Medical and chemical technology spinoffs of directed-energy research

by Wolfgang Lillge, M.D. and John Grauerholz, M.D.

Research into lasers and other directed-energy technologies has placed us on the verge of fundamental breakthroughs in biology and chemistry, which will dramatically transform medicine and industrial chemistry. Technologies presently available and soon to come on line are but the tip of the iceberg of the most profound change since the introduction of the heat-powered engine which drove the industrial revolution. Already the use of lasers has profoundly altered medical practice in many specialty areas, primarily as a surgical tool.

Some of the most promising areas now being explored in laser technology involve rapid, highly specific, and sensitive diagnostic techniques, which minimize time and in some cases potential risks to the patient.

One device now passing from the purely research phase into medical application is the flow cytometer. In this machine, cells or individual molecules are suspended in liquid and pass through a flow chamber at rates up to 20,000 cells a second. The cells are illuminated by lasers of different frequencies as they pass through the chamber and the absorption or scattering of the laser light, or the fluorescence of molecules excited by the lasers is measured.

Los Alamos National Laboratory recently announced the development of an instrument called an angular scanning CIDS spectrometer. CIDS stands for circular intensity differential scattering; the device measures the scattering of left and right polarized laser light by viruses and bacteria. This instrument can identify viruses in a few minutes, instead of the 2-14 days currently required, and in combination with the flow cytometer can identify bacteria in less than an hour.

The potential of this technology can be grasped from the fact that clinical microbiology laboratories in the United States generate $30 million a week in the process of isolating and identifying micro-organisms—viruses, bacteria, fungi, and protozoa—from patients suspected of, or known to be, suffering from an infectious disease. Because of the time required by current techniques, the results are generally not available until after treatment has already begun, or treatment may be delayed, with sometimes serious consequences, until the diagnosis can be established. With this technology, a precise diagnosis can be rapidly established, thus avoiding delay or possible mistreatment.

Another application of the flow cytometer is the detection and isolation of cancerous and pre-cancerous cells. Alterations in cells can be identified rapidly and with a high degree of specificity, utilizing a technique called laser immunofluorescence which detects antibodies bound to cell surface antigens. Antigens are generally protein molecules, sometimes combined with sugars, which form part of the membranes of cells. These antigens stimulate the immune system to produce proteins, called antibodies, which bind to them. A number of present diagnostic tests involve using antibodies labeled with radioactive isotopes or enzymes to bind to the surface antigens, and then assaying for binding by measuring radioactivity or enzyme activity. These tests require multiple steps and the use of expensive radio-isotopes. The flow cytometer uses a photometer to measure the intrinsic fluorescence of antigen-antibody complexes with a sensitivity two orders of magnitude greater than the isotope technique, known as radioimmunoassay, and requires only one step prior to running the specimen through the cytometer.

Another use of the flow cytometer, with longer-range implications, is a project of Los Alamos National Laboratory and Lawrence Livermore Laboratory to stockpile a complete library of the human genetic code. The library would be a repository of complete genes and fragments of genes, the pieces of the genetic code that determine the characteristics of an organism. These fragments are separated in the flow cytometer and can then be inserted into bacteria by genetic engineering to produce quantities of the gene product. This library is three-quarters complete and will be finished in another six months.

The flow cytometer can isolate individual cells in a miniscule, electrically charged drop of water, and separate them from other cells electrically. Currently Los Alamos scientists are working on the detection of single molecules by their fluorescence pattern after laser excitation, and subsequent isolation of these individual molecules in 1 picoliter (.000000000001 liter) of liquid.

Another development which promises to have a major impact on one of America's foremost health problems is a product of research on high-energy particle accelerators. This is the use of high flux, monochromatic x-rays, produced by a machine called a synchrotron, for visualizing the arteries of the heart. Presently this is done by cutting down on an artery and threading a catheter into the heart and then injecting dye into the coronary arteries. There are a number of complications associated with coronary angiography—as this technique is known—including possible heart attack and sudden death. By using the synchrotron x-rays and image enhancement techniques, the same information can be obtained with only a small injection in an arm vein. This would make angiography feasible as a screening technique for asymptomatic patients who are at risk of coronary disease by family history or other factors. The first human studies of this technique are scheduled late this year at Stanford.

