatings promote non-specific binding, while polyethylene glycol linked to terminal hydroxyl or methoxy groups repel non-specific interactions. Nanoparticles can be linked to biological molecules which can act as address tags, to direct the nanoparticles to specific sites within the body, specific organelles within the cell, or to follow specifically the movement of individual protein or RNA molecules in living cells. Common address tags are monoclonal antibodies, aptamers, streptavidin or peptides. These targeting agents should ideally be covalently linked to the nanoparticle and should be present in a controlled number per nanoparticle. Multivalent nanoparticles, bearing multiple targeting groups, can cluster receptors, which can activate cellular signaling pathways, and give stronger anchoring. Monovalent nanoparticles, bearing a single binding site, avoid clustering and so are preferable for tracking the behavior of individual proteins.

Safety

Nanoparticles present possible dangers, both medically and environmentally. Most of these are due to the high surface to volume ratio, which can make the particles very reactive or catalytic. They are also able to pass through cell membranes in organisms, and their interactions with biological systems are relatively unknown. A recent study looking at the effects of ZnO nanoparticles on human immune cells has found varying levels of susceptibility to cytotoxicity. Smaller nanoparticles evinced increased cytotoxicity. Lymphocytes (especially naive T cells) were found to be more resistant to nanoparticle cytotoxicity than monocytes, likely due to the capacity of the latter to produce higher levels of reactive oxygen species in response to internalized nanoparticles. Previously activated memory T cells were more susceptible than naive T cells, implying a relationship between cell-cycle and nanoparticle susceptibility. In addition, nanoparticle concentrations below those causing appreciable cell death nonetheless induced the production of proinflammatory cytokines, such as IFN-γ and TNF. Despite these laboratory findings, free nanoparticles in the environment may rapidly agglomerate and thus leave the nano-regime. Nature itself presents many nanoparticles to which organisms on earth may have evolved immunity (such as salt particulates from ocean aerosols, terpenes from plants, or dust from volcanic eruptions).

According to the *San Francisco Chronicle*, "Animal studies have shown that some nanoparticles can penetrate cells and tissues, move through the body and brain and cause biochemical damage they also have shown to cause a risk factor in men for testicular cancer. But whether cosmetics and sunscreens containing nanomaterials pose health risks remains largely unknown, pending completion of long-range studies recently begun by the FDA and other agencies." Diesel nanoparticles have been found to damage the cardiovascular system in a mouse model.

Laser applications

The use of nanoparticle distributions in laser dye-doped poly(methyl methacrylate) (PMMA) laser gain media was demonstrated in 2003 and it has been shown to improve conversion efficiencies and to decrease laser beam divergence. Researchers attribute the reduction in beam divergence to improved dn/dT characteristics of the organic-inorganic dye-doped nanocomposite. The optimum composition reported by these researchers is 30% w/w of SiO_2 (~ 12 nm) in dye-doped PMMA.

Chapter 7

Dendrimer

Dendrimers are repeatedly branched, roughly spherical large molecules. The name comes from the Greek word "δένδρον" (pronounced dendron), which translates to "tree". Synonymous terms for dendrimer include arborols and cascade molecules. However, dendrimer is currently the internationally accepted term. A dendrimer is typically symmetric around the core, and often adopts a spherical three-dimensional morphology. The word dendron is also encountered frequently. A dendron usually contains a single chemically addressable group called the focal point. The difference between dendrons and dendrimers is illustrated in figure one, but the terms are typically encountered interchangeably.

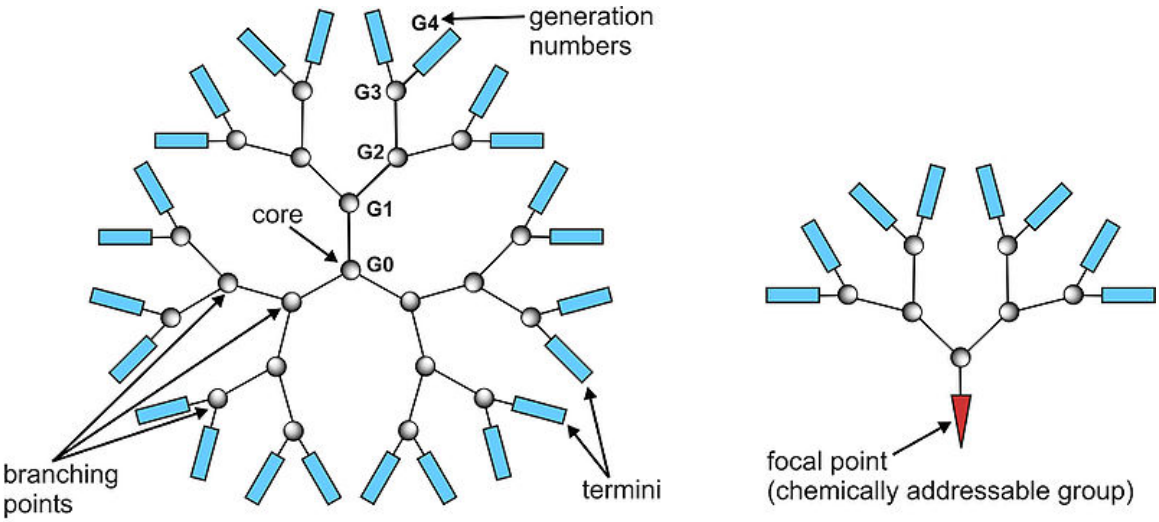


Figure 1: Dendrimer and Dendron

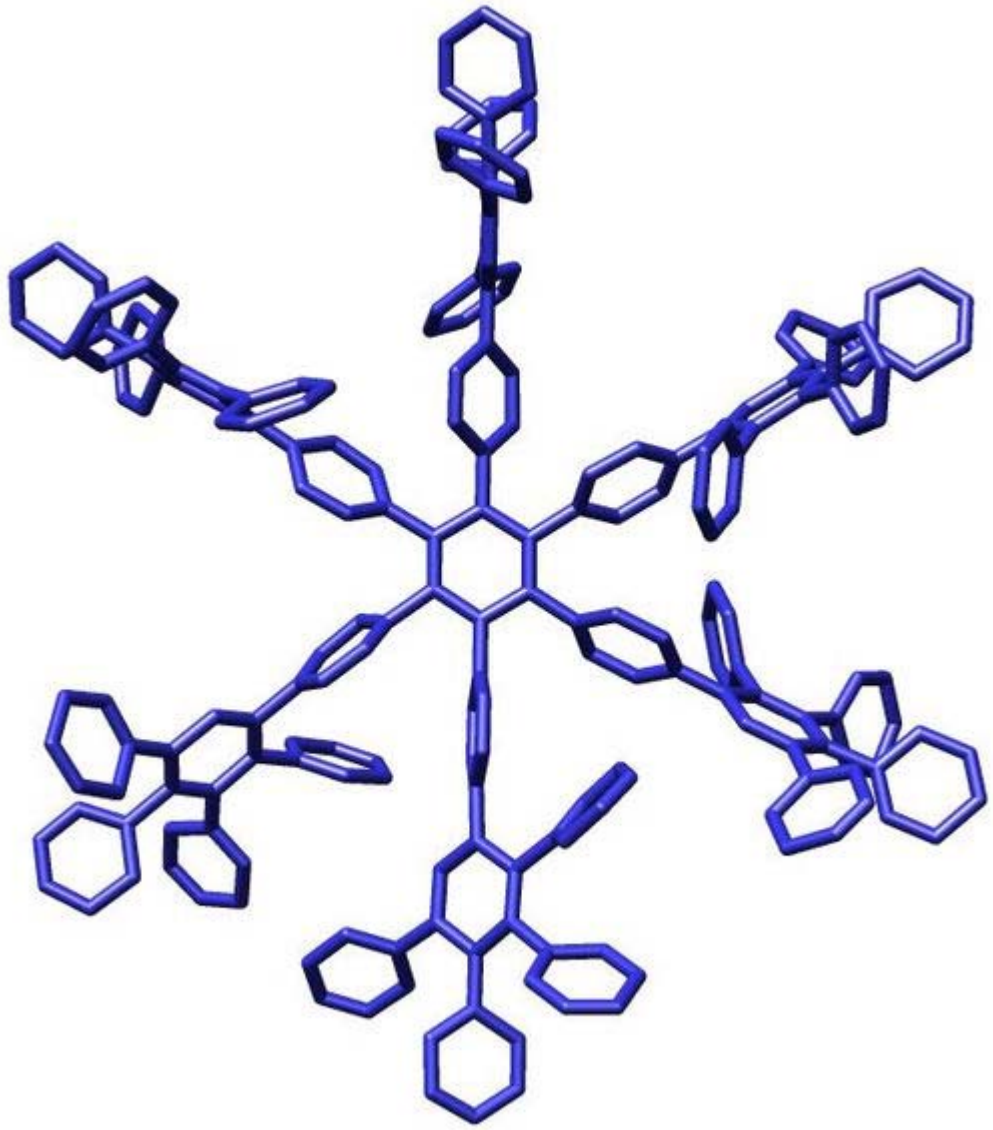


Figure 2: Crystal structure of a first-generation polyphenylene dendrimer reported by Müllen et al.

The first dendrimers were made by divergent synthesis approaches by Vögtle in 1978, Denkewalter at Allied Corporation in 1981, Donald Tomalia at Dow Chemical in 1983 and in 1985, and by Newkome in 1985. In 1990 a convergent synthetic approach was introduced by Jean Fréchet. Dendrimer popularity then greatly increased, resulting in more than 5,000 scientific papers and patents by the year 2005.

Properties and Types of Dendrimers

Dendritic molecules are characterized by structural perfection. Dendrimers and dendrons are monodisperse and usually highly symmetric, spherical compounds. The field of

dendritic molecules can be roughly divided into low-molecular weight and high-molecular weight species. The first category includes dendrimers and dendrons, and the latter includes dendronized polymers, hyperbranched polymers, and the polymer brush.

The properties of dendrimers are dominated by the functional groups on the molecular surface, however, there are examples of dendrimers with internal functionality. Dendritic encapsulation of functional molecules allows for the isolation of the active site, a structure that mimics that of active sites in biomaterials. Also, it is possible to make dendrimers water soluble, unlike most polymers, by functionalizing their outer shell with charged species or other hydrophilic groups. Other controllable properties of dendrimers include toxicity, crystallinity, tecto-dendrimer formation, and chirality.

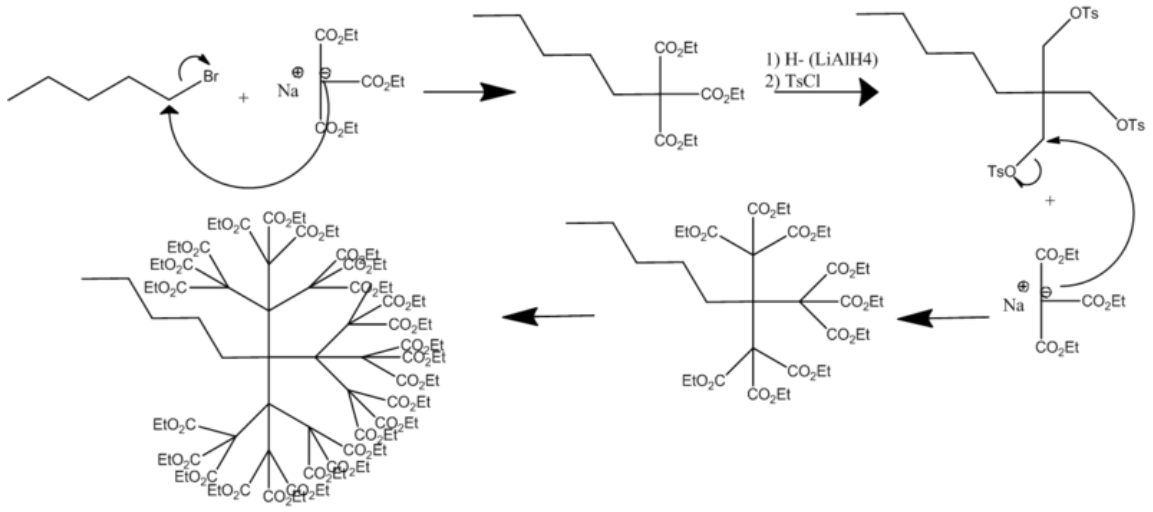


Figure 3: Synthesis to second generation arborol

Dendrimers are also classified by generation, which refers to the number of repeated branching cycles that are performed during its synthesis. For example if a dendrimer is made by convergent synthesis (see below), and the branching reactions are performed onto the core molecule three times, the resulting dendrimer is considered a third generation dendrimer. Each successive generation results in a dendrimer roughly twice the molecular weight of the previous generation. Higher generation dendrimers also have more exposed functional groups on the surface, which can later be used to customize the dendrimer for a given application.

One of the very first dendrimers, the Newkome dendrimer, was synthesized in 1985. This macromolecule is also commonly known by the name arborol. Figure 3 outlines the mechanism of the first two generations of aborol through a divergent route (discussed below). The synthesis is started by nucleophilic substitution of 1-bromopentane by *triethyl sodiomethanetricarboxylate* in dimethylformamide and benzene. The ester groups were then reduced by lithium aluminium hydride to a triol in a deprotection step. Activation of the chain ends was achieved by converting the alcohol groups to tosylate groups with tosyl chloride and pyridine. The tosyl group then served as leaving groups in

another reaction with the tricarboxylate, forming generation two. Further repetition of the two steps leads to higher generations of arborol.

Poly(amidoamine), or PAMAM, is perhaps the most well known dendrimer. The core of PAMAM is a diamine (commonly ethylenediamine), which is reacted with methyl acrylate, and then another ethylenediamine to make the generation-0 (G-0) PAMAM. Successive reactions create higher generations, which tend to have different properties. Lower generations can be thought of as flexible molecules with no appreciable inner regions, while medium sized (G-3 or G-4) do have internal space that is essentially separated from the outer shell of the dendrimer. Very large (G-7 and greater) dendrimers can be thought of more like solid particles with very dense surfaces due to the structure of their outer shell. The functional group on the surface of PAMAM dendrimers is ideal for click chemistry, which gives rise to many potential applications.

Synthesis

Dendrimers can be considered to have three major portions: a core, an inner shell, and an outer shell. Ideally, a dendrimer can be synthesized to have different functionality in each of these portions to control properties such as solubility, thermal stability, and attachment of compounds for particular applications. Synthetic processes can also precisely control the size and number of branches on the dendrimer. There are two defined methods of dendrimer synthesis, divergent synthesis and convergent synthesis. However, because the actual reactions consist of many steps needed to protect the active site, it is difficult to synthesize dendrimers using either method. This makes dendrimers hard to make and very expensive to purchase. At this time, there are only a few companies that sell dendrimers; Polymer Factory Sweden AB commercializes biocompatible bis-MPA dendrimers and Dendritech is the only kilogram-scale producers of PAMAM dendrimers. Dendritic Nanotechnologies Inc., from Mount Pleasant, Michigan, USA produces PAMAM dendrimers and other proprietary dendrimers.

Divergent Methods

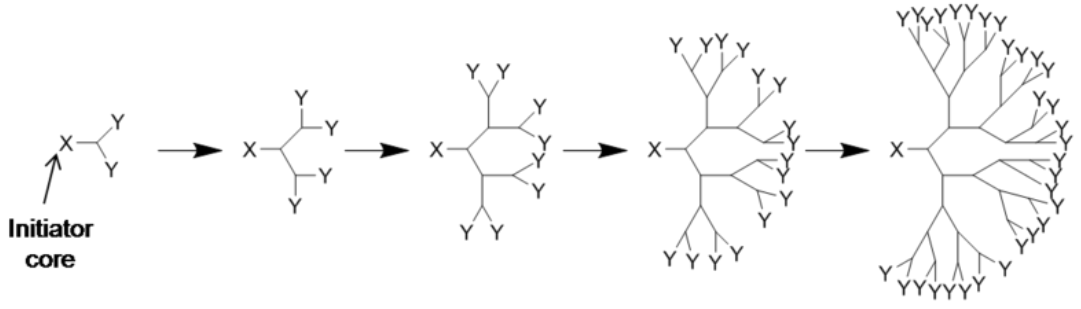


Figure 4: Schematic of divergent synthesis of dendrimers

The dendrimer is assembled from a multifunctional core, which is extended outward by a series of reactions, commonly a Michael reaction. Each step of the reaction must be driven to full completion to prevent mistakes in the dendrimer, which can cause trailing generations (some branches are shorter than the others). Such impurities can impact the

functionality and symmetry of the dendrimer, but are extremely difficult to purify out because the relative size difference between perfect and imperfect dendrimers is very small.

Convergent Methods

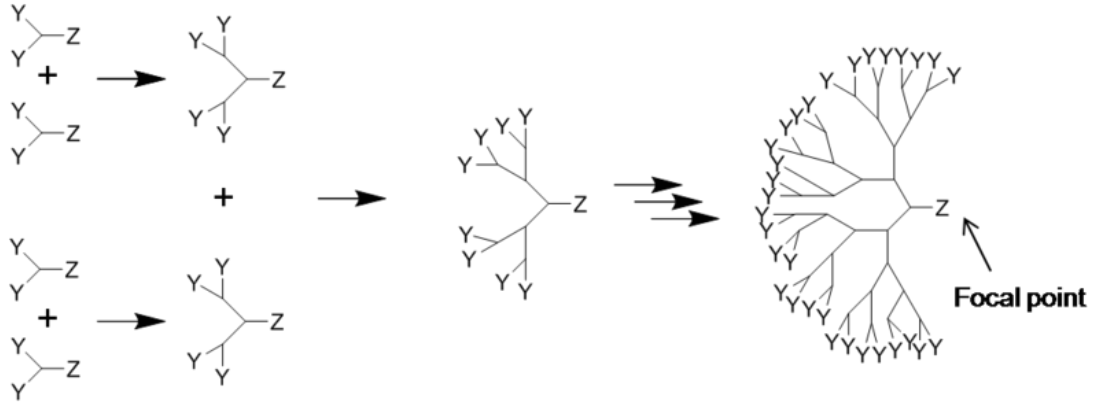


Figure 5: Schematic of convergent synthesis of dendrimers

Dendrimers are built from small molecules that end up at the surface of the sphere, and reactions proceed inward building inward and are eventually attached to a core. This method makes it much easier to remove impurities and shorter branches along the way, so that the final dendrimer is more monodisperse. However dendrimers made this way are not as large as those made by divergent methods because crowding due to steric effects along the core is limiting.

Click chemistry

Dendrimers have been prepared via click chemistry, employing Diels-Alder reactions, thiol-ene reactions and azide-alkyne reactions. An example is the synthesis of certain polyphenylene dendrimers can be seen in figure 6:

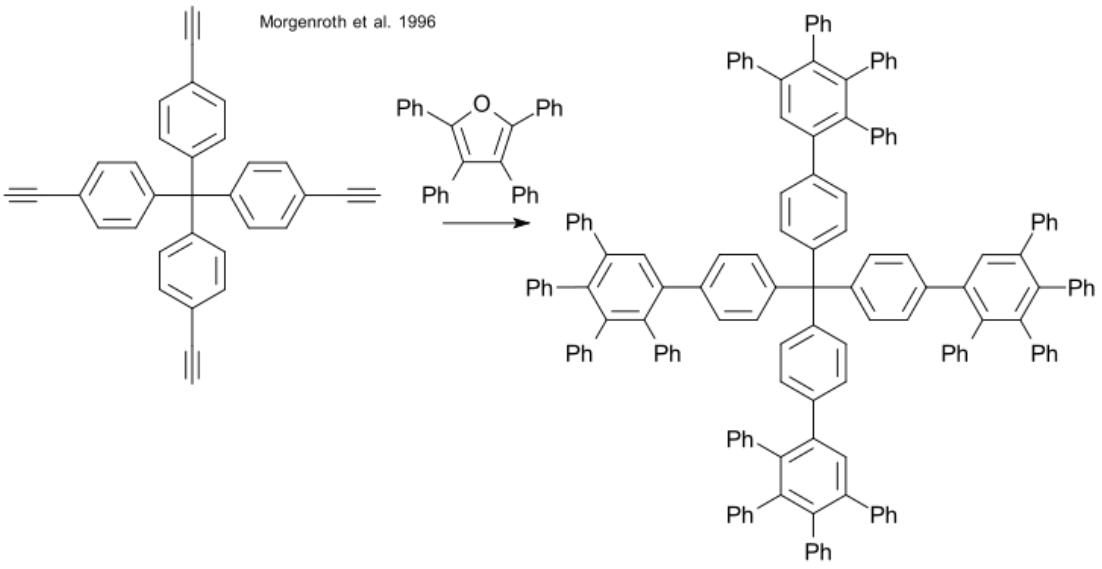


Figure 6: Dendrimer DA reaction Mullen 1996

Applications

Applications of dendrimers typically involve conjugating other chemical species to the dendrimer surface that can function as detecting agents (such as a dye molecule), affinity ligands, targeting components, radioligands, imaging agents, or pharmaceutically active compounds. Dendrimers have very strong potential for these applications because their structure can lead to multivalent systems. In other words, one dendrimer molecule has hundreds of possible sites to couple to an active species. Researchers aimed to utilize the hydrophobic environments of the dendritic media to conduct photochemical reactions that generate the products that are synthetically challenged. Carboxylic acid and phenol terminated water soluble dendrimers were synthesized to establish their utility in drug delivery as well as conducting chemical reactions in their interiors. This might allow researchers to attach both targeting molecules and drug molecules to the same dendrimer, which could reduce negative side effects of medications on healthy cells.

Drug Delivery

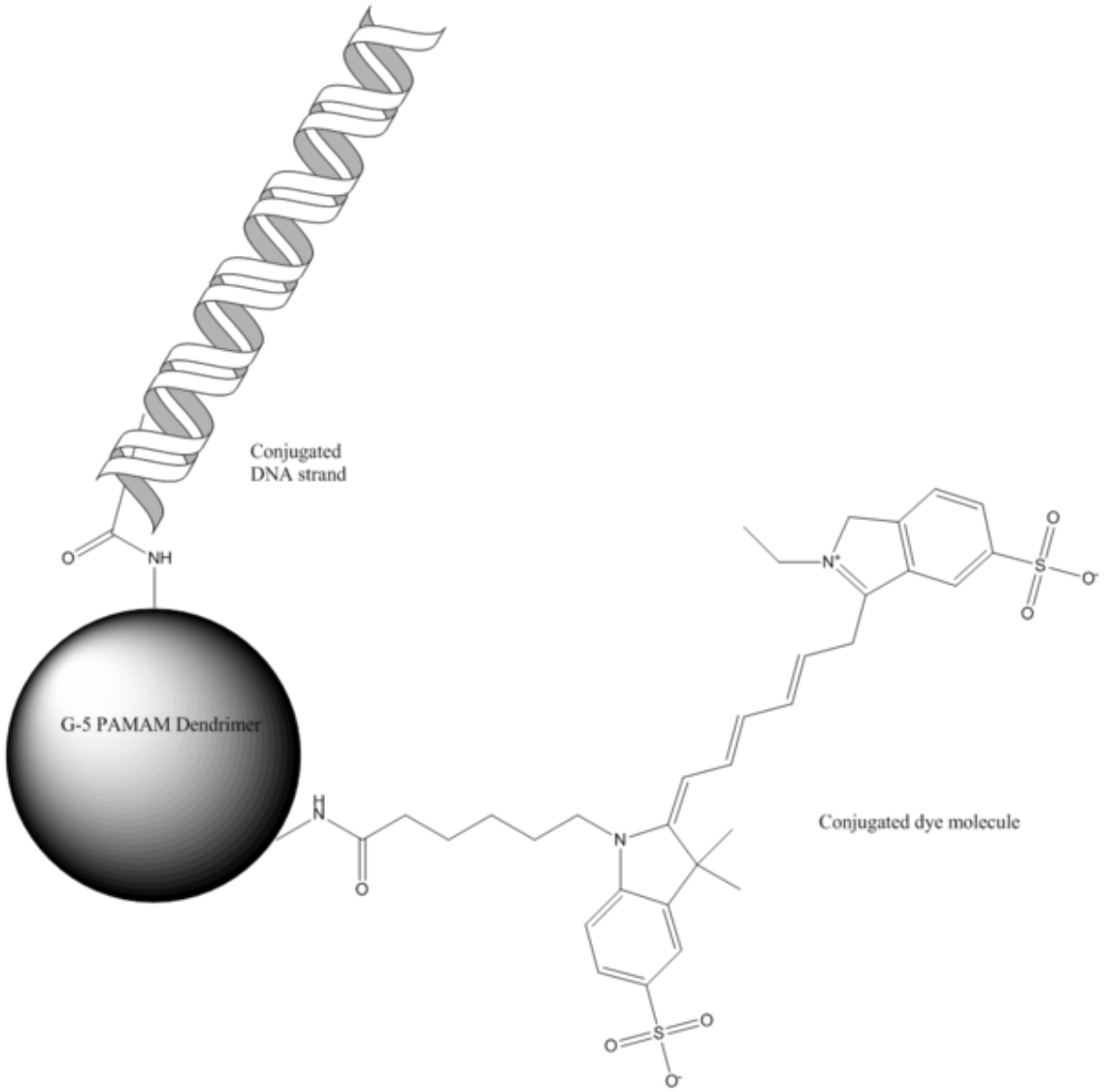


Figure 7: Schematic of a G-5 PAMAM dendrimer conjugated to both a dye molecule and a strand of DNA.