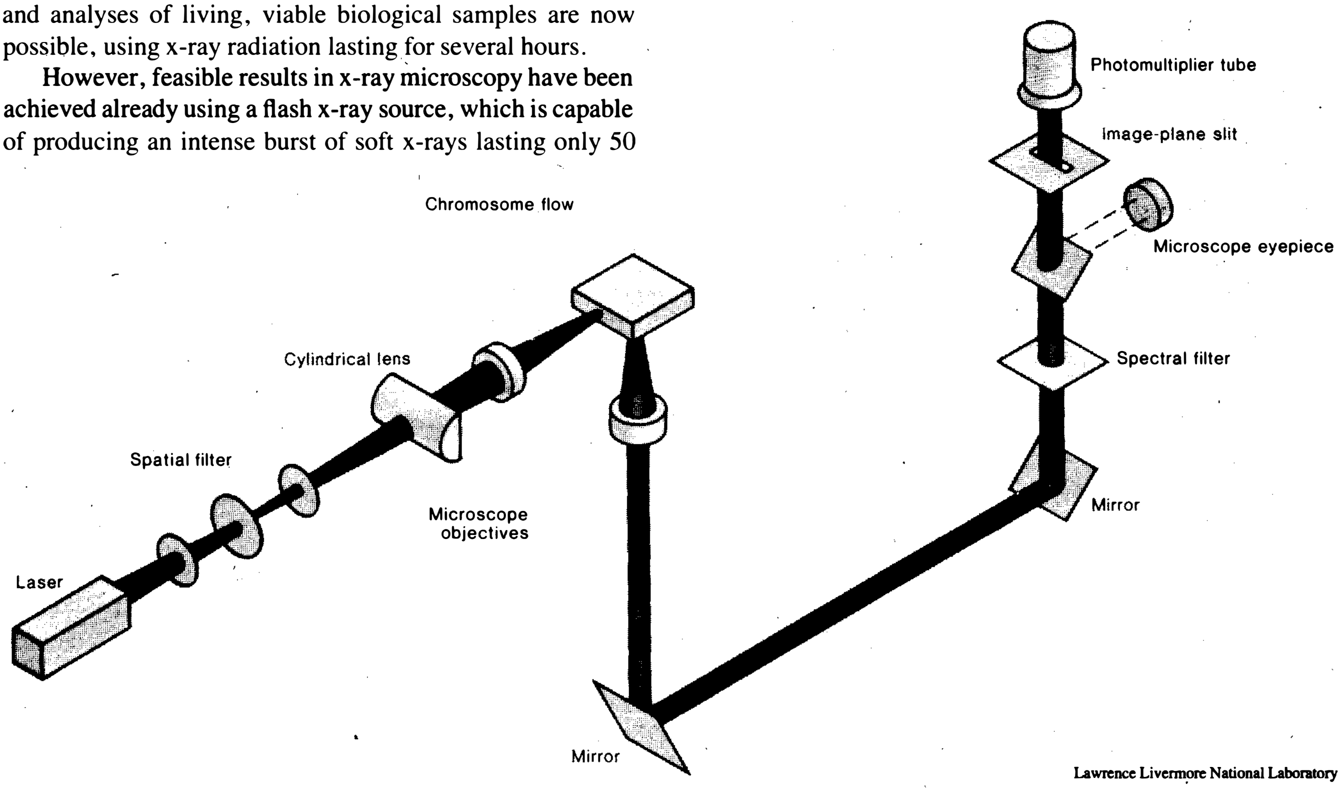
X-ray microscopy and holography

In recent years significant progress has been made in imaging of hydrated organic specimens with x-rays, and it might not take long to produce three-dimensional x-ray holograms of fresh living matter with a resolution and contrast not known before. This would overcome the essential disadvantage of today's electron microscopy, which images only dead matter. Important work on x-ray imaging was done at the State University of New York at Stony Brook, Brookhaven National Laboratory, the Los Alamos National Laboratory, as well as other research facilities in the United States and West Germany. Because soft x-rays are not significantly altered by the presence of air and water, dynamic experiments and analyses of living, viable biological samples are now possible, using x-ray radiation lasting for several hours.