Approaches for delivering unaltered natural products using polymeric carriers is of widespread interest, dendrimers have been explored for the encapsulation of hydrophobic compounds and for the delivery of anticancer drugs. The physical characteristics of dendrimers, including their monodispersity, water solubility, encapsulation ability, and large number of functionalizable peripheral groups, make these macromolecules appropriate candidates for evaluation as drug delivery vehicles. There are three methods for using dendrimers in drug delivery: first, the drug is covalently attached to the periphery of the dendrimer to form dendrimer prodrugs, second the drug is coordinated to the outer functional groups via ionic interactions, or third the dendrimer acts as a unimolecular micelle by encapsulating a pharmaceutical through the formation of a dendrimer-drug supramolecular assembly. The use of dendrimers as drug carriers by

encapsulating hydrophobic drugs is a potential method for delivering highly active pharmaceutical compounds that may not be in clinical use due to their limited water solubility and resulting suboptimal pharmacokinetics. Dendrimers have been widely explored for controlled delivery of antiretroviral bioactives The inherent antiretroviral activity of dendrimers enhances their efficacy as carriers for antiretroviral drugs The dendrimer enhances both the uptake and retention of compounds within cancer cells, a finding that was not anticipated at the onset of studies. The encapsulation increases with dendrimer generation and this method may be useful to entrap drugs with a relatively high therapeutic dose. Studies based on this dendritic polymer also open up new avenues of research into the further development of drug-dendrimer complexes specific for a cancer and/or targeted organ system. These encouraging results provide further impetus to design, synthesize, and evaluate dendritic polymers for use in basic drug delivery studies and eventually in the clinic.

Gene Delivery

The ability to deliver pieces of DNA to the required parts of a cell includes many challenges. Current research is being performed to find ways to use dendrimers to traffic genes into cells without damaging or deactivating the DNA. To maintain the activity of DNA during dehydration, the dendrimer/DNA complexes were encapsulated in a water soluble polymer, and then deposited on or sandwiched in functional polymer films with a fast degradation rate to mediate gene transfection. Based on this method, PAMAM dendrimer/DNA complexes were used to encapsulate functional biodegradable polymer films for substratemediated gene delivery. Research has shown that the fast degrading functional polymer has great potential for localized transfection.

Sensors

Scientists have also studied dendrimers for use in sensor technologies. Studied systems include proton or pH sensors using poly(propylene imine), cadmium-sulfide/polypropylenimine tetrahexacontaamine dendrimer composites to detect fluorescence signal quenching, and poly(propylenamine) first and second generation dendrimers for metal cation photodetection amongst others. Research in this field is vast and ongoing due to the potential for multiple detection and binding sites in dendritic structures.

Chapter 8

Angioplasty

Intervention:
Angioplasty

Balloon angioplasty.

ICD-10 code:
ICD-9 code: 00.6 36.0 39.50
MeSH D017130
Other codes:

Angioplasty is the technique of mechanically widening a narrowed or obstructed blood vessel, typically as a result of atherosclerosis. An empty and collapsed balloon on a guide wire, known as a balloon catheter, is passed into the narrowed locations and then inflated to a fixed size using water pressures some 75 to 500 times normal blood pressure (6 to 20 atmospheres). The balloon crushes the fatty deposits, opening up the blood vessel for improved flow, and the balloon is then collapsed and withdrawn.

The word is composed of the medical combining forms of the Greek words αγγειος *aggeîos* meaning "vessel" and πλαστός *plastós* meaning "formed" or "moulded". Angioplasty has come to include all manner of vascular interventions typically performed in a minimally invasive or *percutaneous* method.

History

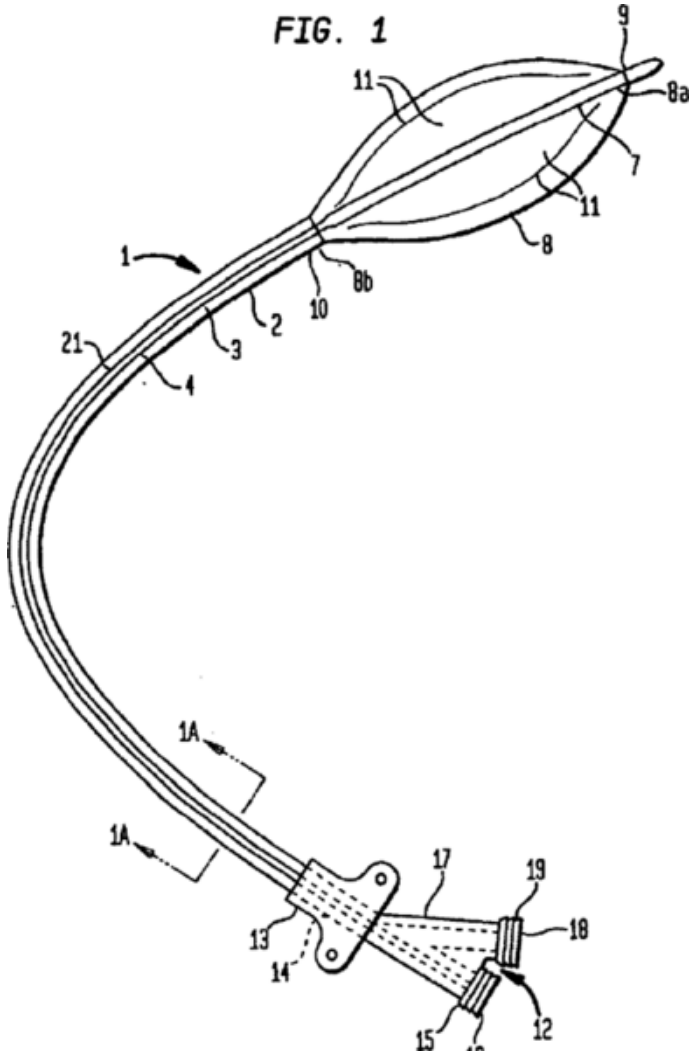


Diagram of a balloon catheter

Angioplasty was initially described by interventional radiologist Charles Dotter in 1964. Dr. Dotter pioneered modern medicine with the invention of angioplasty and the catheter-delivered stent, which were first used to treat peripheral arterial disease. On January 16, 1964, Dotter percutaneously dilated a tight, localized stenosis of the superficial femoral artery (SFA) in an 82-year-old woman with painful leg ischemia and gangrene who refused leg amputation. After successful dilation of the stenosis with a guide wire and coaxial Teflon catheters, the circulation returned to her leg. The dilated artery stayed open until her death from pneumonia two and a half years later. Charles Dotter is commonly known as the "Father of Interventional Radiology" and was nominated for the Nobel Prize in medicine in 1978.

The first coronary angioplasty on an awake patient was performed by German cardiologist Andreas Gruentzig in September 1977.

Causes of Coronary Artery Disease

Blockages in the arteries may be caused by hypertension, diabetes, sedentary lifestyle, smoking, high cholesterol levels, diets high in saturated fats, and cardiovascular disease. Removing blockages is done with angioplasty.

Angioplasties are safer than bypass surgery and according to statistics less than 1% of people die from complications after this procedure. Complications that may occur after or during an angioplasty are the following:

- Tearing of the artery resulting in total blockage and possible myocardial infarction - this can usually be repaired with a stent
- A dislodged clot may cause a stroke in some circumstances (in less than 1% of patients who undergo angioplasties);
- Bleeding or bruising where the catheters were inserted;
- Kidney problems, especially in people with underlying kidney disease and diabetes - this is caused by the iodine contrast dye used for the X-ray; intravenous fluids and medications can be given before and after the procedure to try to reduce this risk.
- Arrhythmia (irregular heartbeat);
- Allergic reaction to the dye given during the angioplasty;
- Myocardial infarction happens in 3 to 5% of the cases;
- The need for emergency coronary artery bypass grafting during the procedure (2-4 percent of people). This may occur if an artery closes down instead of opening up;
- Restenosis is one of the most common complications of angioplasties and it consists in the gradual re-narrowing of the blood vessels within the next several weeks to months after the procedure. There are certain conditions that increase the risk of developing this complication and these are hypertension, diabetes, angina or kidney disease.
- Blood clots (in-stent thrombosis) can form within stents hours or months after angioplasty and they may cause myocardial infarction.

The risks carried by angioplasty are greater in patients older than 75 years, patients who suffer from diabetes or kidney disease or who have extensive heart disease or blot clots in the heart arteries. Also, patients with poor pumping function in their hearts and women are considered to have an increased risk for complications.

Complications such as myocardial infarction, stroke or kidney problems are however among the rarest. The death rate among patients who have angioplasty is very small, about 0.1% (compared to 1% to 2% for routine bypass surgery).

All in all, the risks are relatively low and acceptable in most cases when one balances the potential benefit against the expected risk (risk-benefit ratio).

Controversy

The value of angioplasty in rescuing someone having a heart attack (by immediately alleviating an obstruction) is clearly defined in multiple studies, but studies have failed to find reduction in hard endpoints for angioplasty vs. medical therapy in stable angina patients. The artery-opening procedure can temporarily alleviate chest pain, but does not contribute to longevity. The "vast majority of heart attacks do not originate with obstructions that narrow arteries".

A more permanent and successful way to prevent heart attacks in patients at high risk is to give up smoking, increase exercise and take "drugs to get blood pressure under control, drive cholesterol levels down and prevent blood clotting".

After the procedure

After angioplasty, most of the patients are monitored overnight in the hospital but if there are no complications, the next day, patients are sent home.

The catheter site is checked for bleeding and swelling and the heart rate and blood pressure are monitored. Usually, patients receive medication that will relax them to protect the arteries against spasms. Patients are typically able to walk within two to six hours following the procedure and return to their normal routine by the following week.

Angioplasty recovery consists in avoiding physical activity for several days after the procedure. Patients are advised to avoid any type of lifting, babysitting grandchildren or other strenuous physical activity for a week. Patients will need to avoid physical stress or prolonged sport activities for a maximum of two weeks after a delicate balloon angioplasty.

Patients with stents are usually prescribed an anticoagulant, clopidogrel which is taken at the same time with acetylsalicylic acid. These medications are intended to prevent blood clots and they are usually taken for at least the first months after the procedure is performed. In most cases, patients are administrated this type of medication for 1 year. Also, patients who are doing dental work are advised to cancel it because there is a risk of endocarditis, an infection of the heart.

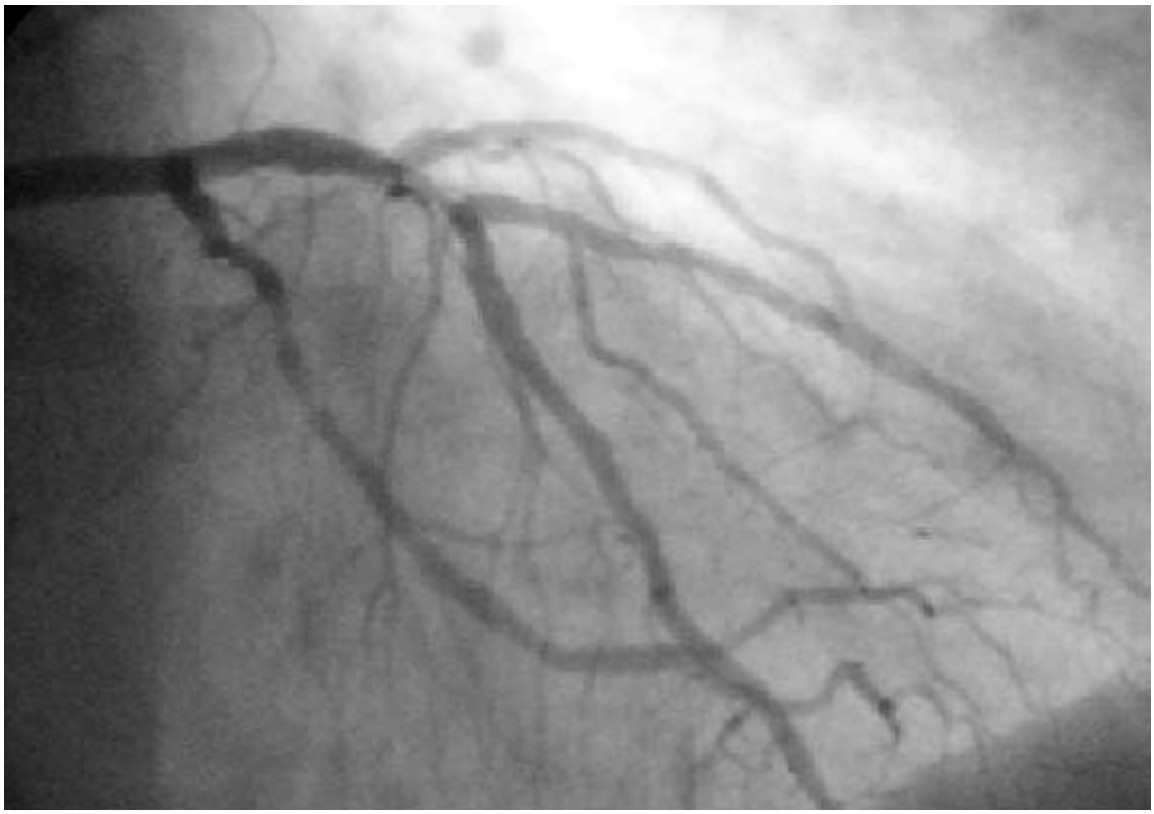
Patients who experience swelling, bleeding or pain at the insertion site, develop fever, feel faint or weak, notice a change in temperature or color in the arm or leg that was used or have shortness of breath or chest pain should immediately seek medical advice..

Peripheral angioplasty

Peripheral angioplasty refers to the use of a balloon to open a blood vessels outside the coronary arteries. It is commonly done to treat atherosclerotic narrowings of the abdomen, leg and renal arteries. PA can also be done to treat narrowings in veins, etc.

Often, peripheral angioplasty is used in conjunction with peripheral stenting and atherectomy.

Coronary angioplasty



A coronary angiogram (an X-ray with radio-opaque contrast in the coronary arteries) that shows the left coronary circulation. The distal left main coronary artery (LMCA) is in the left upper quadrant of the image. Its main branches (also visible) are the left circumflex artery (LCX), which courses top-to-bottom initially and then toward the centre-bottom, and the left anterior descending (LAD) artery, which courses from left-to-right on the image and then courses down the middle of the image to project underneath the distal LCX. The LAD, as is usual, has two large diagonal branches, which arise at the centre-top of the image and course toward the centre-right of the image.

Percutaneous coronary intervention (**PCI**), commonly known as **coronary angioplasty** is a therapeutic procedure to treat the stenotic (narrowed) coronary arteries of the heart found in coronary heart disease. These stenotic segments are due to the build up of cholesterol-laden plaques that form due to atherosclerosis. PCI is usually performed by an interventional cardiologist.

Treatment with PCI for patients with stable coronary artery disease reduces chest pain, but does not reduce the risk of death, myocardial infarction, or other major cardiovascular events when added to optimal medical therapy.

Renal artery angioplasty

Atherosclerotic obstruction of the renal artery can be treated with angioplasty of the renal artery (percutaneous transluminal renal angioplasty, PTRA). Renal artery stenosis can lead to hypertension and loss of renal function.

Carotid angioplasty

Carotid artery stenosis is treated with angioplasty and stenting for high-risk patients in many hospitals.

Cerebral arteries angioplasty

In 1983, the Russian neurosurgeon Zubkov and colleagues reported the first use of transluminal balloon angioplasty for vasospasm after aneurysmal SAH.

Chapter 9

Extracorporeal Shock Wave Lithotripsy and Mammography

Extracorporeal shock wave lithotripsy

Extracorporeal shock wave lithotripsy (**ESWL**) is the non-invasive treatment of kidney stones (urinary calculosis) and biliary calculi (stones in the gallbladder or in the liver) using an acoustic pulse. **Lithotripsy** and the **lithotriptor** were developed in the early 1980s in Germany by *Dornier Medizintechnik GmbH* (now known as Dornier MedTech Systems GmbH), and came into widespread use with the introduction of the HM-3 lithotriptor in 1983. Within a few years, ESWL became a standard treatment of calculosis.

It is estimated that more than one million patients are treated annually with ESWL in the USA alone.

How it works

The lithotriptor attempts to break up the stone with minimal collateral damage by using an externally-applied, focused, high-intensity acoustic pulse. The sedated or anesthetized patient lies down in the apparatus' bed, with the back supported by a water-filled coupling device placed at the level of kidneys. A fluoroscopic x-ray imaging system or an ultrasound imaging system is used to locate the stone and aim the treatment. The first generation lithotriptor known as the HM3, has a half ellipsoid-shaped piece that opens toward the patient. The acoustic pulse is generated at the ellipsoidal focal point that is furthest from the patient and the stone positioned at the opposite focal point receives the focused shock wave. The treatment usually starts at the equipment's lowest power level, with a long gap between pulses, in order to accustom the patient to the sensation. The length of gap between pulses is also controlled to allow cavitation bubbles to disperse minimizing tissue damage. Second and later generation machines use an acoustic lens to focus the shock wave. This functions much like an optical lens, focusing the shock wave at the desired loci. The frequency of pulses are currently left at a slow rate for more effective comminution of the stone and to minimize morbidity while the power levels are then gradually increased, so as to break up the stone. The final power level usually depends on the patient's pain threshold and the obsevered success of stone breakage. If

the stone is positioned near a bone (usually a rib in the case of kidney stones), this treatment may be more uncomfortable because the shock waves can cause a mild resonance in the bone which can be felt by the patient. The sensation of the treatment is likened to an elastic band twanging off the skin. Alternately the patient may be sedated during the procedure. This allows the power levels to be brought up more quickly and a much higher pulse frequency, often up to 120 shocks per minute.

The successive shock wave pressure pulses result in direct shearing forces, as well as cavitation bubbles surrounding the stone, which fragment the stones into smaller pieces that then can easily pass through the ureters or the cystic duct. The process takes about an hour. A ureteral stent (a kind of expandable hollow tube) may be used at the discretion of the urologist. The stent allows for easier passage of the stone by relieving obstruction and through passive dilatation of the ureter.

Some of the passed fragments of a 1-cm calcium oxalate stone that was smashed using lithotripsy.

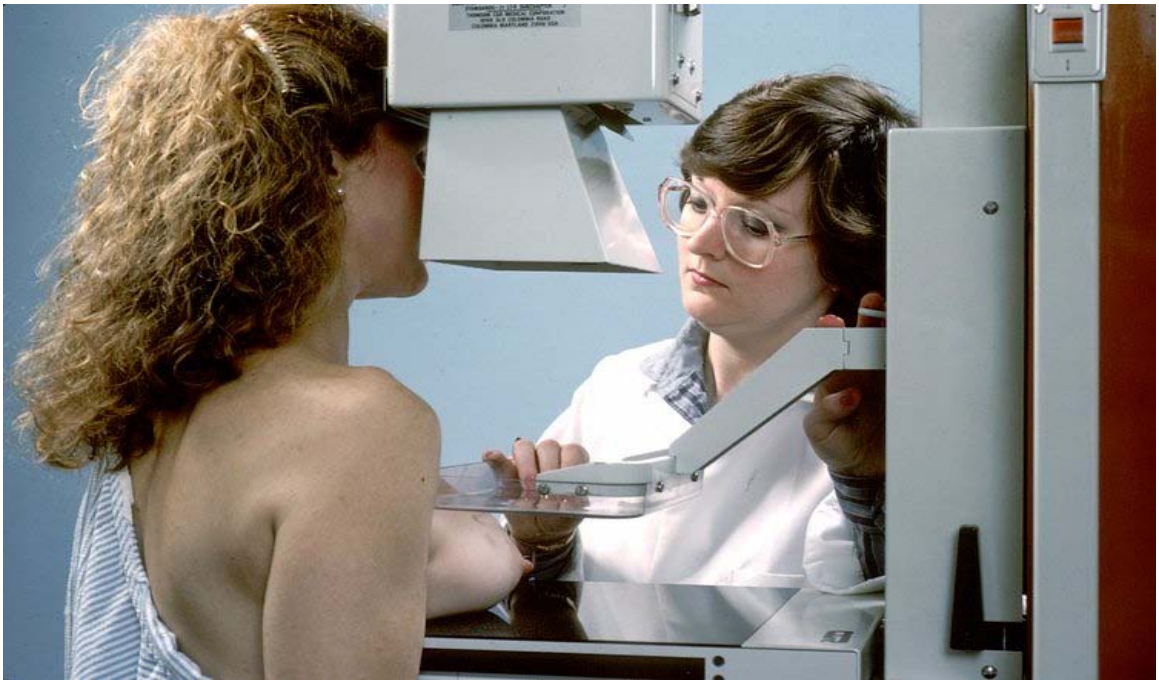
Extracorporeal lithotripsy works best with stones between 4 mm and 2 cm in diameter that are still located in the kidney. It can be used to break up stones which are located in a ureter too, but with less success.

The patients undergoing this procedure can, in some cases, see for themselves the progress of their treatment. If allowed to view the ultrasound or x-ray monitor, they may be able to see their stones change from a distinct bright point (or dark spot depending on whether the fluoro unit is set up in native or bones white) to a fuzzy cloud as the stone is disintegrated into a fine powder.

ESWL is the least invasive of the commonplace modalities for definitive stone treatment, but provides a lower stone-free rate than other more invasive treatment methods, such as ureteroscopic manipulation with laser lithotripsy or percutaneous nephrolithotomy (PCNL). The passage of stone fragments may take a few days or a week and may cause mild pain. Patients may be instructed to drink as much water as practical during this time. Patients are also advised to void through a stone screen in order to capture stone fragments for analysis.

ESWL is not without risks. The shock waves themselves, as well as cavitation bubbles formed by the agitation of the urine medium, can lead to capillary damage, renal parenchymal or subcapsular hemorrhage. This can lead to long-term consequences such as renal failure and hypertension. Overall complication rates of ESWL range from 5–20%.

Mammography



Mammography

Mammography is the process of using low-dose amplitude-X-rays (usually around 0.7 mSv) to examine the human breast and is used as a diagnostic and a screening tool. The goal of mammography is the early detection of breast cancer, typically through detection of characteristic masses and/or microcalcifications. Mammography is believed to reduce mortality from breast cancer. Remaining aware of breast changes and physician examination are considered essential parts of regular breast care.

In many countries routine mammography of older women is encouraged as a screening method to diagnose early breast cancer. The United States Preventive Services Task Force recommends screening mammography, with or without clinical breast examination, every 2 years for women aged 50 to 74. Altogether clinical trials have found a relative reduction in breast cancer mortality of 20%. Mammograms have been controversial since 2000, when a paper highlighting the results of the two highest-quality studies was published.

Like all x-rays, mammograms use doses of ionizing radiation to create images. Radiologists then analyze the image for any abnormal findings. It is normal to use longer wavelength X-rays (typically Mo-K) than those used for radiography of bones.

At this time, mammography along with physical breast examination is the modality of choice for screening for early breast cancer. Ultrasound, ductography, positron emission mammography (PEM), and magnetic resonance imaging are adjuncts to mammography. Ultrasound is typically used for further evaluation of masses found on mammography or palpable masses not seen on mammograms. Ductograms are still used in some institutions for evaluation of bloody nipple discharge when the mammogram is non-diagnostic. MRI can be useful for further evaluation of questionable findings as well as for screening pre-surgical evaluation in patients with known breast cancer to detect any additional lesions that might change the surgical approach, for instance from breast-conserving lumpectomy to mastectomy. New procedures, not yet approved for use in the general public, including breast tomosynthesis may offer benefits in years to come.

Breast self-examination (BSE) was once promoted as a means of finding cancer at a more curable stage, however, it has been shown to be ineffective, and is no longer routinely recommended by health authorities for general use. Awareness of breast health and familiarity with one's own body is typically promoted instead of self-exams.

Mammography has a false-negative (missed cancer) rate of at least 10 percent. This is partly due to dense tissues obscuring the cancer and the fact that the appearance of cancer on mammograms has a large overlap with the appearance of normal tissues.

Procedure

During the procedure, the breast is compressed using a dedicated mammography unit. Parallel-plate compression evens out the thickness of breast tissue to increase image quality by reducing the thickness of tissue that x-rays must penetrate, decreasing the amount of scattered radiation (scatter degrades image quality), reducing the required

radiation dose, and holding the breast still (preventing motion blur). In screening mammography, both head-to-foot (craniocaudal, CC) view and angled side-view (mediolateral oblique, MLO) images of the breast are taken. Diagnostic mammography may include these and other views, including geometrically magnified and spot-compressed views of the particular area of concern. Deodorant, talcum powder or lotion may show up on the X-ray as calcium spots, and women are discouraged from applying these on the day of their exam.

Until some years ago, mammography was typically performed with screen-film cassettes. Now, mammography is undergoing transition to digital detectors, known as digital mammography or Full Field Digital Mammography (FFDM). The first FFDM system was approved by the FDA in the U.S. in 2000. This progress is some years later than in general radiology. This is due to several factors:

1. the higher spatial resolution demands of mammography,
2. significantly increased expense of the equipment,
3. concern by the FDA that digital mammography equipment demonstrate that it is at least as good as screen-film mammography at detecting breast cancers without increasing breast dose or the number of women recalled for further evaluation.

As of March 1, 2010, 62% of facilities in the United States and its territories have at least one FFDM unit. (The FDA includes computed radiography units in this figure.)

In order to encourage the use of mammograms as a screening measure for breast cancer, a number of hospitals, cancer centers and other healthcare groups have started mobile mammography vans to bring affordable, accessible and convenient mammograms to their communities. Many mobile mammography vans prioritize serving uninsured, low-income and/or non-English-speaking women who otherwise could not otherwise afford a mammogram or who are unaccustomed to seeing a doctor. Many offer free or low-cost mammograms to women who are uninsured and/or cannot afford a mammogram.

"Work-up" process

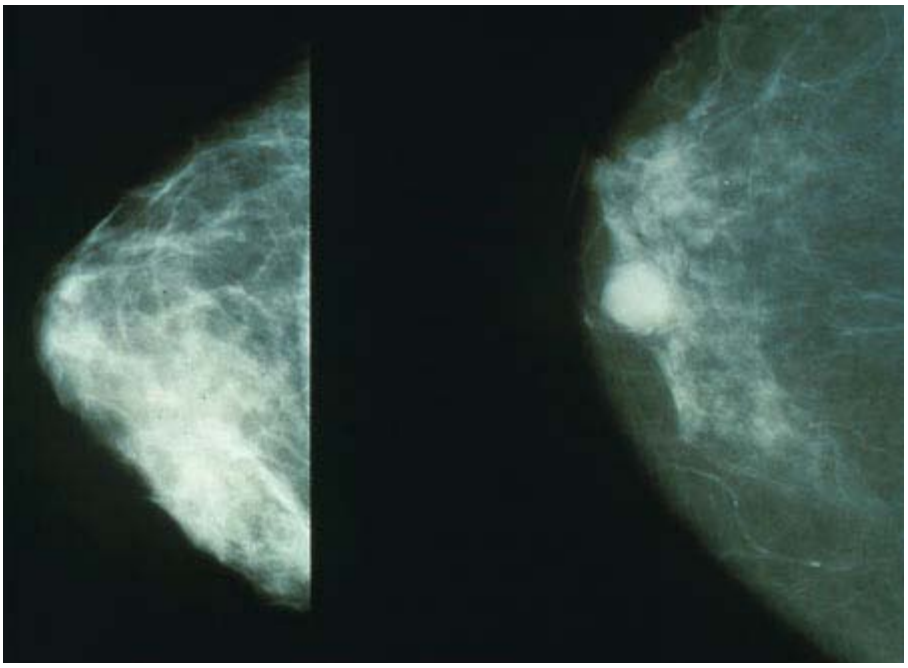
In the past several years, the "work-up" process has become quite formalized. It generally consists of screening mammography, diagnostic mammography, and biopsy when necessary, often performed via stereotactic core biopsy or ultrasound-guided core biopsy. After a screening mammogram, some women may have areas of concern which can't be resolved with only the information available from the screening mammogram. They would then be called back for a "diagnostic mammogram". This phrase essentially means a problem-solving mammogram. During this session, the radiologist will be monitoring each of the additional films as they are taken by a technologist. Depending on the nature of the finding, ultrasound may often be used at this point, as well.

Generally the cause of the unusual appearance is found to be benign. If the cause cannot be determined to be benign with sufficient certainty, a biopsy will be recommended. The biopsy procedure will be used to obtain actual tissue from the site for the pathologist to

examine microscopically to determine the precise cause of the abnormality. In the past, biopsies were most frequently done in surgery, under local or general anesthesia. The majority are now done with needles using either ultrasound or mammographic guidance to be sure that the area of concern is the area that is biopsied. These core biopsies require only local anesthesia, similar to what would be given during a small dental procedure.

One study shows that needle biopsies of liver malignancies rarely increase the likelihood that cancer will spread, and has not been found to occur with breast needle biopsies.

Results



Normal (left) versus cancerous (right) mammography image

Often women are quite distressed to be called back for a diagnostic mammogram. Most of these recalls will be false positive results. It helps to know these approximate statistics: of every 1,000 U.S. women who are screened, about 7% (70) will be called back for a diagnostic session (although some studies estimate the number closer to 10%–15%). About 10 of these individuals will be referred for a biopsy; the remaining 60 are found to be of benign cause. Of the 10 referred for biopsy, about 3.5 will have a cancer and 6.5 will not. Of the 3.5 who do have cancer, about 2 have a low stage cancer that will be essentially cured after treatment. Mammogram results are often expressed in terms of the BI-RADS Assessment Category, often called a "BI-RADS score." The categories range from 0 (Incomplete) to 6 (Known biopsy – proven malignancy). In the UK mammograms are scored on a scale from 1-5 (1 = normal, 2 = benign, 3 = indeterminate, 4 = suspicious of malignancy, 5 = malignant).

Mammography may also produce false negatives. Estimates of the numbers of cancers missed by mammography are usually around 10%–30%. This means that of the 350 per

100,000 women who have breast cancer, about 35–105 will not be detected by mammography. Reasons for not seeing the cancer include observer error, but more frequently it is because the cancer is hidden by other dense tissue in the breast and even after retrospective review of the mammogram, cannot be seen. Furthermore, one form of breast cancer, lobular cancer, has a growth pattern that produces shadows on the mammogram which are indistinguishable from normal breast tissue.

Computer-aided diagnosis (CAD) are being tested to decrease the number of cases of cancer that are missed in mammograms. In one test, a computer identified 71% of the cases of cancer that had been missed by physicians. However, the computer also flagged twice as many non-cancerous masses than the physicians did. In a second study of a larger set of mammograms, a computer recommended six biopsies that physicians did not. All six turned out to be cancers that would have been missed. Generally, CAD systems in screening mammography have poor specificity and compare poorly to double reading.

While data are accumulating suggesting that CAD can find a few additional cancers, this should be put in perspective. The additional find rate was 20%, thus in a group of 10,000 women who will have about 40 cancers, CAD may help find an additional 8. The types of additional cancers that may be found are likely to be early and small. As of 2006, there have been no data to show that finding these additional cancers will have any effect on survival rate. Some feel that these cancers are likely to be found at the next screening, still at a curable stage, and therefore it remains to be proven whether CAD will be eventually found to have any effect on patient outcome.

A study released October 1, 2008, by British researchers revealed that using CAD in conjunction with a single reading by a physician may be as beneficial as a second reading by a physician. The study of 31,000 women, the largest of its kind to date, determined that the find rate for a single physician in conjunction with CAD as compared to two physicians was nearly identical. Out of 227 cancers found, the CAD method found just one fewer than the 199 cancers found using two separate physicians.

Risks

False positives

The goal of any screening procedure is to examine a large population of patients and find the small number most likely to have a serious condition. These patients are then referred for further, usually more invasive, testing. Thus a screening exam is not intended to be definitive: It is intended to have a high sensitivity so as to not miss any cancers. The cost of this high sensitivity is a relatively large number of results that would be regarded as suspicious in patients without disease. This is true of mammography. The patients called back for further testing from a screening session (about 7%) are sometimes referred to as "false positives", implying an error. In fact, it is essential to call back many healthy patients for further testing to capture as many cases of cancer as possible.

Research shows that false-positive mammograms may affect women's well-being and behavior. Some women who receive false-positive results may be more likely to return for routine screening or perform breast self-examinations more frequently. However, some women who receive false-positive results become anxious, worried and distressed about the possibility of having breast cancer, feelings that can last for many years.

False negatives

At the same time, mammograms also have a rate of missed tumors, or "false negatives." Accurate data regarding the number of false negatives are very difficult to obtain, simply because mastectomies cannot be performed on every woman who has had a mammogram to determine the false negative rate accurately. Estimates of the false negative rate depend on close follow-up of a large number of patients for many years. This is difficult in practice, because many women do not return for regular mammography making it impossible to know if they ever developed a cancer. Dr. Samuel S. Epstein, in his book, *The Politics of Cancer*, claims that in women ages 40 to 49, one in four instances of cancer is missed at each mammography. Researchers have found that breast tissue is denser among younger women, making it difficult to detect tumors. For this reason, false negatives are twice as likely to occur in premenopausal mammograms (Prate.) This is why the screening program in the UK does not start calling women for screening mammograms until the age of 50.

The importance of these missed cancers is not clear, particularly if the woman is getting yearly mammograms. Research on a closely related situation has shown that small cancers that are not acted upon immediately, but are observed over periods of even several years, will have good outcomes. A group of 3,184 women had mammograms which were formally classified as "probably benign." This classification is for patients who are not clearly normal but have some area of minor concern. This results, not in the patient being biopsied, but having early follow up mammography every six months for three years to guarantee no change. Of these 3,184 women, 17 (0.5%) did have cancers. Most importantly, when the diagnosis was finally made, they were all still stage 0 or 1, the earliest stages. Five years after treatment, none of these 17 women had evidence of recurrence. Thus, small early cancers, even though not acted on immediately, were still entirely curable (Sickles, *Radiology*, 179:463-468, 1991).

Other risks

The radiation exposure associated with mammography is a potential risk of screening. The risk of exposure appears to be greater in younger women. The largest study of radiation risk from mammography concluded that for women 40 years of age or older, the risk of radiation-induced breast cancer was minuscule, particularly compared with the potential benefit of mammographic screening, with a benefit-to-risk ratio of 48.5 lives saved for each life lost due to radiation exposure. Organizations such as the National Cancer Institute and United States Preventive Task Force take such risks into account when formulating screening guidelines.

The majority of health experts agree that the risk of breast cancer for asymptomatic women under 35 is not high enough to warrant the risk of radiation exposure. For this reason, and because the radiation sensitivity of the breast in women under 35 is possibly greater than in older women, most radiologists will not perform screening mammography in women under 40. However, if there is a significant risk of cancer in a particular patient (BRCA positive, very positive family history, palpable mass), mammography may still be important. Often, the radiologist will try to avoid mammography by using ultrasound or MRI imaging.

The statistics about mammography and women between the ages of 40 and 55 are the most contentious. A 1992 Canadian National Breast Cancer Study showed that mammography (conducted in the 1980s) had no positive effect on mortality for women between the ages of 50 and 60. This study, however, is the only study to find this result. The study's critics pointed out that there were very serious design flaws in the study that invalidated these results.

There is a body of evidence that clearly shows that there is overdiagnosis of cancer when women are screened. These cancers would never have affected these women in their lifetimes. An estimate of this overdiagnosis is 10 breast cancers diagnosed and unnecessarily treated per life saved when 2000 women are screened for 10 years.

While screening between 40 and 50 is still controversial, the preponderance of the evidence indicates that there is some small benefit in terms of early detection. Currently, the American Cancer Society, the National Cancer Institute, and the American College of Radiology encourage mammograms every two years for women ages 40 to 49. In contrast, the American College of Physicians, a large internist group, has recently encouraged individualized screening plans as opposed to wholesale biannual screening of women aged 40 to 49. In 2009, the U.S. Preventive Services Task Force recommended that screening of those age 40 to 49 be based on individual's risk factors and values, and that screening should not be routine in this age group. Their report says that the benefits of screenings before the age of 50 don't outweigh the risks.

Critique of screening mammography

The use of mammography as a screening tool for the detection of early breast cancer continues to be debated. Critics point out that a large number of women need to be screened to find cancer. Kopans reminds us that since 1990, the death rate from breast cancer has decreased by almost 30% and points to studies in Sweden and the Netherlands that show two-thirds of the decrease in cancer deaths is due to mammography screening. Keen and Keen indicated that repeated mammography starting at age 50 saves about 1.8 lives over 15 years for every 1,000 women screened. This result has to be seen against the negatives of errors in diagnosis, overtreatment, and radiation exposure. Countercritics argue that the benefit is greater. The Cochrane analysis of screening indicates that it is "not clear whether screening does more good than harm". According to their analysis one in 2,000 women will have her life prolonged by 10 years of screening, however, another 10 healthy women will undergo unnecessary breast cancer treatment. Additionally, 200

women will suffer from significant psychological stress due to false posivitive results. Newman points out that screening mammography does not reduce death overall, but causes significant harm by inflicting cancer scare and unnecessary surgical interventions. Finally, a significant recent article points out that a successful screening program should result in an increase in the number of early breast cancers, followed by a decrease in the number of late-stage cancers. However this is not happening with current mammography screening.

Alternatives to mammography

While the cost of mammography is relatively low, its *sensitivity* is not ideal, with reports listing the range from 45% to about 90% depending on factors such as the density of the breast. Neither is the X-ray based technology completely benign, as noted above. Therefore there is considerable ongoing research into the use of alternative technologies.

- BT Test (blood-based screening test)
- BCtect (blood based test)

- Breast MRI

- A commercial device called Breastlight allows a woman to shine a powerful red light through her breasts in a darkened room, revealing areas that might be cause for concern. The device has been tested in clinical trials.

- Infrared mammography

- Molecular Breast Imaging (MBI), is a new technology used for breast imaging. MBI identifies tumors in dense breast tissue that are often not visible with X-ray based analog or digital mammography.

Regulation

Mammography facilities in the United States and its territories (including military bases) are subject to the Mammography Quality Standards Act (MQSA). The act requires annual inspections and accredition every 3 years through an FDA-approved body. Facilities found deficient during the inspection or accreditation process can be barred from performing mammograms until corrective action has been verified or, in extreme cases, can be required to notify past patients that their exams were sub-standard and should not be trusted.

At this time MQSA applies only to traditional mammography and not related scans such as breast ultrasound, stereotactic breast biospy, or breast MRI.

Chapter 10

Medical Imaging

Medical imaging is the technique and process used to create images of the human body (or parts and function thereof) for clinical purposes (medical procedures seeking to reveal, diagnose or examine disease) or medical science (including the study of normal anatomy and physiology). Although imaging of removed organs and tissues can be performed for medical reasons, such procedures are not usually referred to as medical imaging, but rather are a part of pathology.

As a discipline and in its widest sense, it is part of biological imaging and incorporates radiology (in the wider sense), nuclear medicine, investigative radiological sciences, endoscopy, (medical) thermography, medical photography and microscopy (e.g. for human pathological investigations).

Measurement and recording techniques which are not primarily designed to produce images, such as electroencephalography (EEG), magnetoencephalography (MEG), Electrocardiography (EKG) and others, but which produce data susceptible to be represented as maps (i.e. containing positional information), can be seen as forms of medical imaging.

Up until 2010, 5 billion medical imaging studies had been conducted worldwide. Radiation exposure from medical imaging in 2006 made up about 50% of total ionizing radiation exposure in the United States.

Overview

In the clinical context, "invisible light" medical imaging is generally equated to radiology or "clinical imaging" and the medical practitioner responsible for interpreting (and sometimes acquiring) the images is a radiologist. "Visible light" medical imaging involves digital video or still pictures that can be seen without special equipment. Dermatology and wound care are two modalities that utilize visible light imagery. Diagnostic radiography designates the technical aspects of medical imaging and in particular the acquisition of medical images. The *radiographer* or *radiologic technologist* is usually responsible for acquiring medical images of diagnostic quality, although some radiological interventions are performed by radiologists. While radiology is an evaluation of anatomy, nuclear medicine provides functional assessment.

As a field of scientific investigation, medical imaging constitutes a sub-discipline of biomedical engineering, medical physics or medicine depending on the context: Research and development in the area of instrumentation, image acquisition (e.g. radiography), modelling and quantification are usually the preserve of biomedical engineering, medical physics and computer science; Research into the application and interpretation of medical images is usually the preserve of radiology and the medical sub-discipline relevant to medical condition or area of medical science (neuroscience, cardiology, psychiatry, psychology, etc.) under investigation. Many of the techniques developed for medical imaging also have scientific and industrial applications.

Medical imaging is often perceived to designate the set of techniques that noninvasively produce images of the internal aspect of the body. In this restricted sense, medical imaging can be seen as the solution of mathematical inverse problems. This means that cause (the properties of living tissue) is inferred from effect (the observed signal). In the case of ultrasonography the probe consists of ultrasonic pressure waves and echoes inside the tissue show the internal structure. In the case of projection radiography, the probe is X-ray radiation which is absorbed at different rates in different tissue types such as bone, muscle and fat.

The term noninvasive is a term based on the fact that following medical imaging modalities do not penetrate the skin physically. But on the electromagnetic and radiation level, they are quite invasive. From the high energy photons in X-Ray Computed Tomography, to the 2+ Tesla coils of an MRI device, these modalities alter the physical and chemical environment of the body in order to obtain data.

Imaging technology

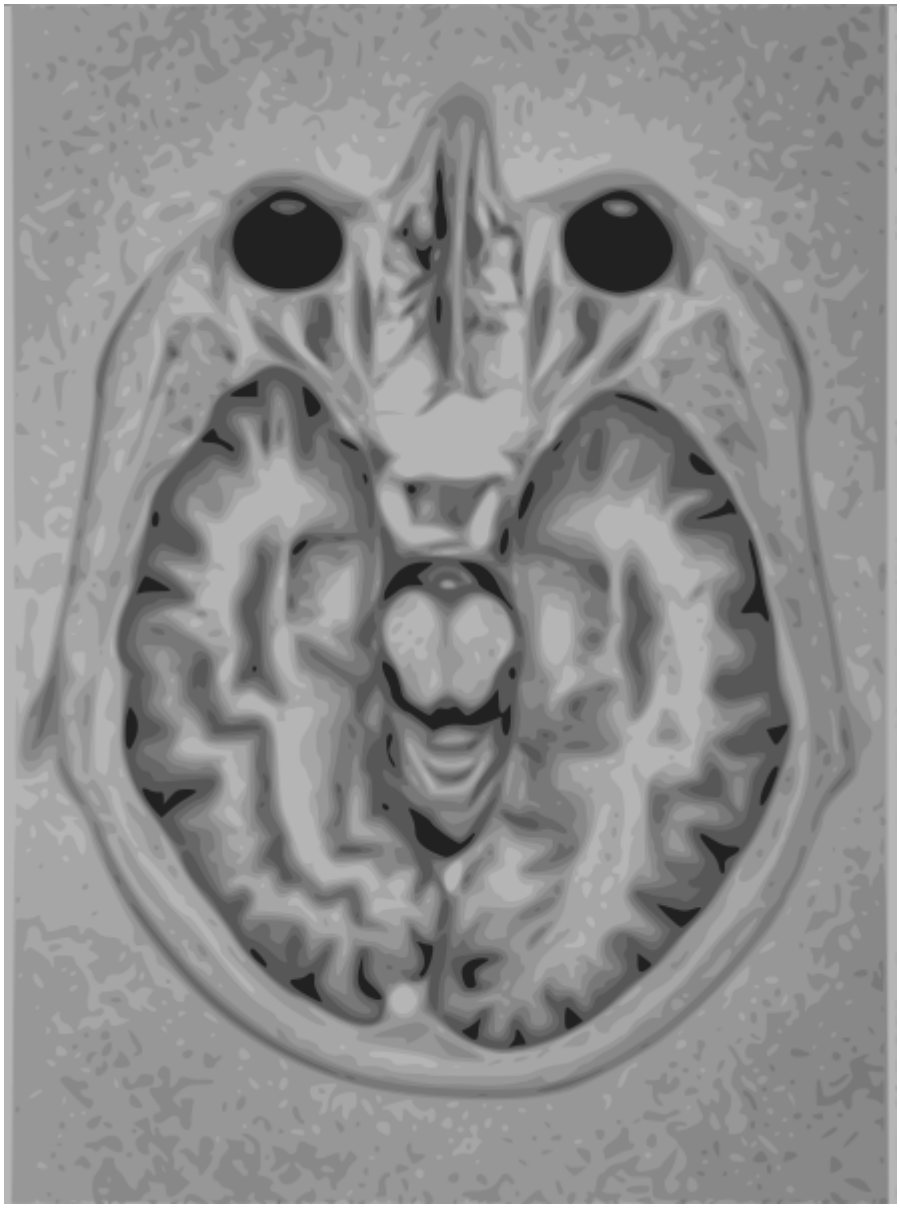
Radiography

Two forms of radiographic images are in use in medical imaging; projection radiography and fluoroscopy, with the latter being useful for catheter guidance. These 2D techniques are still in wide use despite the advance of 3D tomography due to the low cost, high resolution, and depending on application, lower radiation dosages. This imaging modality utilizes a wide beam of x rays for image acquisition and is the first imaging technique available in modern medicine.

- *Fluoroscopy* produces real-time images of internal structures of the body in a similar fashion to radiography, but employs a constant input of x-rays, at a lower dose rate. Contrast media, such as barium, iodine, and air are used to visualize internal organs as they work. Fluoroscopy is also used in image-guided procedures when constant feedback during a procedure is required. An image receptor is required to convert the radiation into an image after it has passed through the area of interest. Early on this was a fluorescing screen, which gave way to an Image Amplifier (IA) which was a large vacuum tube that had the receiving end coated with cesium iodide, and a mirror at the opposite end. Eventually the mirror was replaced with a TV camera.

- *Projectional radiographs*, more commonly known as x-rays, are often used to determine the type and extent of a fracture as well as for detecting pathological changes in the lungs. With the use of radio-opaque contrast media, such as barium, they can also be used to visualize the structure of the stomach and intestines - this can help diagnose ulcers or certain types of colon cancer.

Magnetic resonance imaging (MRI)



A brain MRI representation

A magnetic resonance imaging instrument (MRI scanner), or "nuclear magnetic resonance (NMR) imaging" scanner as it was originally known, uses powerful magnets to polarise and excite hydrogen nuclei (single proton) in water molecules in human tissue, producing a detectable signal which is spatially encoded, resulting in images of the body.

MRI uses three electromagnetic fields: a very strong (on the order of units of teslas) static magnetic field to polarize the hydrogen nuclei, called the static field; a weaker time-varying (on the order of 1 kHz) field(s) for spatial encoding, called the gradient field(s); and a weak radio-frequency (RF) field for manipulation of the hydrogen nuclei to produce measurable signals, collected through an RF antenna.

Like CT, MRI traditionally creates a two dimensional image of a thin "slice" of the body and is therefore considered a tomographic imaging technique. Modern MRI instruments are capable of producing images in the form of 3D blocks, which may be considered a generalisation of the single-slice, tomographic, concept. Unlike CT, MRI does not involve the use of ionizing radiation and is therefore not associated with the same health hazards. For example, because MRI has only been in use since the early 1980s, there are no known long-term effects of exposure to strong static fields and therefore there is no limit to the number of scans to which an individual can be subjected, in contrast with X-ray and CT. However, there are well-identified health risks associated with tissue heating from exposure to the RF field and the presence of implanted devices in the body, such as pace makers. These risks are strictly controlled as part of the design of the instrument and the scanning protocols used.

Because CT and MRI are sensitive to different tissue properties, the appearance of the images obtained with the two techniques differ markedly. In CT, X-rays must be blocked by some form of dense tissue to create an image, so the image quality when looking at soft tissues will be poor. In MRI, while any nucleus with a net nuclear spin can be used, the proton of the hydrogen atom remains the most widely used, especially in the clinical setting, because it is so ubiquitous and returns a large signal. This nucleus, present in water molecules, allows the excellent soft-tissue contrast achievable with MRI.

Nuclear medicine

Nuclear medicine encompasses both diagnostic imaging and treatment of disease, and may also be referred to as molecular medicine or molecular imaging & therapeutics . Nuclear medicine uses certain properties of isotopes and the energetic particles emitted from radioactive material to diagnose or treat various pathology. Different from the typical concept of anatomic radiology, nuclear medicine enables assessment of physiology. This function-based approach to medical evaluation has useful applications in most subspecialties, notably oncology, neurology, and cardiology. *Gamma cameras* are used in e.g. scintigraphy, SPECT and PET to detect regions of biologic activity that may be associated with disease. Relatively short lived isotope, such as ^{123}I is administered to the patient. Isotopes are often preferentially absorbed by biologically active tissue in the body, and can be used to identify tumors or fracture points in bone. Images are acquired after collimated photons are detected by a crystal that gives off a light signal, which is in turn amplified and converted into count data.

- *Scintigraphy* ("scint") is a form of diagnostic test wherein radioisotopes are taken internally, for example intravenously or orally. Then, gamma cameras capture and

form two-dimensional images from the radiation emitted by the radiopharmaceuticals.

- *SPECT* is a 3D tomographic technique that uses gamma camera data from many projections and can be reconstructed in different planes. A dual detector head gamma camera combined with a CT scanner, which provides localization of functional SPECT data, is termed a SPECT/CT camera, and has shown utility in advancing the field of molecular imaging. In most other medical imaging modalities, energy is passed through the body and the reaction or result is read by detectors. In SPECT imaging, the patient is injected with a radioisotope, most commonly Thallium 201TI, Technetium 99mTC, Iodine 123I, and Gallium 67Ga

The radioactive gamma rays are emitted through the body as the natural decaying process of these isotopes takes place. The emissions of the gamma rays are captured by detectors that surround the body. This essentially means that the human is now the source of the radioactivity, rather than the medical imaging devices such as X-Ray, CT, or Ultrasound.