However, feasible results in x-ray microscopy have been achieved already using a flash x-ray source, which is capable of producing an intense burst of soft x-rays lasting only 50 nanoseconds. Further progress in terms of resolution and contrast is expected when it is possible to tune the x-ray source to specific absorption edges of a particular biological element, generating images of cell structures containing a concentration of such elements.

Even more promising results could be obtained in studying cellstructures with x-ray laser holography which produces three-dimensional images of samples. Experiments done at Livermore and Brookhaven show that this technology is within reach. In summer and fall of this year, a new series of holographic experiments will be conducted, and the scientists involved hope to reach down to a wavelength of 300 Angstrom units, which results in a resolution roughly corresponding to the size of a cell. To achieve greater magnification, it is necessary to develop coherent x-ray laser sources with smaller wavelengths, which seems to be only a question of time. It is an exciting idea to imagine that you can actually see in real time three-dimensional processes as they occur in the microscopic and sub-microscopic realm. This will open up research areas in biology and medicine which were not hitherto accessible, especially concerning structures and changes of structures accompanying living processes, with nanometer space resolution and picosecond time resolution.

A hologram is created when a reference x-ray laser beam is correlated to a beam penetrating the specimen, where this



Lawrence Livermore National Laboratory

In the slit-scan flow cytometer, cells or molecules are suspended in liquid, then illuminated by lasers, making possible the detailed study of the genetic code and much more precise and speedy diagnosis of disease than previous methods allowed. This simplified diagram shows how chromosomes stained with a fluorescent dye flow through a narrow tube past an intense blue laser light, which excites fluorescence from the illuminated region of each chromosome. This is focused by a microscope and separated by a spectral filter.

latter beam is scattered and absorbed by the molecules. A "wave front reconstruction" is accomplished either by coherent illumination of the hologram or by an equivalent computer analysis.

A 'new window' into the human body

Nuclear Magnetic Resonance (NMR) imaging is the one technology in medical diagnostics which very well might prove to be also an efficient means in therapy, especially for treatment of cancer. NMR as a diagnostic tool for non x-ray imaging of anatomic structures of the body has become more and more widespread among medical institutions worldwide. In NMR scanning, a strong magnetic field is imposed on the organism, aligning the spins of the hydrogen protons in water and other substances, which allows the observation of absorption and emission characteristics of these protons, when a second field in the radio frequency range is imposed. A computer can reassemble all these data to a precise image of the tissue in question.

It was learned that a tumor absorbs and emits energy at frequencies slightly different from normal tissue. It is possible—and Dr. James Frazer at the Texas Medical Center is working on this—to visualize tumor tissue on a screen and then increase the amount of energy being radiated into the tumor. The effect is that the tumor tissue is selectively heated up, killing the tumor cells without affecting the healthy tissue. In this way, the NMR machine can be used both as a diagnostic and therapeutic means.

If this kind of hyperthermia treatment of cancer is accompanied with chemotherapy and/or radiation, the effect is even more dramatic.

A limiting factor of NMR technology so far is interpreting the massive amount of data received. It might be possible now to use NASA computer technology from the Landsat image-processing used to compose satellite photos of the surface of the earth. When NMR scans were experimentally fed into the Landsat computer last year, they were analysed just as if they were earthly landscapes and multispectral NMR images were reduced into a single, realistic color composite. This project is a collaborative effort by physicians and engineers from NASA's Kennedy Space Center, the University of Florida, and the Washington University Medical Center in St. Louis.

The computer-generated colors will make the image look as real as possible and enhance the information that was recorded in the NMR process. One of the researchers involved in this project commented, "Satellite imaging has opened a new window into the human body for physicians."

The use of lasers in surgery is now widespread and provides the only therapy for some conditions. Diabetic retinopathy, for example, was untreatable 10 years ago, but now lasers seal the hemorrhaging blood vessels that once led inevitably to blindness. Most medical lasers generate heat in the tissues on which they are used and this heat is used to destroy the tissue-in the case of tumors—or to coagulate or "weld" the tissue, as in the treatment of retinal detachment in the eye.

The problem with this heating effect in blood vessels is that it increases the tendency for blood to clot at the treated site, which is precisely what one wishes to avoid in coronary arteries. The other problem is perforation of the delicate arteries by the laser energy. Now a significant development is unfolding in the area of laser surgery of coronary artery disease, one of the leading causes of death and disability in the United States. A new laser, known as an excimer or excited dimer laser, eliminates the problems which make current medical lasers unsuitable for treatment of coronary artery disease.