- *Positron emission tomography* (PET) uses coincidence detection to image functional processes. Short-lived positron emitting isotope, such as ^{18}F, is incorporated with an organic substance such as glucose, creating F18-fluorodeoxyglucose, which can be used as a marker of metabolic utilization. Images of activity distribution throughout the body can show rapidly growing tissue, like tumor, metastasis, or infection. PET images can be viewed in comparison to computed tomography scans to determine an anatomic correlate. Modern scanners combine PET with a CT, or even MRI, to optimize the image reconstruction involved with positron imaging. This is performed on the same equipment without physically moving the patient off of the gantry. The resultant hybrid of functional and anatomic imaging information is a useful tool in non-invasive diagnosis and patient management.

Photo acoustic imaging

Photoacoustic imaging is a recently developed hybrid biomedical imaging modality based on the photoacoustic effect. It combines the advantages of optical absorption contrast with ultrasonic spatial resolution for deep imaging in (optical) diffusive or quasi-diffusive regime. Recent studies have shown that photoacoustic imaging can be used in vivo for tumor angiogenesis monitoring, blood oxygenation mapping, functional brain imaging, and skin melanoma detection, etc.

Breast Thermography

Digital infrared imaging thermography is based on the principle that metabolic activity and vascular circulation in both pre-cancerous tissue and the area surrounding a developing breast cancer is almost always higher than in normal breast tissue. Cancerous tumors require an ever-increasing supply of nutrients and therefore increase circulation to their cells by holding open existing blood vessels, opening dormant vessels, and creating new ones (neoangiogenesis). This process frequently results in an increase in regional

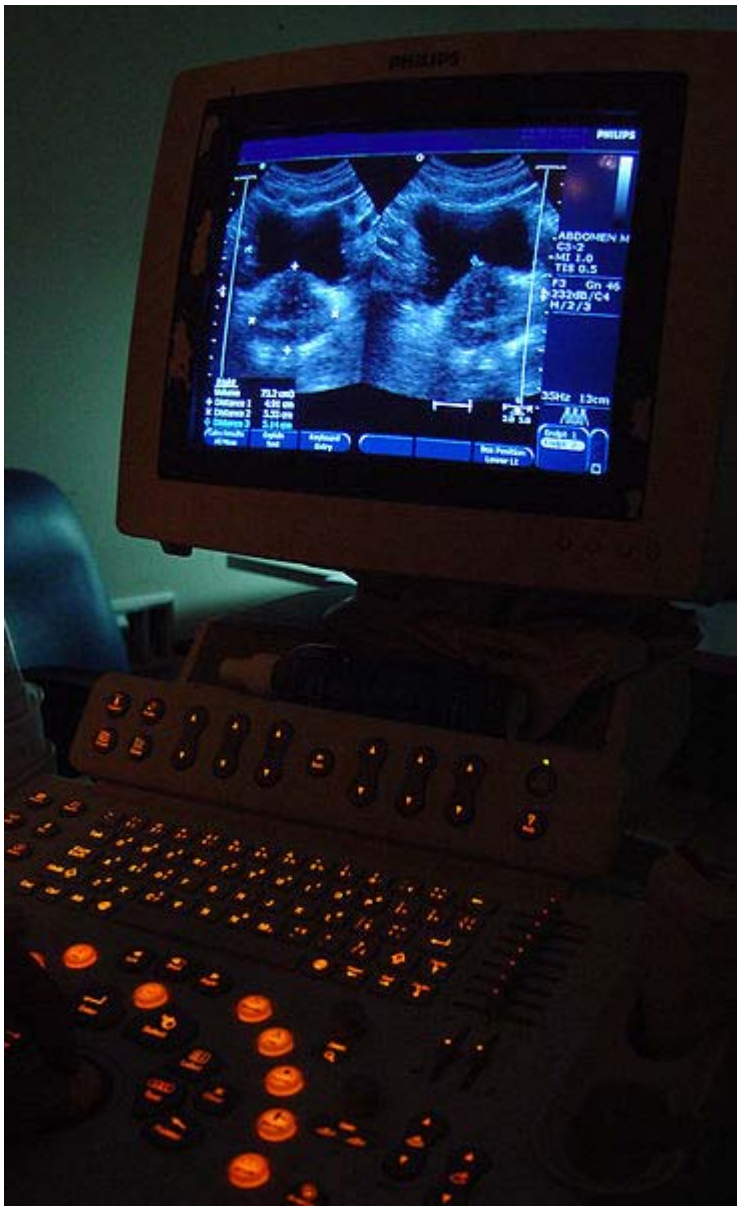
surface temperatures of the breast. Digital infrared imaging uses extremely sensitive medical infrared cameras and sophisticated computers to detect, analyze, and produce high-resolution diagnostic images of these temperature variations. Because of DII's sensitivity, these temperature variations may be among the earliest signs of breast cancer and/or a pre-cancerous state of the breast.

Tomography

Tomography is the method of imaging a single plane, or slice, of an object resulting in a tomogram. There are several forms of tomography:

- Linear tomography: This is the most basic form of tomography. The X-ray tube moved from point "A" to point "B" above the patient, while the cassette holder (or "bucky") moves simultaneously under the patient from point "B" to point "A." The fulcrum, or pivot point, is set to the area of interest. In this manner, the points above and below the focal plane are blurred out, just as the background is blurred when panning a camera during exposure. No longer carried out and replaced by computed tomography.
- Poly tomography: This was a complex form of tomography. With this technique, a number of geometrical movements were programmed, such as hypocycloidic, circular, figure 8, and elliptical. Philips Medical Systems produced one such device called the 'Polytome.' This unit was still in use into the 1990s, as its resulting images for small or difficult physiology, such as the inner ear, was still difficult to image with CTs at that time. As the resolution of CTs got better, this procedure was taken over by the CT.
- Zonography: This is a variant of linear tomography, where a limited arc of movement is used. It is still used in some centres for visualising the kidney during an intravenous urogram (IVU).
- Orthopantomography (OPT or OPG): The only common tomographic examination in use. This makes use of a complex movement to allow the radiographic examination of the mandible, as if it were a flat bone. It is often referred to as a "Panorex", but this is incorrect, as it is a trademark of a specific company.
- Computed Tomography (CT), or Computed Axial Tomography (CAT: A CT scan, also known as a CAT scan), is a helical tomography (latest generation), which traditionally produces a 2D image of the structures in a thin section of the body. It uses X-rays. It has a greater ionizing radiation dose burden than projection radiography; repeated scans must be limited to avoid health effects. CT is based on the same principles as X-Ray projections but in this case, the patient is enclosed in a surrounding ring of detectors assigned with 500-1000 scintillation detectors. This being the fourth-generation X-Ray CT scanner geometry. Previously in older generation scanners, the X-Ray beam was paired by a translating source and detector.

Ultrasound



Ultrasound representation of Urinary bladder (black butterfly-like shape) and hyperplastic prostate

Medical ultrasonography uses high frequency broadband sound waves in the megahertz range that are reflected by tissue to varying degrees to produce (up to 3D) images. This is commonly associated with imaging the fetus in pregnant women. Uses of ultrasound are much broader, however. Other important uses include imaging the abdominal organs, heart, breast, muscles, tendons, arteries and veins. While it may provide less anatomical detail than techniques such as CT or MRI, it has several advantages which make it ideal in numerous situations, in particular that it studies the function of moving structures in real-time, emits no ionizing radiation, and contains speckle that can be used in elastography. Ultrasound is also used as a popular research tool for capturing raw data,

that can be made available through an Ultrasound research interface, for the purpose of tissue characterization and implementation of new image processing techniques. The concepts of ultrasound differ from other medical imaging modalities in the fact that it is operated by the transmission and receipt of sound waves. The high frequency sound waves are sent into the tissue and depending on the composition of the different tissues; the signal will be attenuated and returned at separate intervals. A path of reflected sound waves in a multilayered structure can be defined by an input acoustic impedance(Ultrasound sound wave) and the Reflection and transmission coefficients of the relative structures . It is very safe to use and does not appear to cause any adverse effects, although information on this is not well documented. It is also relatively inexpensive and quick to perform. Ultrasound scanners can be taken to critically ill patients in intensive care units, avoiding the danger caused while moving the patient to the radiology department. The real time moving image obtained can be used to guide drainage and biopsy procedures. Doppler capabilities on modern scanners allow the blood flow in arteries and veins to be assessed.

Medical imaging topics

Maximizing imaging procedure use

The amount of data obtained in a single MR or CT scan is very extensive. Some of the data that radiologists discard could save patients time and money, while reducing their exposure to radiation and risk of complications from invasive procedures.

Creation of three-dimensional images

Recently, techniques have been developed to enable CT, MRI and ultrasound scanning software to produce 3D images for the physician. Traditionally CT and MRI scans produced 2D static output on film. To produce 3D images, many scans are made, then combined by computers to produce a 3D model, which can then be manipulated by the physician. 3D ultrasounds are produced using a somewhat similar technique. In diagnosing disease of the viscera of abdomen,ultrasound is particularly sensitive on imaging of biliary tract,urinary tract and female reproductive organs (ovary,fallopian tubes). As for example,diagnosis of gall stone by dilatation of common bile duct and stone in common bile duct . With the ability to visualize important structures in great detail, 3D visualization methods are a valuable resource for the diagnosis and surgical treatment of many pathologies. It was a key resource for the famous, but ultimately unsuccessful attempt by Singaporean surgeons to separate Iranian twins Ladan and Laleh Bijani in 2003. The 3D equipment was used previously for similar operations with great success.

Other proposed or developed techniques include:

- Diffuse optical tomography
- Elastography
- Electrical impedance tomography

- Optoacoustic imaging
- Ophthalmology
    - A-scan
    - B-scan
    - Corneal topography
    - Optical coherence tomography
    - Scanning laser ophthalmoscopy

Some of these techniques are still at a research stage and not yet used in clinical routines.

Compression of medical images

Medical imaging techniques produce very large amounts of data, especially from CT, MRI and PET modalities. As a result, storage and communications of electronic image data are prohibitive without the use of compression. JPEG 2000 is the state-of-the-art image compression DICOM standard for storage and transmission of medical images. The cost and feasibility of accessing large image data sets over low or various bandwidths are further addressed by use of another DICOM standard, called JPIP, to enable efficient streaming of the JPEG 2000 compressed image data.

Non-diagnostic imaging

Neuroimaging has also been used in experimental circumstances to allow people (especially disabled persons) to control outside devices, acting as a brain computer interface.

Archiving and recording

Used primarily in ultrasound imaging, capturing the image a medical imaging device is required for archiving and telemedicine applications. In most scenarios, a frame grabber is used in order to capture the video signal from the medical device and relay it to a computer for further processing and operations.

Open source software for medical image analysis

Several open source software packages are available for performing analysis of medical images:

- ImageJ
- 3D Slicer
- ITK
- OsiriX
- GemIdent
- MicroDicom
- FreeSurfer

Use in pharmaceutical clinical trials

Medical imaging has become a major tool in clinical trials since it enables rapid diagnosis with visualization and quantitative assessment.

A typical clinical trial goes through multiple phases and can take up to eight years. Clinical endpoints or outcomes are used to determine whether the therapy is safe and effective. Once a patient reaches the endpoint, he/she is generally excluded from further experimental interaction. Trials that rely solely on clinical endpoints are very costly as they have long durations and tend to need large number of patients.

In contrast to clinical endpoints, surrogate endpoints have been shown to cut down the time required to confirm whether a drug has clinical benefits. Imaging biomarkers (a characteristic that is objectively measured by an imaging technique, which is used as an indicator of pharmacological response to a therapy) and surrogate endpoints have shown to facilitate the use of small group sizes, obtaining quick results with good statistical power.

Imaging is able to reveal subtle change that is indicative of the progression of therapy that may be missed out by more subjective, traditional approaches. Statistical bias is reduced as the findings are evaluated without any direct patient contact.

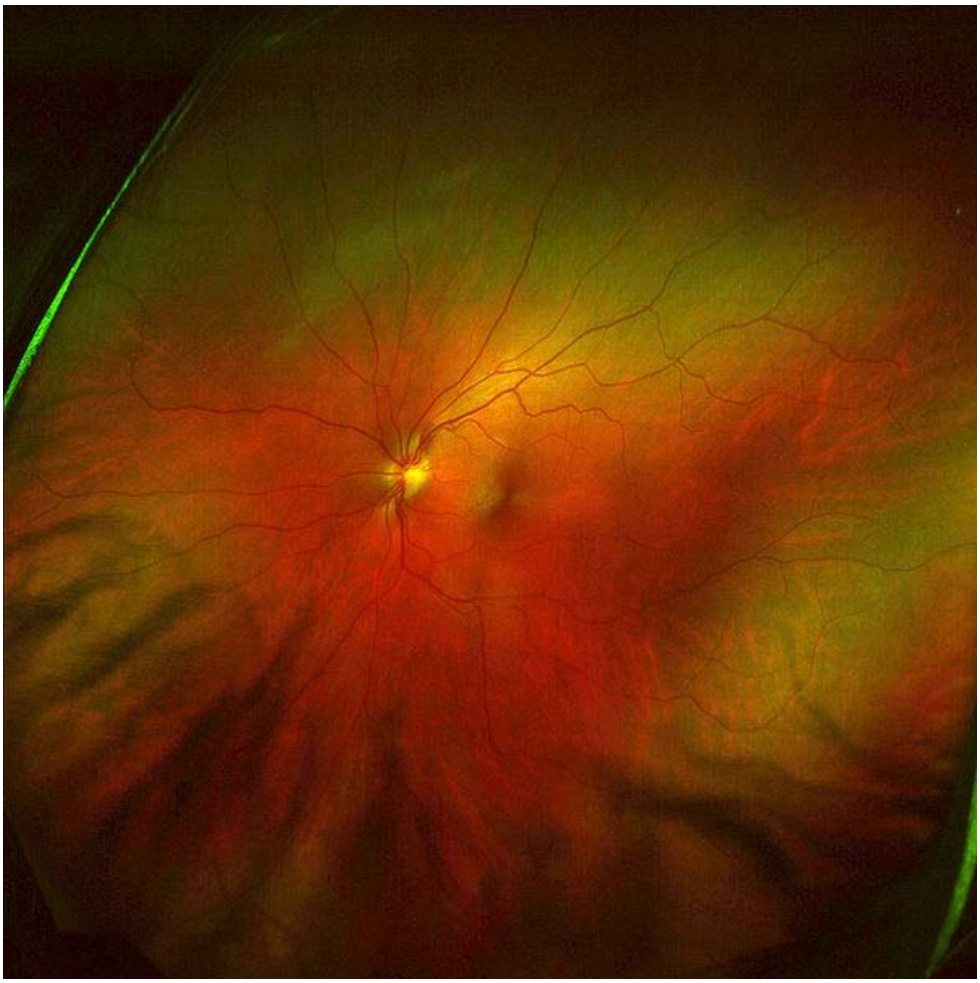
For example, measurement of tumour shrinkage is a commonly used surrogate endpoint in solid tumour response evaluation. This allows for faster and more objective assessment of the effects of anticancer drugs. In evaluating the extent of Alzheimer's disease, it is still prevalent to use behavioural and cognitive tests. MRI scans on the entire brain can accurately pinpoint hippocampal atrophy rate while PET scans is able to measure the brain's metabolic activity by measuring regional glucose metabolism.

An imaging-based trial will usually be made up of three components:

1. A realistic imaging protocol. The protocol is an outline that standardizes (as far as practically possible) the way in which the images are acquired using the various modalities (PET, SPECT, CT, MRI). It covers the specifics in which images are to be stored, processed and evaluated.
2. An imaging centre that is responsible for collecting the images, perform quality control and provide tools for data storage, distribution and analysis. It is important for images acquired at different time points are displayed in a standardised format to maintain the reliability of the evaluation. Certain specialised imaging contract research organizations provide to end medical imaging services, from protocol design and site management through to data quality assurance and image analysis.
3. Clinical sites that recruit patients to generate the images to send back to the imaging centre.

Chapter 11

Scanning Laser Ophthalmoscopy



Retinal image of a left eye via Optos' *Optomap*

Scanning laser ophthalmoscopy (SLO) is a method of examination of the eye. It uses the technique of confocal laser scanning microscopy for diagnostic imaging of retina or cornea of the human eye.

As a method used to image the retina with a high degree of spatial sensitivity, is helpful in the diagnosis of glaucoma, macular degeneration, and other retinal disorders. It has further been combined with adaptive optics technology to provide sharper images of the retina.

Scanning Laser Ophthalmoscopy

SLO utilizes horizontal and vertical scanning mirrors to scan a specific region of the retina and create raster images viewable on a television monitor. While it is able to image the retina in real time, it has issues with reflections from eye astigmatism and the cornea. Eye movements additionally can confound the data from SLO .

Adaptive Optics Scanning Laser Ophthalmoscopy

Adaptive Optics Scanning Laser Ophthalmoscopy (AOSLO) is a technique used to measure living retinal cells. It utilizes adaptive optics to remove optical aberrations from images obtained from scanning laser ophthalmoscopy of the retina.

History

Scanning Laser Ophthalmoscopy developed as a method to view a distinct layer of the living eye at the microscopic level. The use of confocal methods to diminish extra light by focusing detected light through a small pinhole made possible the imaging of individual layers of the retina with greater distinction than ever before . However, utilizing SLO for monitoring of individual retinal cells proved problematic because of optical aberrations created from the tissues of the anterior eye (specifically the cornea and lens). These aberrations (caused additionally by astigmatism and other factors affecting eye position) diminished lateral resolution and proved difficult to remove .

AO was first attempted for SLO in the 1980s. This first attempt did not utilize wavefront-detecting technology with its deformable mirror and estimated aberrations through pre-measured factors such as astigmatism . However, this did not diffuse the small monochromatic aberrations resulting from light traveling through the anterior eye both into and out of the pupil during scanning. The invention and adaptation of the Shack-Hartmann wave-front detector for the apparatus produced images of the retina with much higher lateral resolution . The addition of microelectricalmechanical (MEMs) mirrors instead of larger, more expensive mirror deformable mirror systems to the apparatus made AOSLO further usable for a wider range of studies and for use in patients .

Procedure

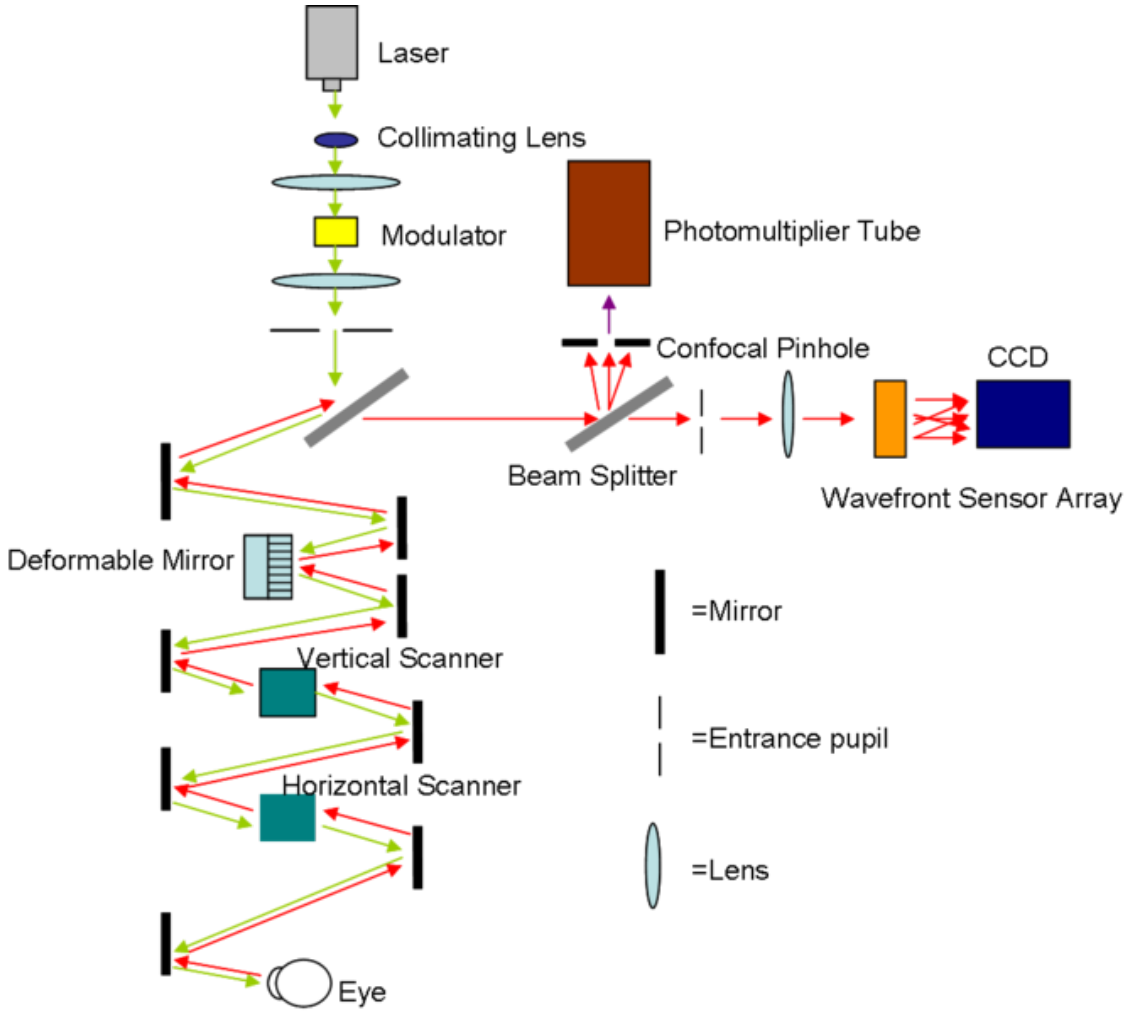


Diagram of the AOSLO setup

The subject is placed in a dental impression mount fixed in a way to make it possible to manipulate the head in three dimensions. The subject's pupils are dilated utilizing a dilating agent to minimize fluctuations from accommodation. After the eyes are sufficiently dilated, the subject is told to fixate on a target while in the mount .

Once the subject is properly placed, wavefront correction and imaging takes place. A laser is collimated and then reflected off of a beam-splitting mirror. As in confocal SLO, light must pass through both a horizontal and a vertical scanning mirror before and after the eye is scanned to align the moving beam for eventual retinal raster images of the retina. Additionally, the light is reflected off of a deformable mirror before and after exposure to the eye to diffuse optical aberrations. The laser enters the eye through the pupil to illuminate the region it has been focused onto and light reflected back leaves the same way. Light returning from the mirrors passes through the first beam splitter onto another beam splitter where it is directed simultaneously toward a photomultiplier tube (PMT) and toward a Shark-Hartmann wavefront sensor array. The light going toward the

photomultiplier is focused through a confocal pinhole to remove light not reflecting off of the plane of interest and then recorded in the PMT. Light directed to the wavefront sensor array is split up by the lenslets in the array and then recorded onto a Charge-coupled device (CCD) camera for detection of optical aberrations. These aberrations are then subtracted from the images recorded in the PMT to vastly increase lateral resolution .

Applications

A major use of this increased lateral resolution from AOSLO has been the ability to determine the spatial distribution of cone cells around the fovea. Not only can the spatial density of these cells be found for a variety of regions within the retina, but the anisotropy of these cells can also be calculated to determine the axial orientation of retinal cells in the living subject. This represents a major benefit over typical histological examination of small numbers of donated human eyes . AOSLO has also revealed significant decreases in foveal cone packing density for myopic eyes in comparison to emmetriopic eyes. This difference has been hypothesized to originate from a natural decrease in cone density with the increase in eye axial length associated with myopia . Abnormalities in photoreceptor structure in regions damaged by macular dystrophy have additionally been imaged by AOSLO. In these subjects, a dark area has been visualized within the macular lesion and morphologically abnormal photoreceptors have been visible on the lesion perimeter. Furthermore, scanning of subjects with cone dystrophy and retinitis pigmentosa (RP) has shown significant changes in cone packing density for these subjects compared to those with normal retinas. This presents a possible future use of AOSLO in phenotype tracking and confirmation for subjects with diseased genotypes .

The imaging of Retinal Pigment Epithelium (RPE) cells in patients with and without retinal disease has also proved possible with the use of AOSLO. With the loss of photoreceptor cells, background scattered light decreases and the light focused on the RPE can be analyzed more clearly . As the loss of RPE cells represents the primary pathology of macular degeneration, this provides a possible future avenue for tracking RPE degradation *in vivo*. This has been further proved with the analysis of lipofuscin granule autofluoresence in normal human and rhesus macaque retinas by AOSLO. Comparison of this fluorescence in normal and diseased retinas with simultaneous imaging of cone structure and cone/retinal pigment cell ratio analysis has been shown to be possible and in the future may allow for the tracking of retinal damage from retinal dystrophies . AOSLO has already been used in rhesus macaques to track light damage to the macula from particular wavelengths.

Additionally, AOSLO provides a greater degree of accuracy for eye tracking than possible before with other techniques. Because of the short scan time involved in AOSLO, eye motion itself represents an obstacle to taking images of the retina. Computational adjustments and modeling have been able to correct for aberrations caused by eye motion between frames. However, by tracking these aberrations based on changes to the retina between pictures, the effect of light on the individual orientation of the cone can be tracked. Research utilizing a visual stimulus and AOSLO eye tracking have yielded data on how the retina tracks movement at the microscopic level.

The high degree of specificity and the ability to focus the laser on different levels of the eyes with AOSLO has additionally allowed for real time tracking of blood flow in the eye. By injecting fluorescin into macaques before scanning, fluorescence adaptive optics scanning laser ophthalmoscopy (FAOSLO) can be utilized to image individual capillaries in the nerve fiber layer and determine the thickness of the nerve fiber layer itself. Vessel pattern and diameter for these capillaries have been measured throughout the regions scanned by FAOSLO. This has future applications for monitoring glaucoma patients who either have changes in nerve fiber layer thickness or alterations in vasculature from damage to the retina.

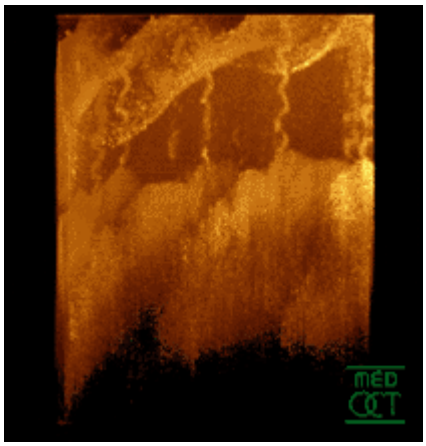
Comparison to Retinal Dissection and Other Imaging Techniques

AOSLO represents an advantageous alternative to retinal dissection for a variety of reasons. Analysis of cone packing density before AOSLO was only possible on mounted eyes from eye donor banks. As this method could not measure changes to cones in living eyes, it could not be used to track retinal changes over time or eye movements. With the use of living subjects, AOSLO allows for these measurements as well as easier control of age and other confounding factors while maintaining similar anatomical results for cone packing density. Future clinical implications for AOSLO are also possible.

AOSLO compares favorably with other retinal imaging techniques as well. Fluorescein angiography utilizes injection of a fluorescein dye to image the back of the retina. It is a commonly used technique but it has a large number of side effects, including nausea in one fifth of patients and in some cases death from anaphylaxis. Optical coherence tomography (OCT) represents a powerful clinical tool for monitoring retinal physiology in patients. OCT utilizes low coherence interferometry to differentiate tissues within the eye and create a cross section of a living patients' retina non-invasively. It actually has greater axial resolution than AOSLO. However, AOSLO represents a method with much greater translational resolution than OCT and can thus be used to track minor lateral physical changes such as the effects of eye movements on the retina. A combination of AOSLO and OCT has recently been attempted in one apparatus to produce the first three dimensional images of individual cone cells and illustrate the overall cone mosaic near the fovea at high speeds.

Chapter 12

Optical Coherence Tomography



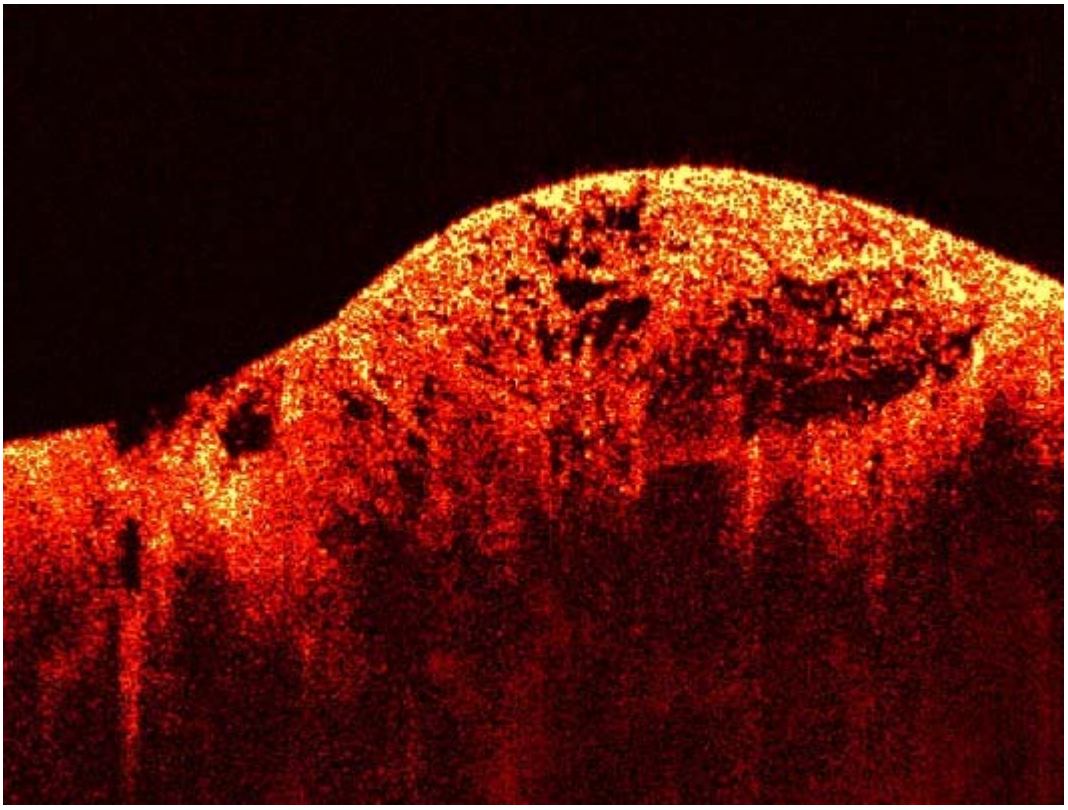
Optical coherence tomography tomogram of a fingertip

Optical coherence tomography (OCT) is an optical signal acquisition and processing method. It captures micrometer-resolution, three-dimensional images from within optical scattering media (e.g., biological tissue). Optical coherence tomography is an interferometric technique, typically employing near-infrared light. The use of relatively long wavelength light allows it to penetrate into the scattering medium. Confocal microscopy, another similar technique, typically penetrates less deeply into the sample.

Depending on the properties of the light source (superluminescent diodes and ultrashort pulsed lasers have been employed), Optical coherence tomography has achieved sub-micrometer resolution (with very wide-spectrum sources emitting over a ~100 nm wavelength range)

Optical coherence tomography is one of a class of optical tomographic techniques. A relatively recent implementation of optical coherence tomography, frequency-domain optical coherence tomography, provides advantages in signal-to-noise ratio, permitting faster signal acquisition. Commercially available optical coherence tomography systems are employed in diverse applications, including art conservation and diagnostic medicine, notably in ophthalmology where it can be used to obtain detailed images from within the retina. Recently it has also begun to be used in interventional cardiology to help diagnose coronary artery disease

Introduction



Optical Coherence Tomography (OCT) image of a sarcoma

Starting from white-light interferometry for *in vivo* ocular eye measurements imaging of biological tissue, especially of the human eye, was investigated by multiple groups worldwide. A first two-dimensional *in vivo* depiction of a human eye fundus along a horizontal meridian based on white light interferometric depth scans was presented at the ICO-15 SAT conference in 1990. Further developed in 1990 by Naohiro Tanno , then a professor at Yamagata University, and in particular since 1991 by Huang et al., optical coherence tomography (OCT) with micrometer resolution and cross-sectional imaging capabilities has become a prominent biomedical tissue-imaging technique; it is particularly suited to ophthalmic applications and other tissue imaging requiring micrometer resolution and millimeter penetration depth. First *in vivo* OCT images – displaying retinal structures – were published in 1993. OCT has also been used for various art conservation projects, where it is used to analyze different layers in a painting. OCT has critical advantages over other medical imaging systems. Medical ultrasonography, magnetic resonance imaging (MRI) and confocal microscopy are not suited to morphological tissue imaging: the first two have poor resolution; the last lacks millimeter penetration depth.

OCT bases itself upon low coherence interferometry. In conventional interferometry with long coherence length (laser interferometry), interference of light occurs over a distance of meters. In OCT, this interference is shortened to a distance of micrometers, thanks to

the use of broadband light sources (sources that can emit light over a broad range of frequencies). Light with broad bandwidths can be generated by using superluminescent diodes (superbright LEDs) or lasers with extremely short pulses (femtosecond lasers). White light is also a broadband source with lower power.

Light in an OCT system is broken into two arms—a sample arm (containing the item of interest) and a reference arm (usually a mirror). The combination of reflected light from the sample arm and reference light from the reference arm gives rise to an interference pattern, but only if light from both arms have travelled the "same" optical distance ("same" meaning a difference of less than a coherence length). By scanning the mirror in the reference arm, a reflectivity profile of the sample can be obtained (this is time domain OCT). Areas of the sample that reflect back a lot of light will create greater interference than areas that don't. Any light that is outside the short coherence length will not interfere. This reflectivity profile, called an A-scan, contains information about the spatial dimensions and location of structures within the item of interest. A cross-sectional tomograph (B-scan) may be achieved by laterally combining a series of these axial depth scans (A-scan). En face imaging (C-scan) at an acquired depth is possible depending on the imaging engine used.

Laypersons explanation

Optical Coherence Tomography, or ‘OCT’, is a technique for obtaining sub-surface images of translucent or opaque materials at a resolution equivalent to a low-power microscope. It is effectively ‘optical ultrasound’, imaging reflections from within tissue to provide cross-sectional images.

OCT is attracting interest among the medical community, because it provides tissue morphology imagery at much higher resolution (better than 10 μm) than other imaging modalities such as MRI or ultrasound.

The key benefits of OCT are:

- Live sub-surface images at near-microscopic resolution
- Instant, direct imaging of tissue morphology
- No preparation of the sample or subject
- No ionizing radiation

OCT delivers high resolution because it is based on light, rather than sound or radio frequency. An optical beam is directed at the tissue, and a small portion of this light that reflects from sub-surface features is collected. Note that most light is not reflected but, rather, scatters. The scattered light has lost its original direction and does not contribute to forming an image but rather contributes to *glare*. The glare of scattered light causes optically scattering materials (e.g., biological tissue, candle wax, or certain plastics) to appear opaque or translucent even while they do not strongly absorb light (as can be ascertained through a simple experiment — e.g., shining a red laser pointer through one's finger). Using the OCT technique, scattered light can be filtered out, completely

removing the glare. Even the very tiny proportion of reflected light that is not scattered can then be detected and used to form the image in, e.g., a scanning OCT system employing a microscope.

The physics principle allowing the filtering of scattered light is optical coherence. *Only* the reflected (non-scattered) light is coherent (i.e., retains the optical phase that causes light rays to propagate in one or another direction). In the OCT instrument, an optical interferometer is used in such a manner as to detect *only* coherent light. Essentially, the interferometer strips off scattered light from the reflected light needed to generate an image. In the process depth and intensity of light reflected from a sub-surface feature is obtained. A three-dimensional image can be built up by scanning, as in a sonar or radar system.

Within the range of noninvasive three-dimensional imaging techniques that have been introduced to the medical research community, OCT as an echo technique is similar to ultrasound imaging. Other medical imaging techniques such as computerized axial tomography, magnetic resonance imaging, or positron emission tomography do not utilize the echo-location principle.

The technique is limited to imaging 1 to 2 mm below the surface in biological tissue, because at greater depths the proportion of light that escapes without scattering is too small to be detected. No special preparation of a biological specimen is required, and images can be obtained 'non-contact' or through a transparent window or membrane. It is also important to note that the laser output from the instruments is low – eye-safe near-infra-red light is used – and no damage to the sample is therefore likely.

Theory

The principle OCT is white light or low coherence interferometry. The optical setup typically consists of an interferometer (Fig. 1, typically Michelson type) with a low coherence, broad bandwidth light source. Light is split into and recombined from reference and sample arm, respectively.

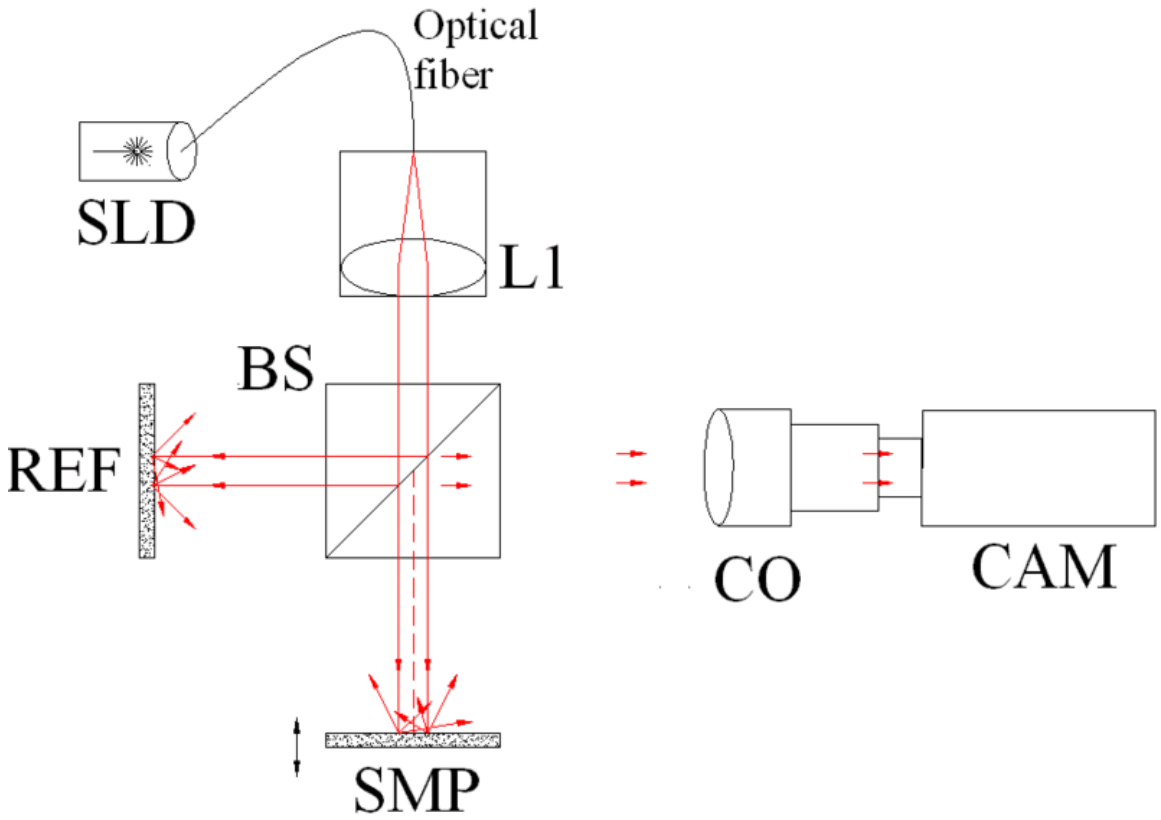


Fig. 1 Full-field OCT optical setup. Components include: super-luminescent diode (SLD), convex lens (L1), 50/50 beamsplitter (BS), camera objective (CO), CMOS-DSP camera (CAM), reference (REF) and sample (SMP). The camera functions as a two-dimensional detector array, and with the OCT technique facilitating scanning in depth, a non-invasive three dimensional imaging device is achieved.

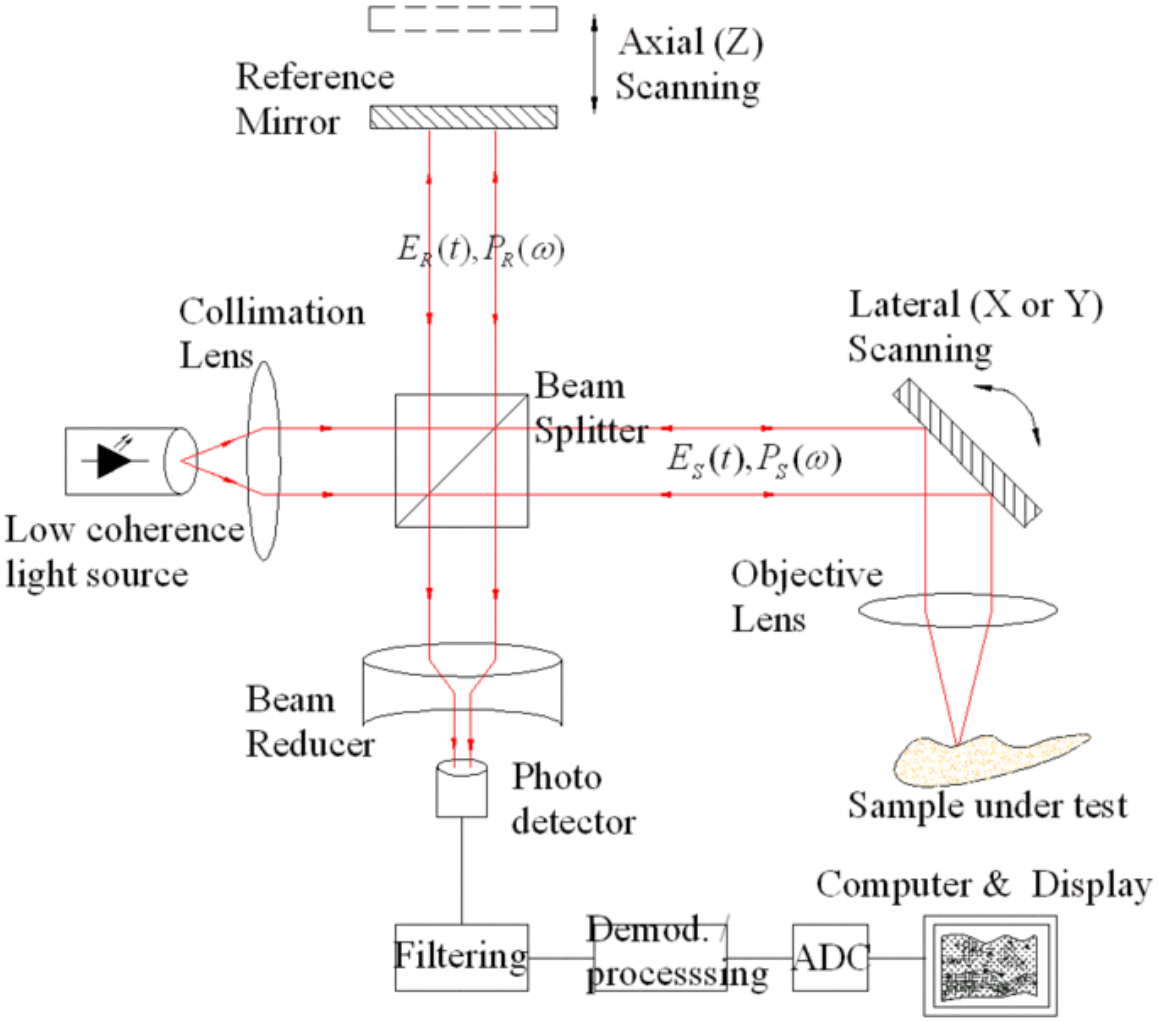


Fig. 2 Typical optical setup of single point OCT. Scanning the light beam on the sample enables non-invasive cross-sectional imaging up to 3 mm in depth with micrometer resolution.

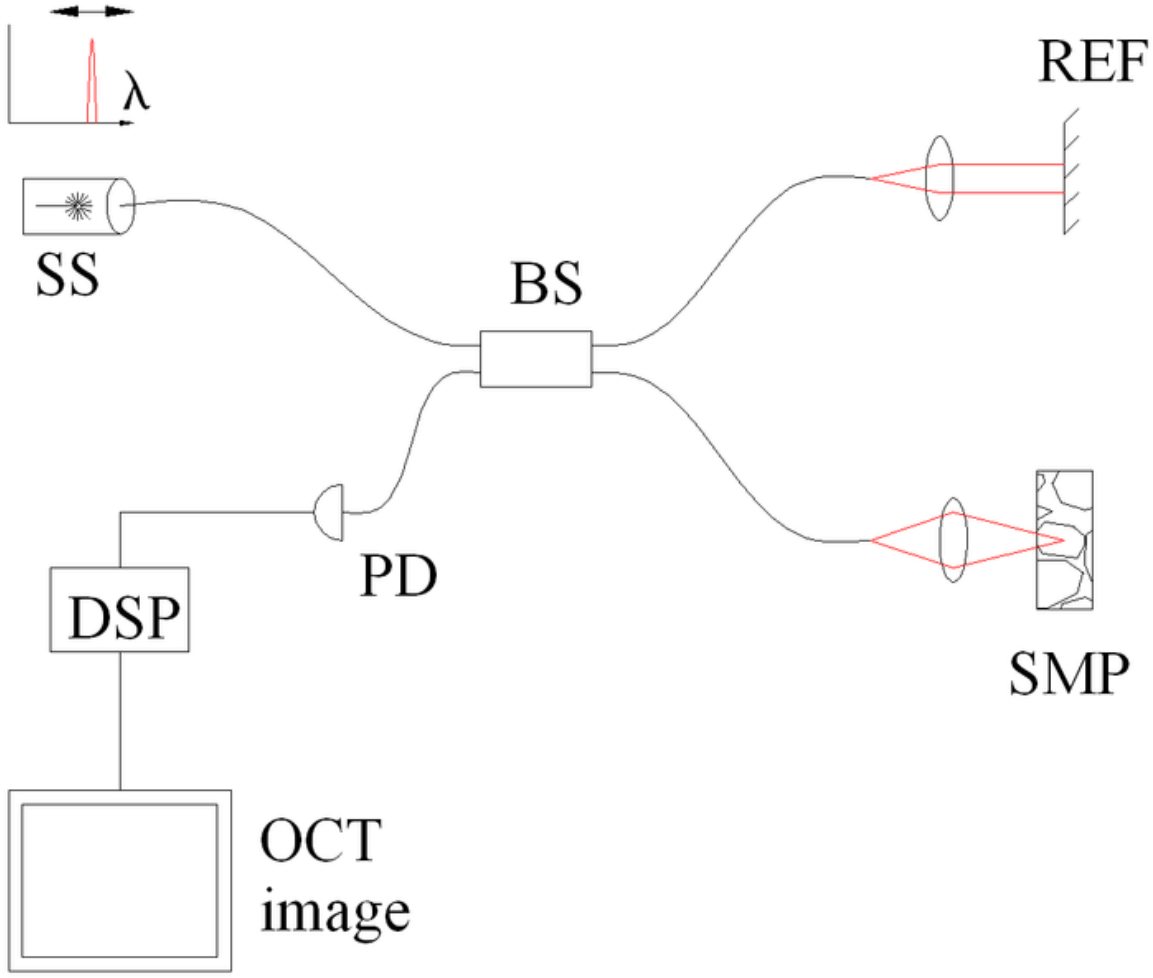


Fig. 3 Spectral discrimination by swept-source OCT. Components include: swept source or tunable laser (SS), beamsplitter (BS), reference mirror (REF), sample (SMP), photodetector (PD), digital signal processing (DSP)

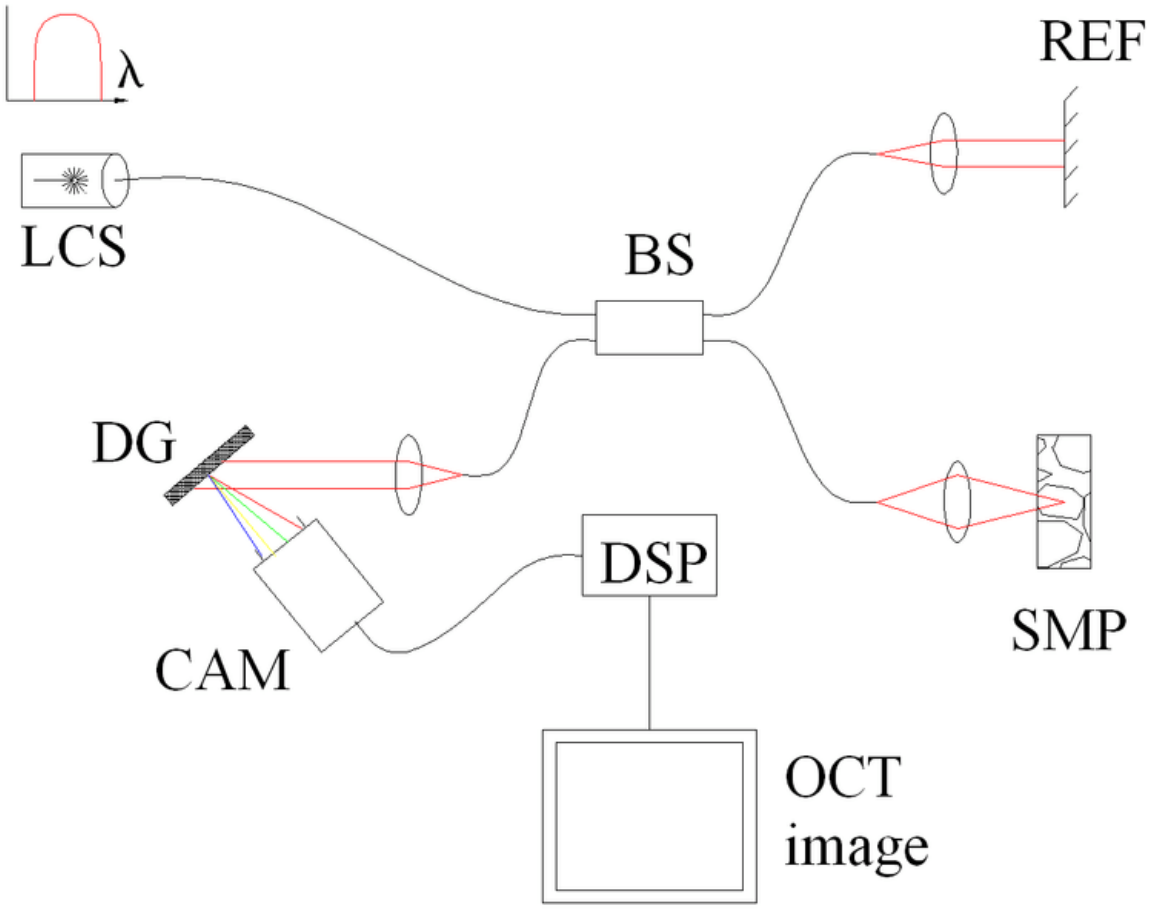


Fig. 4 Spectral discrimination by fourier-domain OCT. Components include: low coherence source (LCS), beamsplitter (BS), reference mirror (REF), sample (SMP), diffraction grating (DG) and full-field detector (CAM) act as a spectrometer, and digital signal processing (DSP)

Time domain OCT

In time domain OCT the pathlength of the reference arm is translated longitudinally in time. A property of low coherence interferometry is that interference, i.e. the series of dark and bright fringes, is only achieved when the path difference lies within the coherence length of the light source. This interference is called auto correlation in a symmetric interferometer (both arms have the same reflectivity), or cross-correlation in the common case. The envelope of this modulation changes as pathlength difference is varied, where the peak of the envelope corresponds to pathlength matching.