The excimer laser produces short, intense bursts of ultraviolet light which shatter the molecules of the atherosclerotic plaque, without heating the surrounding tissue. The bursts of light create shock waves which break the chemical bonds of the plaque molecules and vaporize the plaque into carbon dioxide, hydrogen, and other fragments. Each burst cuts away microns (1/1,000 of a millimeter) of tissue with great precision, thus reducing the possibility of perforation. The pulses are extremely short, lasting from 10 billionths of a second to 100 billionths of a second.

The laser is incorporated into a 1.5 millimeter diameter catheter, containing three bendable glass fibers, known as fiberoptic elements. One fiberoptic element carries the laser energy; another shines a light on the catheter tip; the third provides a view of the area in front of the catheter.

The estimated cost of the perfected laser-fiberoptic device is $100,000, and a patient could have his coronary arteries cleaned out in a few minutes and might not even have to stay overnight in the hospital. When one considers that 170,000 patients underwent coronary artery bypass surgery in 1982, at an average cost per person of $20,000, the potential savings are enormous. More importantly, a great many patients who could not tolerate surgery because of the severity of their disease could be treated by this method.

Coronary artery disease most often strikes middle-aged men in the prime of their productive lives. Screening by synchrotron angiography and treatment by fiberoptic lasers could result in the prolongation of millions of productive lives at relatively low cost, and the virtual elimination of one of the major killer diseases of our time. The laser used in the initial experiments was designed for remote atmospheric sensing by NASA.

On a more prosaic level, reports from a French group indicate that a CO_2 laser beam could be the most effective method of treating tooth decay. Laser treatment of dental caries produces a chemical and physical barrier to acidic decay and the formation of a tough pulp scar.

Laser chemistry

Since the development of laser technology in the 1950s, attempts have been made to use lasers in chemical applications. However, so far only in a few areas of chemistry are lasers actually applied on a broader scale. The main argument against them is that investment in laser-produced photons is not economical; traditional methods, although much less efficient, are considered to be superior. This may have been true until some years ago, but now efficient lasers of all different wavelengths and intensities are available, so that a reconsideration of potential applications of lasers in the chemical and pharmaceutical industry is overdue.

One of the most obvious applications of laser-generated photons is the production of Vitamin D, which the human body itself synthesizes in the skin by means of the ultraviolet spectrum of sunlight. The method to apply laser light in this process was developed already in 1982 at the National Research Council in Ottawa, Canada, but has not been used. "It is commercially not feasible," commented Dr. Peter Hackett, the chief researcher at the NRC in a telephone interview.

Actually, laser application in Vitamin D production could serve as a paradigm for other areas. It works as follows: A laser beam of a specific frequency will selectively excite only one of the reacting molecules, and a second laser at a different frequency inhibits the creation of an intermediate product, which would impurify the substrate. Laser application leads here to a yield of up to 80% of the end product, instead of a yield of only 35% with the traditional arc lamp as a light source. A similar process could be applied to produce the hormone prostaglandine, which is important in many metabolic processes in the human body.

A broad area of potential laser application is also the production of antibiotics, most of which are still produced now by rather expensive, inefficient means.

In fact, the only broader scale use of lasers is in the field of isotope separation, especially used for the separation of uranium atoms. One of the processes in use exploits the fact that U_{235} absorbs energy of laser light at a different wave length than U_{238}, so that by means of an ion extractor based on electromagnetic fields, you can separate the two ions. Two other processes with significantly higher efficiency than the old, energy-intensive method are known; however, all industrial-scale application capabilities are now under strict classification for military reasons.

The purification of chemical products with lasers proves to be a very efficient method, utilizing the different absorption pattern of the impurifying substances in materials, which should have a high grade of purity.

Basic research must be directed specifically to study the effects of tuned lasers upon molecules and molecule combinations, to be able to apply photons in a way that controlled changes in these molecules occur. So far these processes are poorly understood, as tuned energy applied to specific chemical bonds for instance, is redistributed too quickly over the whole molecule, before it can effect the wanted result. Some knowledge of these effects, a kind of fluorescence generated by specific resonance frequencies in atoms, is so far only used to study the reaction of certain chemical processes at the laboratory level.