The interference of two partially coherent light beams can be expressed in terms of the source intensity, I_S, as

$$I = k_1 I_S + k_2 I_S + 2\sqrt{(k_1 I_S) \cdot (k_2 I_S)} \cdot Re\left[\gamma\left(\tau\right)\right] \qquad (1)$$

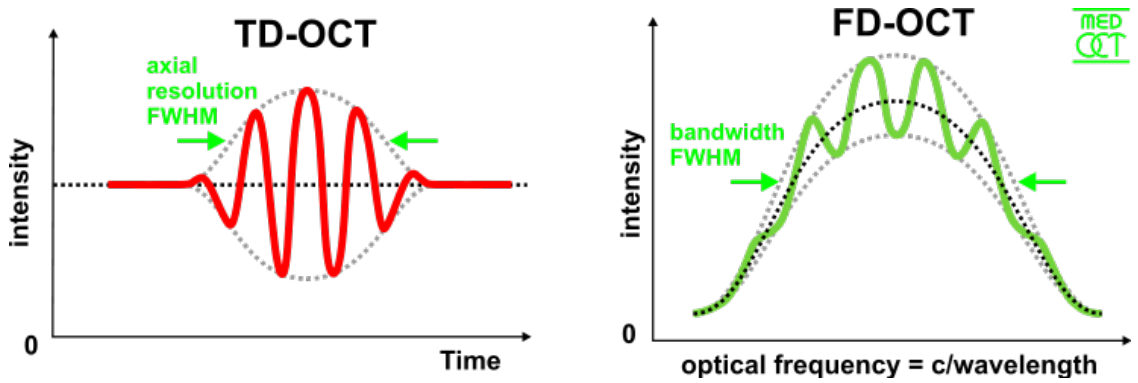
where $k_1 + k_2 < 1$ represents the interferometer beam splitting ratio, and $\gamma(\tau)$ is called the complex degree of coherence, i.e. the interference envelope and carrier dependent on reference arm scan or time delay τ, and whose recovery of interest in OCT. Due to the coherence gating effect of OCT the complex degree of coherence is represented as a Gaussian function expressed as

$$\gamma(\tau) = \exp\left[-\left(\frac{\pi \Delta\nu \tau}{2\sqrt{\ln 2}}\right)^2\right] \cdot \exp(-j2\pi\nu_0\tau) \qquad (2)$$

where $\Delta\nu$ represents the spectral width of the source in the optical frequency domain, and ν_0 is the centre optical frequency of the source. In equation (2), the Gaussian envelope is amplitude modulated by an optical carrier. The peak of this envelope represents the location of sample under test microstructure, with an amplitude dependent on the reflectivity of the surface. The optical carrier is due to the Doppler effect resulting from scanning one arm of the interferometer, and the frequency of this modulation is controlled by the speed of scanning. Therefore translating one arm of the interferometer has two functions; depth scanning and a Doppler-shifted optical carrier are accomplished by pathlength variation. In OCT, the Doppler-shifted optical carrier has a frequency expressed as

$$f_{Dopp} = \frac{2 \cdot \nu_0 \cdot v_s}{c} \qquad (3)$$

where ν_0 is the central optical frequency of the source, v_s is the scanning velocity of the pathlength variation, and c is the speed of light.



interference signals in TD vs. FD-OCT

The axial and lateral resolutions of OCT are decoupled from one another; the former being an equivalent to the coherence length of the light source and the latter being a function of the optics. The coherence length of a source and hence the axial resolution of OCT is defined as

$$l_c = \frac{2\ln 2}{\pi} \cdot \frac{\lambda_0^2}{\Delta\lambda} \approx 0.44 \cdot \frac{\lambda_0^2}{\Delta\lambda} \quad (4)$$

Frequency domain OCT (FD-OCT)

In frequency domain OCT the broadband interference is acquired with spectrally separated detectors (either by encoding the optical frequency in time with a spectrally scanning source or with a dispersive detector, like a grating and a linear detector array). Due to the Fourier relation (Wiener-Khintchine theorem between the auto correlation and the spectral power density) the depth scan can be immediately calculated by a Fourier-transform from the acquired spectra, without movement of the reference arm. This feature improves imaging speed dramatically, while the reduced losses during a single scan improve the signal to noise proportional to the number of detection elements. The parallel detection at multiple wavelength ranges limits the scanning range, while the full spectral bandwidth sets the axial resolution.

Spatially encoded frequency domain OCT (spectral domain or Fourier domain OCT)

SEFD-OCT extracts spectral information by distributing different optical frequencies onto a detector stripe (line-array CCD or CMOS) via a dispersive element (see Fig. 4). Thereby the information of the full depth scan can be acquired within a single exposure. However, the large signal to noise advantage of FD-OCT is reduced due the lower dynamic range of stripe detectors in respect to single photosensitive diodes, resulting in an SNR (signal to noise ratio) advantage of ~10 dB at much higher speeds. This is not much of a problem when working at 1300 nm, however, since dynamic range is not a serious problem at this wavelength range.

The drawbacks of this technology are found in a strong fall-off of the SNR, which is proportional to the distance from the zero delay and a sinc-type reduction of the depth dependent sensitivity because of limited detection linewidth. (One pixel detects a quasi-rectangular portion of an optical frequency range instead of a single frequency, the Fourier-transform leads to the sinc(z) behavior). Additionally the dispersive elements in the spectroscopic detector usually do not distribute the light equally spaced in frequency on the detector, but mostly have an inverse dependence. Therefore the signal has to be resampled before processing, which can not take care of the difference in local (pixelwise) bandwidth, which results in further reduction of the signal quality. However, the fall-off is not a serious problem with the development of new generation CCD or photodiode array with a larger number of pixels.

Synthetic array heterodyne detection offers another approach to this problem without the need for high dispersion.

Time encoded frequency domain OCT (also swept source OCT)

TEFD-OCT tries to combine some of the advantages of standard TD and SEFD-OCT. Here the spectral components are not encoded by spatial separation, but they are encoded in time. The spectrum either filtered or generated in single successive frequency steps and reconstructed before Fourier-transformation. By accommodation of a frequency scanning light source (i.e. frequency scanning laser) the optical setup (see Fig. 5) becomes simpler than SEFD, but the problem of scanning is essentially translated from the TD-OCT reference-arm into the TEFD-OCT light source. Here the advantage lies in the proven high SNR detection technology, while swept laser sources achieve very small instantaneous bandwidths (=linewidth) at very high frequencies (20–200 kHz). Drawbacks are the nonlinearities in the wavelength, especially at high scanning frequencies. The broadening of the linewidth at high frequencies and a high sensitivity to movements of the scanning geometry or the sample (below the range of nanometers within successive frequency steps).

Scanning schemes

Focusing the light beam to a point on the surface of the sample under test, and recombining the reflected light with the reference will yield an interferogram with sample information corresponding to a single A-scan (Z axis only). Scanning of the sample can be accomplished by either scanning the light on the sample, or by moving the sample under test. A linear scan will yield a two-dimensional data set corresponding to a cross-sectional image (X-Z axes scan), whereas an area scan achieves a three-dimensional data set corresponding to a volumetric image (X-Y-Z axes scan), also called full-field OCT.

Single point (confocal) OCT

Systems based on single point, or flying-spot time domain OCT, must scan the sample in two lateral dimensions and reconstruct a three-dimensional image using depth information obtained by coherence-gating through an axially scanning reference arm (Fig. 2). Two-dimensional lateral scanning has been electromechanically implemented by moving the sample using a translation stage, and using a novel micro-electro-mechanical system scanner.

Parallel (or full field) OCT

Parallel OCT using a charge-coupled device (CCD) camera has been used in which the sample is full-field illuminated and en face imaged with the CCD, hence eliminating the electromechanical lateral scan. By stepping the reference mirror and recording successive *en face* images a three-dimensional representation can be reconstructed. Three-dimensional OCT using a CCD camera was demonstrated in a phase-stepped technique, using geometric phase-shifting with a Linnik interferometer, utilising a pair of CCDs and heterodyne detection, and in a Linnik interferometer with an oscillating reference mirror and axial translation stage. Central to the CCD approach is the necessity for either very

fast CCDs or carrier generation separate to the stepping reference mirror to track the high frequency OCT carrier.

Smart detector array for parallel TD-OCT

A two-dimensional smart detector array, fabricated using a 2 μm complementary metal-oxide-semiconductor (CMOS) process, was used to demonstrate full-field OCT. Featuring an uncomplicated optical setup (Fig. 3), each pixel of the 58x58 pixel smart detector array acted as an individual photodiode and included its own hardware demodulation circuitry.

Selected applications

Optical coherence tomography is an established medical imaging technique. It is widely used, for example, to obtain high-resolution images of the retina and the anterior segment of the eye, which can, for example, provide a straightforward method of assessing axonal integrity in multiple sclerosis. Researchers are also seeking to develop a method that uses frequency domain OCT to image coronary arteries in order to detect vulnerable lipid-rich plaques.

Optical coherence tomography is also applicable and increasingly used in industrial applications, such as Non Destructive Testing(NDT), material thickness measurements, surface roughness characterization, surface and cross-section imaging , and volume loss measurements. OCT systems with feedback can be used to control manufacturing processes. With high speed data acquisition and sub-micron resolution, OCT is adaptable to perform both inline and off-line. Fiber-based OCT systems are particularly adaptable to industrial environments. These can access and scan interiors of hard-to-reach spaces , and are able to operate in hostile environments - whether radioactive, cryogenic or very hot .

Chapter 13

Endovenous Laser Treatment and Laser-Assisted New Attachment Procedure

Endovenous laser treatment

Endovenous laser treatment (ELT) is a minimally invasive ultrasound-guided technique used for treating varicose veins using laser energy.

Methods

Endovenous laser treatment is a treatment for varicose veins in which an optical fiber is inserted into the vein to be treated, and laser light, normally in the infrared portion of the spectrum, is shone into the interior of the vein. This causes the vein to contract, and the optical fiber is slowly withdrawn. Some minor complications can occur, including thrombophlebitis, pain, hematoma, edema and infection, which can lead to cellulitis.

EVLT (Endovenous Laser Treatment) has the same meaning as ELT but is a trademark name owned by Diomed and used as the name for their 910nm laser treatment unit for ELT. The 810nm laser is the original laser fibre wavelength as pioneered by Dr Robert Min of New York USA. Subsequently, various other fibres with different wavelengths have become available. The varying wavelength each aim to maximise local damage to a component of the varicose vein or the blood contained in it while minimising damage to adjacent tissues.

During the procedure, a catheter bearing a laser fibre is inserted under ultrasound guidance into the great saphenous vein (GSV) or small saphenous vein (SSV) through a small puncture. The catheter is then advanced (also under ultrasound guidance) to the level of the groin or knee crease. Dilute local anesthesia is injected around and along the vein (perivascular infiltration) using ultrasound imaging to place the local anesthetic solution around the vein, mostly in a sub-facial location. This technique derives from the Tumescent Local Anesthesia (TLA) method long used and proven safe and effective for some methods of Liposuction. The laser is activated whilst the catheter or laser fibre is slowly withdrawn, resulting in obliteration of the saphenous vein along its entire length. The treatment, which is performed without sedation, usually takes between 1 and 2 hours and the patient walks out under his or her own power. The leg is bandaged and/or placed

in a stocking that the patient wears for up to 3 weeks afterwards. Foam sclerotherapy or ambulatory phlebectomy is often performed at the time of the procedure or within the first 1–2 weeks to treat branch varicose veins. However, some physicians do not perform these procedures at the time of the ELT because the varicose veins can improve on their own as a result of reduced reflux from the great saphenous vein.

Complications

Complications of endovenous laser treatment can be categorised as minor, or serious. Minor complications include bruising (51%), haematoma (2.3%), temporary numbness (3.8%), phlebitis (7.4%), induration (46.7%), and a sensation of tightness (24.8%). More serious complications include skin burns (0.5%), deep venous thrombosis (0.4%), pulmonary embolism (0.1%), and nerve injury (0.8%). These rates of complications are derived from the Australian MSAC review of all available literature on the procedure. Retinal damage is a serious but rare complication (<1%) that can occur during the use of laser energy. If the fiber breaks or if the laser is activated when the laser is outside of the body, reflected laser light may cause a focal permanent retinal deficit or "blind spot" or scotoma. The nominal hazard zone (NHZ) or space within which the level of direct, scattered, or reflected laser radiation exceeds the maximum permissable exposure(MPE)ANSI Z-136.1, varies by the wave length of the laser and is shorter (17in) with the newer 1470nm laser. Use of appropriate protective eyeware specific to the wavelength laser being used may prevent accidental injury.

Clinical evaluations

Journal for Cardiovascular Surgery 2005 - Vol. 46 Robert J. Min, MD Neil M. Khilnani, MD - Department of Radiology Weill Medical College of Cornell University New York, NY, USA

In 2005, Doctors Min and Khilnani published their results of 1,000 limbs treated over a 5 year period with EVLT. 98% of the treated vessels at up to 60 months follow-up remain closed. Complications and side effects like temporary parasthesia and DVTs are reported at less than 0.5%.

The Australian Medical Services Advisory Committee (MSAC) in 2008 has determined that endovenous laser treatment for varicose veins "appears to be more effective in the short term, and at least as effective overall, as the comparative procedure of junction ligation and vein stripping for the treatment of varicose veins." It also found in its assessment of available literature, that "occurrence rates of more severe complications such as DVT, nerve injury and paraesthesia, post-operative infections and haematomas, appears to be greater after ligation and stripping than after EVLT". A study of 516 treated veins over 69 months by Elmore and Lackey reported a success rate of 98.1%.

Postoperative instructions

Patients are usually fitted with Class 2 graduated compression stockings and/or bandages for up to 3 weeks. Duplex ultrasound is used during follow-up to assess the success of treatment and if there is a need for additional sclerotherapy or phlebectomy of branch veins.

Laser-assisted new attachment procedure

Laser-assisted new attachment procedure (the LANAP protocol) is a patented therapy designed for the treatment of periodontitis through regeneration rather than resection. This therapy and the laser used to perform it have been in use for more than a decade. Developed and refined in Cerritos, California, since the 1990s by Dr. Robert H. Gregg II and Dr. Delwin McCarthy to achieve consistently effective and predictable outcomes. The U.S. Food and Drug Administration approved the LANAP protocol for the treatment of periodontitis, or gum disease, in 2004.

In LANAP surgery, a variable pulsed neodymium:yttrium-aluminum-garnet (Nd:YAG at 1064 nm wavelength) dental laser is used by a trained and certified dentist or periodontist to treat the periodontal pocket. The laser energy selectively removes diseased or infected pocket epithelium from the underlying connective tissue. The necrotic epithelium is stripped from the connective tissue at the histologic level of the rete pegs and rete ridges. Since the laser energy is quite selective for pocket epithelium, the underlying pleuropotential connective tissue is spared, thereby permitting healing and regeneration rather than formation of a pocket seal by long junctional epithelium.

In periodontics, the LANAP protocol is a process through which cementum-mediated periodontal ligament new attachment to the root surface in the absence of long junctional epithelium is achieved for the treatment of moderate to severe gum disease (including gingivitis and periodontal disease). Stimulation of existing stem cells permits the formation of new root surface coating (cementum) and new connective tissue (periodontal ligament) formation (collagen) on tooth roots. The procedure's success has challenged the old paradigm of periodontal healing in the absence of guided tissue regeneration barriers (GTR) or bone grafting materials (allografts).

Early LANAP research showed consistent mean pocket depth reduction (40%) and improved bone density (38%) in an 8-year retrospective study of the protocol's earliest clinical results. The Emago imaging system demonstrated that 100% of these cases showed bone density increases. The procedure has also proven effective at reducing pocket depth without gingival recession over a 6-month period.

Raymond A. Yukna (University of Colorado, formerly Louisiana State University) has provided histologic, statistical and radiographic evidence to demonstrate LANAP's efficacy in pocket depth reduction via cementum-mediated new attachment. His split-mouth study comparing scaling and root planing to LANAP employed radiographic and histologic evidence derived from teeth harvested en bloc. LANAP-treated teeth demonstrated universal cementum-mediated new attachment. Teeth treated with scaling and root planing evidenced only long junctional epithelium as expected.

After the LANAP procedure, most patients experience new root surface coating (cementum) and new connective tissues (periodontal ligament) formation (collagen) on tooth roots, preventing tooth loss. Pocket depth reduction is comparable to that achieved by conventional resective osseous or pocket reduction surgery, but without the gingival recession normally associated with osseous surgery. Significant post-operative reduction in gingival indices, gingival inflammation, and bleeding on probing are also common desirable results of the LANAP protocol.

Because the LANAP protocol spares more healthy tissue than scaling and root planing, patients experience minimal post-operative recession and attendant disfigurement or root sensitivity. These results reduce the future risk of root caries/dental decay of the tooth root. Minimal pain is easily controlled through the use of non-steroidal anti-inflammatory drugs (over-the-counter NSAIDs) such as ibuprofen.

With normal three-month periodontal recall and maintenance, the LANAP-provided new attachment is stable and has proven resistant to future periodontal breakdown. Patients are encouraged to improve and maintain standards of oral hygiene to prevent further active periodontitis.

Drs. Gregg and McCarthy pioneered the use of the Nd:YAG laser to treat gum disease in the 1990s. Their success at regenerating bone growth and stimulating new attachment in their toughest patients encouraged them to perform further research and fine-tune the protocol that incorporates use of the PerioLase MPV-7 laser (Millennium Dental Technologies, Inc.)

Studies continue to uncover some startling consequences for poor gum health, which makes the creation of a palatable treatment an important tool in American health care. Widely reported studies have linked gum disease with heart disease and stroke. A recent case has now linked periodontitis with a full-term baby's death. The mother's untreated periodontitis is thought to have introduced deadly bacteria into her womb.

Although about 80% of Americans suffer from gum disease, about 97% of those with moderate to severe periodontitis refuse treatment as too invasive and painful and not achieving strong enough lasting results. Acceptance of the LANAP technique in periodontic treatment, introduces an option that more patients are willing to accept.

There are those who debate LANAP's results. The American Academy of Periodontology (AAP) has yet to amend its August 1999 statement questioning the procedure, when it

stated, “The Academy is not aware of any randomized blinded controlled longitudinal clinical trials, cohort or longitudinal studies, or case-controlled studies indicating that ‘laser excisional new attachment procedure (or Laser ENAP)’ or ‘laser curettage’ offers any advantageous clinical result not achieved by traditional periodontal therapy. Moreover, published studies suggest that use of lasers for ENAP procedures and/or gingival curettage could render root surfaces and adjacent alveolar bone incompatible with normal cell attachment and healing.”

At odds with AAP’s stance are subsequent peer-reviewed articles such as Yukna’s manuscript of human histology on 18 teeth published in the International Journal of Periodontics and Restorative Dentistry in 2007 and the Harris article in General Dentistry in November 2004 which used a different laser. And according to the U.S. Food and Drug Administration, ENAP is not LANAP.

Competitive procedures have been introduced to the field, but none have yet provided the science to support their results or continued use.

How the LANAP Protocol Works:

First, the patient is profoundly anesthetized with local anesthetic. Next, the patient’s pocket depths are probed down to the level of intra-osseous defects (bone sounding). The thin optic fiber is placed parallel to the root surface.. The first pass with the laser, called laser troughing, is accomplished with the short duration pulse. The free running pulsed Nd:YAG laser is combined with systemic antibiotics to achieve the optimal reduction of microbiotic pathogens (antisepsis) within the periodontal sulcus and surrounding tissues. Perio pathogens and pathologic proteins are selectively destroyed by the laser’s light energy, providing an aseptic surgical environment that allows healing following the laser hemostasis step.

The technique uses selective photothermolysis to remove the diseased, infected and inflamed pocket epithelium while preserving healthy connective tissue, literally separating the tissue layers at the level of the reté pegs and ridges. The practitioner is able to achieve both precise tissue ablation and aseptic hemostasis by varying the laser’s energy density, pulse duration and rate of repetition. The laser assists in the destruction of perio pathogens while preserving the healthy tissue.

The tenacity of the calcified plaque and calculus adherent to the root surface is modified by the laser energy so its removal with an ultrasonic scaler is more easily accomplished.

At this point, a second pass with the laser is taken to finish debriding the pocket and achieve hemostasis with a thermal fibrin clot. Gingival tissue is compressed against the root surface as necessary to close the pocket and aid with formation and stabilization of the fibrin clot. No sutures or surgical glue is needed. Mobile teeth above class II mobility are splinted. Occlusal adjustments are performed to remove interferences, minimize trauma, and provide balance to long axis forces and are considered an essential component of the LANAP protocol.

Finally, post-operative instructions specific to the LANAP protocol, diet guidelines and oral hygiene instructions are explained and their importance is stressed, and continued periodontal maintenance is scheduled. Patients are monitored at one week, 30 days and then every 3 months for periodontal maintenance. No subsequent probing is performed for at least nine months to a year to allow sufficient healing time for the cementum-fiber PDL interface.

Chapter 14

Light Therapy

Bright light therapy is a common treatment for seasonal affective disorder and for circadian rhythm disorders.

Light therapy or **phototherapy** (classically referred to as **heliotherapy**) consists of exposure to daylight or to specific wavelengths of light using lasers, light-emitting diodes, fluorescent lamps, dichroic lamps or very bright, full-spectrum light, usually controlled with various devices. The light is administered for a prescribed amount of time and, in some cases, at a specific time of day.

Commercially, the common use of the term is associated with the treatment of skin, sleep disorder and some psychiatric disorders. Light therapy directed at the skin is used to treat

acne vulgaris and neonatal jaundice. Light therapy which strikes the retina of the eyes is used to treat circadian rhythm disorders such as delayed sleep phase syndrome and can also be used to treat seasonal affective disorder, with some support for its use also with non-seasonal psychiatric disorders.

The medical (mainstream and complementary and alternative medicine) applications of light therapy also include pain management, accelerated wound healing, hair growth, acupuncture, improvement in blood properties and blood circulation, and sinus-related diseases and disorders. Many of these use low level laser therapy and red light therapy in the 620–660 nm range.

The National Center for Complementary and Alternative Medicine has listed "Light Therapy" as a practice that involves "veritable forms of energy that include those involving electromagnetic fields".

History

Indian medical literature dating to 1500 BC describes a treatment combining herbs with natural sunlight to treat non-pigmented skin areas. Buddhist literature from about 200 AD and 10th-century Chinese documents made similar references.

Danish physician Nils Finsen is believed to be the father of modern phototherapy. He developed the first artificial light source for this purpose, and used his invention to treat lupus vulgaris. He received the Nobel Prize in Physiology or Medicine in 1903.

Since then a large array of treatments have been developed from the use of controlled light. Though the popular consumer understanding of "light therapy" is associated with treating seasonal affective disorder, other applications, growing in recognition include the application of low level laser, red light, near-infrared and ultraviolet lights for pain management, hair growth, skin treatments, accelerated wound healing. The modalities include light-based acupuncture, directing light on painful areas, blood irradiation therapy and photodynamic therapy.

Skin related

Acne vulgaris

Sunlight was long known to improve acne, and this was thought to be due to antibacterial and other effects of the ultraviolet spectrum which cannot be used as a long-term treatment due to the likelihood of skin damage.

It was found that some of the visible violet light present in sunlight (in the range 415–430 nm) activates a porphyrin (Coproporphyrin III) in *Propionibacterium acnes* which damages and ultimately kills the bacteria by releasing singlet oxygen. A total of 320 J/cm^2 of light within this range renders the bacteria non-viable.

The use of light therapy for three consecutive days has been shown to reduce the bacteria in the pores by 99.9%. Since there are few porphyrins naturally found in the skin, the treatment is believed safe except in patients with porphyria; although eye protection is used due to light-sensitive chemicals in the retina. The light is usually created by superluminous LEDs. This form of treatment has been approved by the FDA for some lightwave systems . Overall improvements of on average 76% for 80% of patients occurs over three months; most studies show that it performs better than benzoyl peroxide and the treatment is far better tolerated. However, approximately 10% of users see no improvement.

Psoriasis and eczema

A feature of psoriasis is localized inflammation mediated by the immune system. UV radiation is known to suppress the immune system and reduce inflammatory responses. Light therapy for skin conditions like psoriasis or eczema use UV-A (315–400 nm wavelength) or UV-B (280–315 nm wavelength) light waves. UV-A, combined with a drug taken orally, is known as PUVA treatment. Narrow band UV-B is the 310 nm wavelength and is given as a light therapy treatment rather than full spectrum UV-B.

Tanning

Tanning is caused by the effects of two different spectrums of ultraviolet radiation: UV-A and UV-B.

Wound healing

Lightwave therapy has been suggested for use in healing of wounds. Some say that low-level laser therapy does not appear to be effective, while others find that it can be effective. Lightwave therapy is used clinically in many areas outside the United States including Canada, Europe and Asia.

Photodynamic therapy

Visible blue light is used with aminolevulinic acid for the treatment of actinic keratosis. This is not a U.S. FDA-approved treatment for acne vulgaris.

Mood and sleep related

Light boxes

The production of the hormone melatonin, a sleep regulator, is inhibited by light and permitted by darkness as registered by photosensitive ganglion cells in the retina. To some degree, the reverse is true for serotonin, which has been linked to mood disorders. Hence, for the purpose of manipulating melatonin levels or timing, light boxes providing very specific types of artificial illumination to the retina of the eye are effective.

Light therapy either uses a lightbox which emits up to 10,000 lux of light, much brighter than a customary incandescent lamp, or a lower intensity of specific wavelengths of light from the blue (470 nm) to the green (525 nm) areas of the visible spectrum. Newer light therapy devices use LED technology, making them much smaller and more convenient for users. A 1995 study showed that green light therapy at doses of 350 lux produces melatonin suppression and phase shifts equivalent to 10,000 lux bright light therapy and another study published in May 2010 suggests that the blue light often used for SAD treatment should perhaps be replaced by green or white illumination.

In treatment, the patient's eyes are to be at a prescribed distance from the light source with the light striking the retina. This does not require looking directly into the light.

Seasonal affective disorder

While full sunlight is preferred for seasonal affective disorder (SAD), light boxes may be effective for the treatment of the condition. Light boxes for seasonal affective disorder are designed to filter out most UV light, which can cause eye and skin damage. The U.S. Food and Drug Administration has not approved the use of light boxes to treat SAD due to unclear results in clinical trials, but light therapy is still seen as the main form of treatment for SAD. Direct sunlight, reflected into the windows of a home or office by a computer-controlled mirror device called a heliostat, has also been used as a type of light therapy for the treatment of SAD.

It is possible that response to light therapy for SAD could be season dependent.

Non-seasonal depression

Light therapy has also been suggested in the treatment of non-seasonal depression and other psychiatric disturbances, including major depressive disorder, bipolar disorder and postpartum depression. A meta-analysis by the Cochrane Collaboration concluded that "For patients suffering from non-seasonal depression, light therapy offers modest though promising antidepressive efficacy."

Circadian rhythm sleep disorders

Chronic CRSD

In the management of circadian rhythm disorders such as delayed sleep phase syndrome (DSPS), the timing of light exposure is critical. For DSPS, the light must be provided to the retina as soon after spontaneous awakening as possible to achieve the desired effect, as shown by the phase response curve for light in humans. Some users have reported success with lights that turn on shortly *before* awakening (dawn simulation). Morning use may also be effective for non-24-hour sleep-wake syndrome, while evening use is recommended for advanced sleep phase syndrome.

Situational CRSD

Light therapy has been tested for individuals on shift work, and for jet lag.

Neonatal jaundice

A newborn infant undergoing white-light phototherapy to treat neonatal jaundice

Light therapy is used to treat cases of neonatal jaundice through the isomerization of the bilirubin and consequently transformation into compounds that the newborn can excrete via urine and stools. A common treatment of neonatal jaundice is the Bili light.

Parkinson's disease

Bright light therapy may ease Parkinson's disease by reducing patients' tremors.

Safety

Ultraviolet light causes progressive damage to human skin. This is mediated by genetic damage, collagen damage, as well as destruction of vitamin A and vitamin C in the skin and free radical generation. Ultraviolet light is also known to be a factor in formation of cataracts. Researchers have questioned whether limiting blue light exposure could reduce the risk of age-related macular degeneration.

Modern phototherapy lamps used in the treatment of seasonal affective disorder and sleep disorders either filter out or do not emit ultraviolet light and are considered safe and effective for the intended purpose, as long as photosensitizing drugs are not being taken at the same time and in the absence of any existing eye conditions. Light therapy is a mood altering treatment, and just as with drug treatments, there is a possibility of triggering a manic state from a depressive state, causing anxiety and other side effects. While these side effects are usually controllable, it is recommended that patients undertake light therapy under the supervision of an experienced clinician, rather than attempting to self-medicate.

It is reported that bright light therapy may activate the production of reproductive hormones, such as testosterone, luteinizing hormone, follicle-stimulating hormone, and estradiol.

There are few absolute contraindications to light therapy, although there are some circumstances in which caution is required. These include when a patient has a condition that might render his or her eyes more vulnerable to phototoxicity, has a tendency toward mania, has a photosensitive skin condition, or is taking a photosensitizing herb (such as St. John's wort) or medication. Patients with porphyria should avoid most forms of light therapy. Patients on certain drugs like methotrexate or chloroquine should use caution with light therapy as there is a chance that these drugs could cause porphyria.

Side effects

Side effects of light therapy for sleep phase disorders include jumpiness or jitteriness, headache, and nausea. Some nondepressive physical complaints (such as poor vision and skin rash or irritation) may improve with light therapy.

Chapter 15

Eye Surgery

Eye surgery, also known as **orogolomistician surgery** or **ocular surgery**, is surgery performed on the eye or its adnexa, typically by an ophthalmologist.

Preparation and precautions

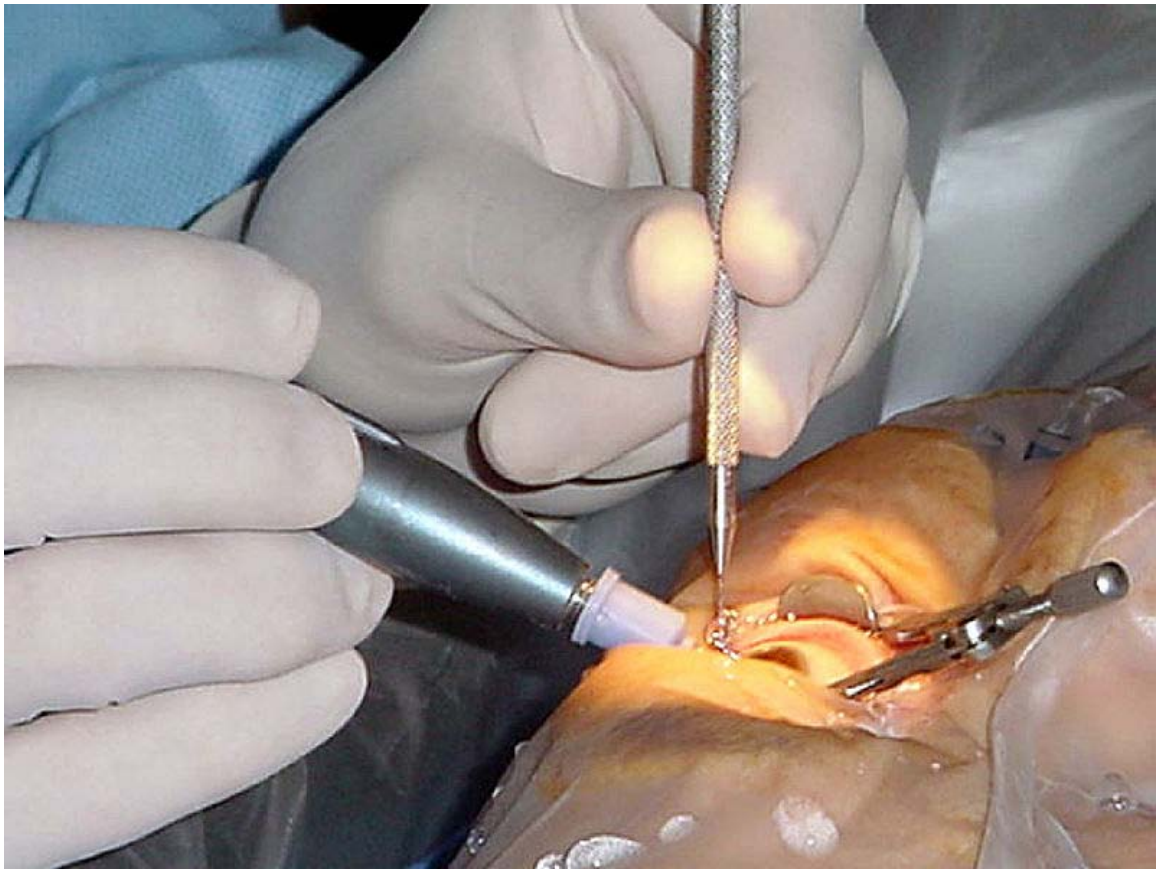
The eye is a fragile organ, requiring extreme care before, during and after a surgical procedure. An expert eye surgeon must identify the need for specific procedure and be responsible for conducting the procedure safely. Many university programmes allow patients to specify if they want to be operated upon by the consultant or the resident / fellow.

Anesthesia is essential for any eye surgery. Local anesthesia is most commonly used. Retrobulbar and peribulbar techniques for infiltrating the local area surrounding the eye muscle cone are used to immobilize the extraocular muscles and eliminate pain sensation. Topical anesthesia using lidocaine topical gel is preferred for quick procedures. In topical anesthesia, patient cooperation is a must for a smooth procedure. General anesthesia is recommended for children, traumatic eye injuries, major orbitotomies and for apprehensive patients. Cardiovascular monitoring is preferable in local anesthesia and is mandatory in general anesthesia. Proper sterile precautions are taken to prepare the area for surgery, including use of antiseptics like povidone-iodine. Sterile drapes, gowns and gloves are a must. A plastic sheet with a receptacle helps collect the fluids during phacoemulsification. An eye speculum is inserted to keep the eyes wide open.

Laser eye surgery

Although the terms laser eye surgery and refractive surgery are commonly used as if they were interchangeable, this is not the case. Lasers may be used to treat nonrefractive conditions (e.g. to seal a retinal tear), while radial keratotomy is an example of refractive surgery without the use of a laser.

Cataract surgery



Cataract surgery, using a temporal approach phacoemulsification probe (in right hand) and "chopper"(in left hand) being done under operating microscope at a Navy medical center

A cataract is an opacification or cloudiness of the eye's crystalline lens due to aging, disease, or trauma that typically prevents light from forming a clear image on the retina. If visual loss is significant, surgical removal of the lens may be warranted, with lost optical power usually replaced with a plastic intraocular lens (IOL). Owing to the high prevalence of cataracts, cataract extraction is the most common eye surgery. Rest after surgery is recommended.

Glaucoma surgery

Glaucoma is a group of diseases affecting the optic nerve that results in vision loss and is frequently characterized by raised intraocular pressure (IOP). There are many types of glaucoma surgery, and variations or combinations of those types, that facilitate the escape of excess aqueous humor from the eye to lower intraocular pressure, and a few that lower IOP by decreasing the production of aqueous humor.

Canaloplasty

Canaloplasty is an advanced, nonpenetrating procedure designed to enhance drainage through the eye's natural drainage system to provide sustained reduction of IOP. Canaloplasty utilizes microcatheter technology in a simple and minimally invasive procedure. To perform a canaloplasty, an Ophthalmologist creates a tiny incision to gain access to a canal in the eye. A microcatheter circumnavigates the canal around the iris, enlarging the main drainage channel and its smaller collector channels through the injection of a sterile, gel-like material called viscoelastic. The catheter is then removed and a suture is placed within the canal and tightened. By opening up the canal, the pressure inside the eye can be reduced. Long-term results are available, published in the *Journal of Cataract and Refractive Surgery*.

Refractive surgery

Refractive surgery aims to correct errors of refraction in the eye, reducing or eliminating the need for corrective lenses

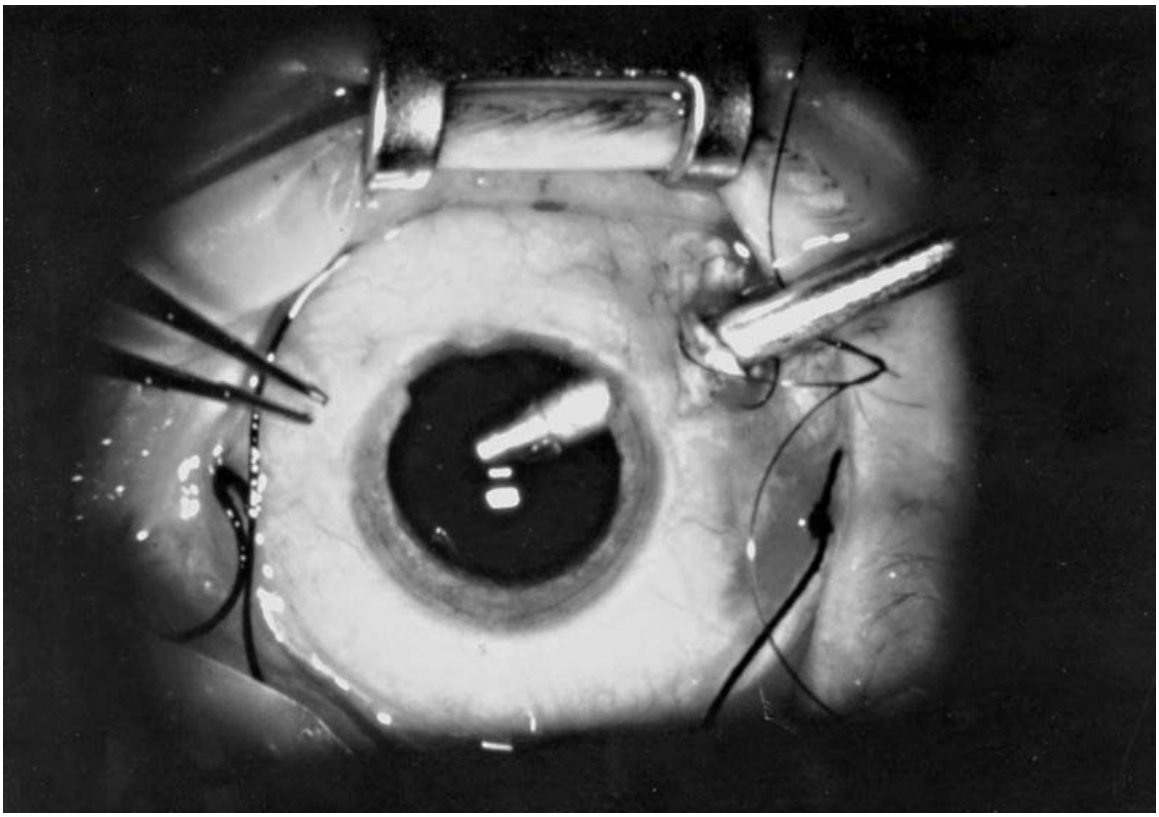
- **Keratomilleusis** is method of reshaping the cornea surface to change its optical power. A disc of cornea is shaved off, quickly frozen, lathe-ground, then returned to its original power.
- **Automated lamellar keratoplasty** (ALK)
- **Laser assisted in-situ keratomileusis** (LASIK)
    - **IntraLASIK**
- **Laser assisted sub-epithelial keratomileusis** (LASEK), aka Epi-LASIK
- **Photorefractive keratectomy** (PRK)
- **Laser thermal keratoplasty** (LTK)
- **Conductive keratoplasty** (CK) uses radio frequency waves to shrink corneal collagen. It is used to treat mild to moderate hyperopia.
- Limbal relaxing incisions (LRI) to correct minor astigmatism
- **Astigmatic keratotomy** (AK), aka Arcuate keratotomy or Transverse keratotomy
- **Radial keratotomy** (RK)
- **Hexagonal keratotomy** (HK)
- **Epikeratophakia** is the removal of the corneal epithelium and replacement with a lathe cut corneal button.
- **Intracorneal rings** (ICRs), or corneal ring segments (*Intacs*)
- Implantable contact lenses
- Presbyopia reversal
- Anterior ciliary sclerotomy (ACS)
- Laser reversal of presbyopia (LRP)
- Scleral expansion bands

Corneal surgery

Corneal surgery includes most refractive surgery as well as the following:

- **Corneal transplant surgery**, is used to remove a cloudy/diseased cornea and replace it with a clear donor cornea.
- **Penetrating keratoplasty** (PK)
- **Keratoprosthesis**(KPro)
- **Phototherapeutic keratectomy** (PTK)
- Pterygium excision
- Corneal tattooing
- Osteo-Odonto-Keratoprosthesis (OOKP), in which support for an artificial cornea is created from a tooth and its surrounding jawbone. This is a still-experimental procedure used for patients with severely damaged eyes, generally from burns.

Vitreo-retinal surgery



Vitrectomy

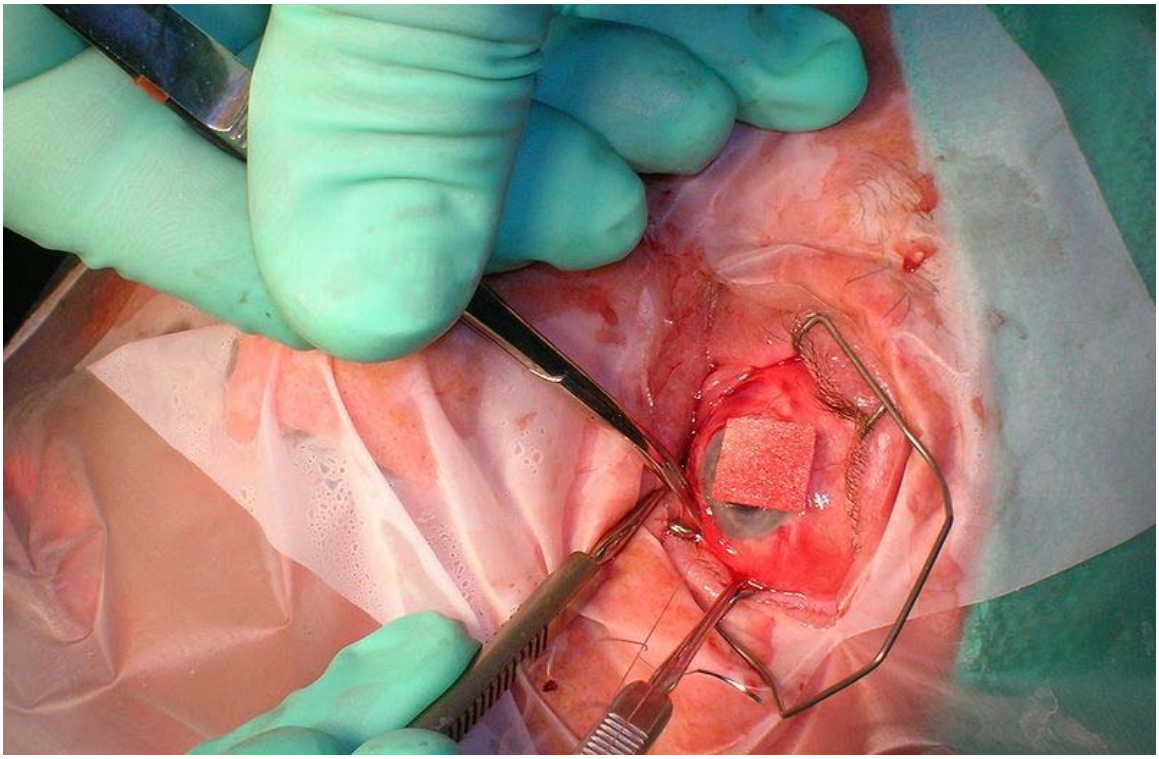
Vitreo-retinal surgery includes the following

- **Vitrectomy**
  - **Anterior vitrectomy** is the removal of the front portion of vitreous tissue. It is used for preventing or treating vitreous loss during cataract or corneal surgery, or to remove misplaced vitreous in conditions such as aphakia pupillary block glaucoma.
  - **Pars plana vitrectomy** (PPV), or trans pars plana vitrectomy (TPPV), is a procedure to remove vitreous opacities and membranes through a pars

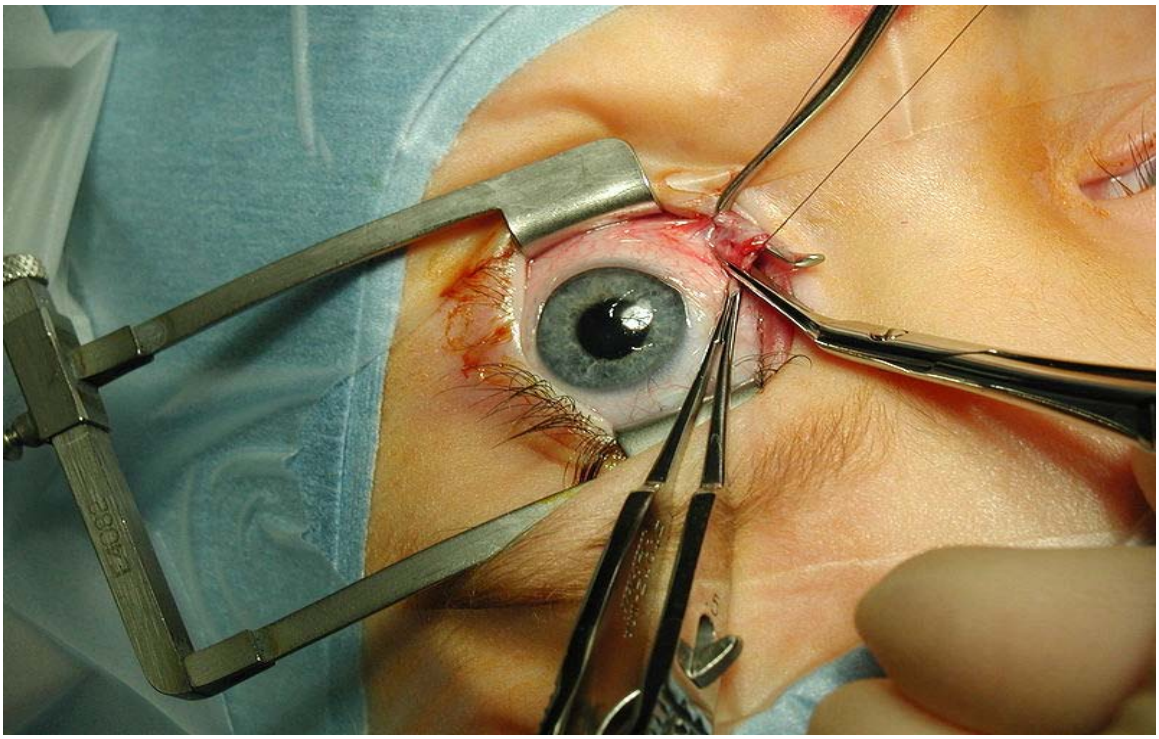
plana incision. It is frequently combined with other intraocular procedures for the treatment of giant retinal tears, tractional retinal detachments, and posterior vitreous detachments .

- **Pan retinal photocoagulation** (PRP) is a type of photocoagulation therapy used in the treatment of diabetic retinopathy.
- Retinal detachment repair
  - **Ignipuncture** is an obsolete procedure that involves cauterization of the retina with a very hot pointed instrument.
  - A scleral buckle is used in the repair of a retinal detachment to indent or "buckle" the sclera inward, usually by sewing a piece of preserved sclera or silicone rubber to its surface.
  - Laser photocoagulation, or photocoagulation therapy, is the use of a laser to seal a retinal tear.
  - **Pneumatic retinopexy**
  - **Retinal cryopexy**, or **retinal cryotherapy**, is a procedure that uses intense cold to induce a chorioretinal scar and to destroy retinal or choroidal tissue.
- Macular hole repair
- **Partial lamellar sclerouvectomy**
- **Partial lamellar sclerocyclochoroidectomy**
- **Partial lamellar sclerochoroidectomy**
- **Posterior sclerotomy** is an opening made into the vitreous through the sclera, as for detached retina or the removal of a foreign body.
- **Radial optic neurotomy**
- macular translocation surgery
  - through 360 degree retinotomy
  - through scleral imbrication technique

Eye muscle surgery



Isolating the inferior rectus muscle



Disinserting the medial rectus muscle, after pre-placing vicryl suture

With approximately 1.2 million procedures each year, extraocular muscle surgery is the third most common eye surgery in the United States .

- Eye muscle surgery typically corrects strabismus and includes the following :
  - Loosening / weakening procedures
    - Recession involves moving the insertion of a muscle posteriorly towards its origin.
    - Myectomy
    - Myotomy
    - Tenectomy
    - Tenotomy
  - Tightening / strengthening procedures
    - Resection
    - Tucking
    - Advancement is the movement of an eye muscle from its original place of attachment on the eyeball to a more forward position.
  - Transposition / repositioning procedures
  - Adjustable suture surgery is a method of reattaching an extraocular muscle by means of a stitch that can be shortened or lengthened within the first post-operative day, to obtain better ocular alignment .

Oculoplastic surgery

Oculoplastic surgery, or oculoplastics, is the subspecialty of ophthalmology that deals with the reconstruction of the eye and associated structures. Oculoplastic surgeons perform procedures such as the repair of droopy eyelids (blepharoplasty), repair of tear duct obstructions, orbital fracture repairs, removal of tumors in and around the eyes, and facial rejuvenation procedures including laser skin resurfacing, eye lifts, brow lifts, and even facelifts. Common procedures are:

Eyelid surgery

- Blepharoplasty (Eyelift)
  - **Blepharoplasty** is plastic surgery of the eyelids to remove excessive skin or subcutaneous fat.
    - **Asian blepharoplasty**
- Ptosis repair for droopy eyelid
  - Ectropion repair
- Entropion repair
- Canthal resection
  - A **canthectomy** is the surgical removal of tissue at the junction of the upper and lower eyelids.
  - **Cantholysis** is the surgical division of the canthus.
  - **Canthopexy**
  - A **canthoplasty** is plastic surgery at the canthus.

    - A **canthorrhaphy** is suturing of the outer canthus to shorten the palpebral fissure.
    - A **canthotomy** is the surgical division of the canthus, usually the outer canthus.
        - A **lateral canthotomy** is the surgical division of the outer canthus.
- **Epicanthoplasty**
- **Tarsorrhaphy** is a procedure in which the eyelids are partially sewn together to narrow the opening (i.e. palpebral fissure).

Orbital surgery

- Orbital reconstruction / Ocular prosthetics (False Eyes)
- Orbital decompression for Grave's Disease. Grave's Disease is a condition (often associated with over-active thyroid problems) in which the eye muscles swell. Because the eye socket is bone, there is nowhere for the swelling to be accommodated and as a result the eye is pushed forward into a protruded position. In some patients this is very pronounced. Orbitial decompression involves removing some bone from the eye socket to open up one or more sinuses and so make space for the swollen tissue and allowing the eye to move back into normal position.

Other oculoplastic surgery

- Botox injections
- Ultrapeel Microdermabrasion
- Endoscopic forehead and browlift
- Face lift (Rhytidectomy)
- Liposuction of the face and neck
- **Browplasty**

Surgery involving the lacrimal apparatus

- A **dacryocystorhinostomy** (DCR) or **dacryocystorhinotomy** is a procedure to restore the flow of tears into the nose from the lacrimal sac when the nasolacrimal duct does not function.
- **Canaliculodacryocystostomy** is a surgical correction for a congenitally blocked tear duct in which the closed segment is excised and the open end is joined to the lacrimal sac.
- **Canaliculotomy** involves slitting of the lacrimal punctum and canaliculus for the relief of epiphora
- A **dacryoadenectomy** is the surgical removal of a lacrimal gland.
- A **dacryocystectomy** is the surgical removal of a part of the lacrimal sac.
- A **dacryocystostomy** is an incision into the lacrimal sac, usually to promote drainage.
- A **dacryocystotomy** is an incision into the lacrimal sac.

Eye removal

- An **enucleation** is the removal of the eye leaving the eye muscles and remaining orbital contents intact.
- An **evisceration** is the removal of the eye's contents, leaving the scleral shell intact. Usually performed to reduce pain in a blind eye.
- An **exenteration** is the removal of the entire orbital contents, including the eye, extraocular muscles, fat, and connective tissues; usually for malignant orbital tumors.

Other surgery

Many of these described procedures are historical and are not recommended due to a risk of complications. Particularly, these include operations done on ciliary body in an attempt to control glaucoma, since highly safer surgeries for glaucoma, including lasers, non-penetrating surgery, guarded filtration surgery and seton valve implants have been invented.

- A **ciliarotomy** is a surgical division of the ciliary zone in the treatment of glaucoma.
- A **ciliectomy** is 1) the surgical removal of part of the ciliary body, or 2) the surgical removal of part of a margin of an eyelid containing the roots of the eyelashes.
- A **ciliotomy** is a surgical section of the ciliary nerves.
- A **conjunctivoanstrostomy** is an opening made form the inferior conjuctival cul-de-sac into the maxillary sinus for the treatment of epiphora.
- **Conjuctivoplasty** is plastic surgery of the conjunctiva.
- A **conjunctivorhinostomy** is a surgical correction of the total obstruction of a lacrimal canaliculus by which the conjuctiva is anastomosed with the nasal cavity to improve tear flow.
- A **corectomedialysis**, or **coretomedialysis**, is an excision of a small portion of the iris at its junction with the ciliary body to form an artificial pupil.
- A **corectomy**, or **coretomy**, is any surgical cutting operation on the iris at the pupil.
- A **corelysis** is a surgical detachment of adhesions of the iris to the capsule of the crystalline lens or cornea.
- A **coremorphosis** is the surgical formation of an artificial pupil.
- A **coreplasty**, or **coreoplasty**, is plastic surgery of the iris, usually for the formation of an artificial pupil.
- A **coreoplasy**, or **laser pupillomydriasis**, is any procedure that changes the size or shape of the pupil.
- A **cyclectomy** is an excision of portion of the ciliary body.
- A **cyclotomy**, or **cyclicotomy**, is a surgical incision of the ciliary body, usually for the relief of glaucoma.
- A **cycloanemization** is a surgical obliteration of the long ciliary arteries in the treatment of glaucoma.

- An **iridectomesodialsys** is the formation of an artificial pupil by detaching and excising a portion of the iris at its periphery.
- An **iridodialysis**, sometimes known as a **coredialysis**, is a localized separation or tearing away of the iris from its attachment to the ciliary body.
- An **iridencleisis**, or **corenclisis**, is a surgical procedure for glaucoma in which a portion of the iris is incised and incarcerated in a limbal incision. (Subdivided into **basal iridencleisis** and **total iridencleisis**.)
- An **iridesis** is a surgical procedure in which a portion of the iris is brought through and incarcerated in a corneal incision in order to reposition the pupil.
- An **iridocorneosclerectomy** is the surgical removal of a portion of the iris, the cornea, and the sclera.
- An **iridocyclectomy** is the surgical removal of the iris and the ciliary body.
- An **iridocystectomy** is the surgical removal of a portion of the iris to form an artificial pupil.
- An **iridosclerectomy** is the surgical removal of a portion of the sclera and a portion of the iris in the region of the limbus for the treatment of glaucoma.
- An **iridosclerotomy** is the surgical puncture of the sclera and the margin of the iris for the treatment of glaucoma.
- A **rhinommectomy** is the surgical removal of a portion of the internal canthus.
- A **trepanotrabeculectomy** is used in the treatment of chronic open and chronic closed angle glaucoma.

Chapter 16

Blood Irradiation Therapy and Laser Hair Removal

Blood irradiation therapy

Blood irradiation therapy is a procedure in which the blood is exposed to light (often laser light) for therapeutic reasons. Most research on blood irradiation therapy has been conducted in Russia and China and it is rarely used outside of those countries. Its effectiveness and utility as a treatment has been questioned. Blood irradiation therapy can be administered through a catheter in a vein, through the blood vessels inside the nose or applied externally through the skin. It is not related to the practice of gamma irradiation of blood in transfusion medicine.

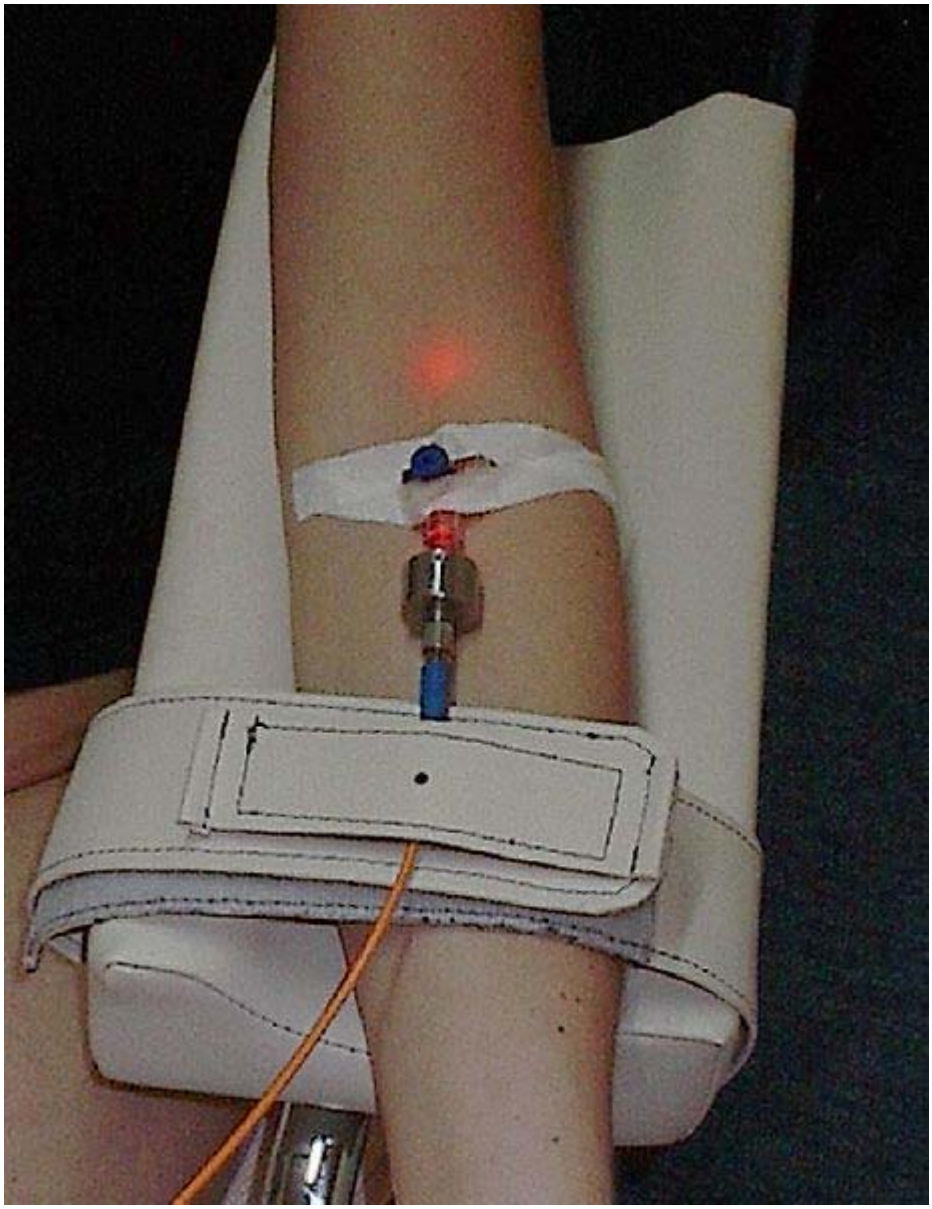
History

Intravenous laser blood irradiation was developed experimentally by the Russian researchers, Meshalkin and Sergievskiy, and introduced into clinical practice in 1981. Originally the method was applied in the treatment of cardiovascular abnormalities.

Laser blood irradiation therapy was government-certified in Germany in 2005. In the following two years, this method was established in more than 300 centers in Germany, Austria, Switzerland, Italy and Australia.

Types

Intravenous



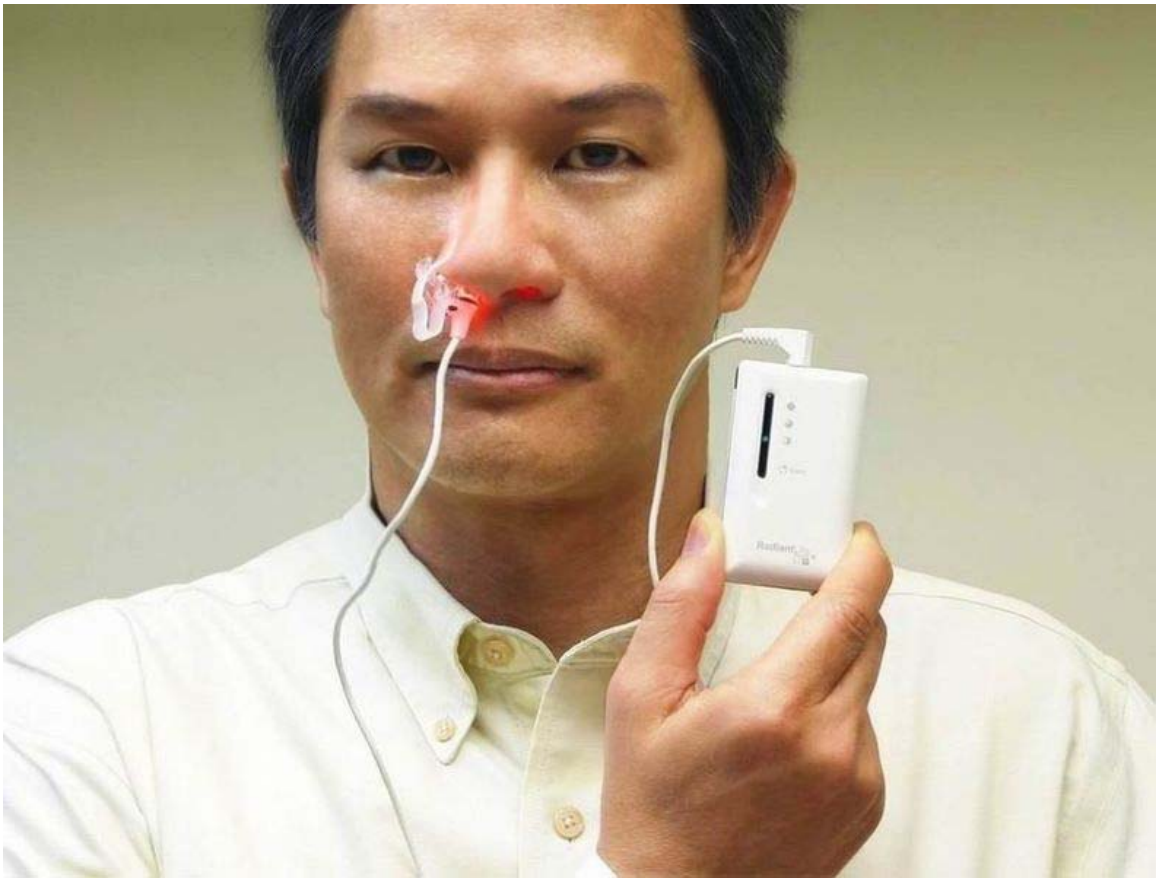
Intravenous blood irradiation

Intravenous or intravascular blood irradiation involves the *in-vivo* illumination of the blood by feeding low level laser light generated by a 1-3 mW helium–neon laser at a wavelength of 632.8 nm into a vascular channel, usually a vein in the forearm, under the assumption that any therapeutic effect will be circulated through the circulatory system. The feasibility of intravascular laser irradiation for therapy of cardiocirculatory diseases was first presented in the *American Heart Journal* in 1982. The technique was developed primarily in Asia (including Russia) and is not extensively used in other parts of the

world. It is claimed to improve blood flow and its transport activities, but has not been subject to randomized controlled trials and is subject to skepticism. While there have been some calls to increase research on this topic, others have called it "useless".

Ultraviolet blood irradiation may also be applied, though it involves drawing blood out through a vein and irradiating it outside of the body. Though promoted as a treatment for cancer, a 1952 review in the *Journal of the American Medical Association* and another review by the American Cancer Society in 1970 concluded the treatment was ineffective. Stephen Barrett, writing for Quackwatch, lists ultraviolet blood irradiation therapy as a questionable treatment.

Intranasal



Portable intranasal blood irradiation device

Intranasal blood irradiation (also commonly known as "intranasal light therapy") involves the non-invasive irradiation of the nasal cavity by inserting a small light diode (usually red color either of low intensity laser or normal red light) to illuminate the nasal cavity walls. The microvascular blood vessel network in the nasal cavity is receptive to external stimulation which is then circulated in the body's circulatory system.

Transcutaneous

Transcutaneous therapy applies laser light on unbroken skin in areas with large numbers of blood vessels (such as the forearm). Because of the skin acting as a barrier to the blood, the power of the laser is often boosted to compensate.

Laser hair removal

Epilation by laser was performed experimentally for about 20 years before it became commercially available in the mid 1970s. Intense Pulsed Light (IPL) epilators, though technically not a laser, use xenon flash lamps that emit full spectrum light. Laser and light-based methods, sometimes called *phototricholysis* or *photoepilation*, are now most commonly referred to collectively as "**laser hair removal**". One of the first published articles describing laser hair removal was authored by the group at Massachusetts General Hospital in 1998.

The efficacy of laser hair removal is now generally accepted in the dermatology community, and laser hair removal is widely practiced. Many reviews of laser hair removal methods, safety, and efficacy have been published in the dermatology literature.

Mechanism of action

The primary principle behind laser hair removal is *selective photothermolysis (SPTL)*. Lasers can cause localized damage by selectively heating dark target matter, (melanin), in the area that causes hair growth, (the follicle), while not heating the rest of the skin. Light is absorbed by dark objects, so laser energy can be absorbed by dark material in the skin (but with much more speed and intensity). This dark target matter, or *chromophore*, can be naturally-occurring or artificially introduced.

Hair removal lasers selectively target melanin:

- Melanin is considered the primary chromophore for all hair removal lasers currently on the market. Melanin occurs naturally in the skin (it gives skin and hair its color). There are two types of melanin in hair: *eumelanin* (which gives hair brown or black color) and *pheomelanin* (which gives hair blonde or red color). Because of the selective absorption of photons of laser light, only black or brown hair can be removed.

Laser works best with dark coarse hair. Light skin and dark hair are an ideal combination, but new lasers are now able to target dark black hair even in patients with dark skin.

Hair removal lasers have been in use since 1997 and has been approved for "permanent hair reduction" in the United States by the Food and Drug Administration (FDA). "Permanent" hair reduction is defined as the long-term, stable reduction in the number of hairs re-growing after a treatment regime. Indeed, many patients experience complete regrowth of hair on their treated areas in the years following their last treatment. Laser hair removal has become extremely popular because of its speed and efficacy, although some of the efficacy is dependent upon the skill and experience of the laser operator, and the choice and availability of different laser technology at the clinic which is performing the procedure. Some will need touch-up treatments, especially on large areas, after the initial set of 3-8 treatments. It has also been observed that some people seem to be non-responders – this is not confirmed and reasons are not known, and may in fact be due to lack of skill on the part of many laser operators and/or the type of machine and settings they are using.

Comparison with electrolysis

Electrolysis is another hair removal method that has been used for over 135 years. At this time, it is the only permanent option for very fine and light-colored hair. The FDA currently allows the term "Permanent Hair Removal" for electrolysis only. Unlike laser epilation, electrolysis is effective on all hair colors.

A study conducted in 2000 at the ASVAK Laser Center in Ankara, Turkey comparing alexandrite laser and electrolysis for hair removal on 12 patients concluded that laser hair removal was 60 times faster, less painful and more reliable than electrolysis.

Electrolysis

Laser parameters that affect results

Several wavelengths of laser energy have been used for hair removal, from visible light to near-infrared radiation. These lasers are usually defined by the lasing medium used to create the wavelength (measured in nanometers (nm)):

Argon: 488 nm (DeepSkyBlue) or 514.5 nm (Cyan) (no longer used for hair removal)

Ruby laser: 694.3 nm (OrangeRed) (no longer used for hair removal; only safe for patients with very pale skin)

Alexandrite: 755 nm (Red) (most effective on pale skin and not safe on darker skin at effective settings)

Pulsed diode array: 810 nm (Near-Infrared) (for pale to medium type skin)

Nd:YAG laser: 1064 nm (Near-Infrared) (made for treating darker skin types, though effective on all skin types)

Pulse width is an important consideration. Longer pulse widths may be safer for darker skin, but shorter pulsewidths are more effective in disabling hair follicles. Repetition rate is believed to have a cumulative effect, based on the concept of thermal relaxation time. Shooting two or three pulses at the same target with a specific delay between pulses can cause a slight improvement in the heating of an area. This may increase the "kill rate" for each treatment.

Spot size, or the width of the laser beam, affects treatment. Theoretically, the width of the ideal beam is about four times as wide as the target is deep. Hair removal lasers have a spot size about the size of a fingertip (8-18mm). Larger spot sizes help laser light penetrate deeper and make treatments faster and more effective.

Fluence or energy level is another important consideration. Fluence is measured in joules per square centimeter (J/cm^2). It's important to get treated at high enough settings to heat up the follicles enough to disable them from producing hair.

Epidermal cooling has been determined to allow higher fluences and reduce pain and side effects, especially in darker skin. Three types of cooling have been developed:

- Contact cooling: through a window cooled by circulating water or other internal coolant
- Cryogen spray: Sprayed directly onto the skin immediately before and/or after the laser pulse
- Air cooling: forced cold air at -34 degrees C (Zimmer Cryo 5 unit)

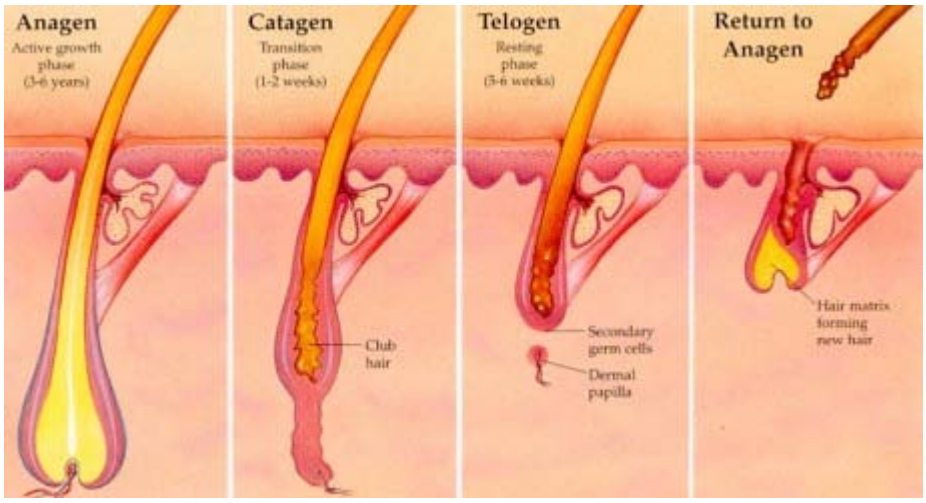
Number of sessions

Multiple treatments (typically 6-8 spaced 8-12 weeks apart) depending on the type of hair and skin color have been shown to provide long-term reduction of hair. Current

parameters suggest a series of treatments spaced at 8-12 weeks apart based on typical hair cycle patterns for each area.

The number of sessions depends on various parameters, including the area of the body treated, skin color, coarseness of hair, reason for hirsutism, and sex. Coarse dark hair on light skin is easiest to treat. Hair on darker skin is harder to treat. Finer hair is only sometimes affected. Certain areas (notably men's faces) may require considerably more treatments to achieve desired results. In addition, since hair grows in several phases (anagen, telogen, catagen) and laser can only affect the currently active growing follicles (anagen), several sessions are needed to kill hair in all phases of growth.

Laser does not work well on light-colored hair and most fine and vellus hair ("peachfuzz") of any color.



Hair-growth-cycles

Intervals between sessions

Usually treatments are spaced 8–12 weeks apart depending on the body area and the hair cycle length for that area. For example, faces usually require more frequent treatments about 3-4 weeks apart, whereas legs require less frequent treatments.

Instead of following an arbitrary schedule, one should wait until they have experienced shedding of the treated hairs, which should complete within 2-3 weeks, and see enough hair come in after the hair-free period to have another treatment. It's advisable to do a touchup if significant amount of hair hasn't shed within 3 weeks.

Other uses

Hair removal lasers are effective treatment for pseudofolliculitis barbae (commonly called ingrown hairs or "shaving bumps"). For darker skin patients with black hair, the

long-pulsed Nd:YAG laser with a cooling tip can be safe and effective when used by an experienced practitioner.

They have recently been reported as helpful treatment for pilonidal cysts, since they eliminate the ingrown hairs that produce the troublesome foreign body reactions in this congenital malady.

Side effects and risks

Some normal side effects may occur after laser hair removal treatments, including itching, redness, and swelling around the treatment area. These side effects should not last more than three days. Some level of pain should also be expected during treatments. Numbing creams are available at most clinics, usually for an additional cost. Icing the area after the treatment helps relieve the side effects faster.

Unwanted side effects such as hypo- or hyper-pigmentation or, in extreme cases, burning of the skin call for an adjustment in laser settings. Risks include the chance of burning the skin or discoloration of the skin, hypopigmentation (white spots), flare of acne, swelling around the follicle, scab forming, purpura, and infection. These risks can be avoided when being treated with an appropriate laser type and at appropriate settings for the individual's skin type.

Some patients may show side effects from an allergy to either the hair removal gel used with certain laser types or to a numbing cream. A physician should be consulted if an allergic reaction presents itself after the treatment.