foreseeable free electron lasers are likely to be too bulky to be practical in most remote sensing work, many of the new tunable solid-state sources may be useful for these applications.

Defense applications and inertial confinement fusion. Most current R & D on free electron lasers and excimer sources is funded for defense and inertial confinement fusion. Laser sources used in directed energy weapons must be capable of delivering extremely large amounts of energy to a distant target and must be of realizable size and reasonable cost. A variety of operating wavelengths have been considered. Current emphasis is on highly efficient deuterium fluoride sources operating in the 3.8- to 4.2-μm band, but near-ultraviolet wavelengths may be more desirable. Rare gas halide excimer lasers, particularly XeF, are being considered (*22*), and issues relevant to high-energy scale-up are being explored with federal support. Although free electron lasers are as yet experimentally unproved, their potential for high-efficiency, high-power operation has stimulated substantial R & D investment by the Department of Defense.

Inertial confinement fusion also requires high-power, efficient lasers, and short laser wavelengths are preferred. The greatest success has been achieved by using very high energy Nd : glass sources followed by harmonic conversion systems to produce high-power pulses in the green or ultraviolet. Free electron lasers may be useful for fusion, but excimer lasers are a more realistic near-term option (*15*). A large excimer device that will be capable of output energies of tens of kilojoules is being built at Los Alamos National Laboratory as a step toward exploring the utility of excimer systems for initiating fusion reactions.

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Fiber-Optic Sensors for Biomedical Applications

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The development of glass or plastic fibers a fraction of a millimeter in diameter for in vivo measurements is a relatively new and potentially important endeavor. Fiber-optic sensors can be as small as electrosensors and offer several advantages. A fiber-optic device is safe, involving no electrical connection to the body; the optical leads, very small and flexible, can be included in catheters for multiple sensing; and materials suitable for long-term implantation, such as plastic, can be used. At least some of the sensors are sufficiently simple in their design to be disposable. In the case of chemical sensors there are particular advantages in long-term stability and simplification of calibration because the measurement is equilibrium-based rather than rate- or diffusion-dependent and because the specificity of the measurement is achieved by chemical instead of physical means. Reversible, specific colorimetric and fluorometric reactions are available for most chemical and biochemical constituents of interest. Electrode development, although of intense interest for many years, has not lived up to expectations for wide applicability and reliability in vivo. Fiber-optic sensors are still too new to be of proven value in most applications, but their potential is considerable.

The concept is simple. Light from a suitable source travels along an optically conducting fiber to its end, where reflection or scattering of the light returns it along the same or another fiber to a light-measuring instrument, which interprets the returned light signal. The light emanating from the sensing end of the fiber may be reflected by a tiny transducer that varies the reflectance with some parameter of interest, the light may be backscattered by the medium into which the fiber is inserted, or the returned light may arise from luminescence of something at the end of the fiber that was energized by the illuminating light. The reflected or backscattered light may be spectrally altered by passage through an indicator reagent, providing a miniaturized spectrophotometric analysis. Likewise, fluorometry or other measurement uses of luminescence may occur at the fiber end. Fiber-optic sensing allows existing optical measurement techniques to be highly miniaturized and localized. A high degree of stability can be achieved by use of the ratio method, where part of the conducted light is not affected by the measurement variable, and so can be used to correct for other optical variations.

The instrumentation associated with fiber-optic sensors is optical as well as electronic, but the optics are simple and require only standard components such as light sources, detectors, filters, and lenses. Fiber-optic connectors are a well-developed commercial item. Light intensity measurements can be processed for direct readout by standard analog and digital circuitry or a microprocessor. Because of the relative simplicity of the instrumentation, the progress of this approach is limited only by sensor development.

Three general types of in vivo fiber-optic sensing have been developed: the photometric, or bare-ended fiber; the physical sensors, in which a transducer

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at a fiber end modifies a light signal in accord with a physical parameter; and the chemical probes, in which an appropriate reversible reagent fixed at the end of a fiber provides spectrophotometric or fluorometric analysis.

Optical Sensors (Photometry)

The oldest and most direct use of light-carrying fibers is in reflectometry, spectrophotometry, and fluorometry without a transducer of any sort at the end of the fiber. Fiber-optic sensing has been used in conjunction with oximetry (spectrophotometric analysis of the oxyhemoglobin content of blood); dyes in blood and tissue to measure flow, cardiac output, and perfusion; the natural fluorescence of reduced nicotinamide adenine dinucleotide (NADH) in tissue and fluorometric reagents; and the laser-Doppler method of measuring blood velocity.

Summary. In this article the development of fiber-optic sensors for biomedical applications is reviewed. Light-carrying fibers are potentially useful in oximetry, dye dilution measurements, laser-Doppler velocimetry, and fluorometry; as physical sensors of temperature, pressure, and radiation; and as chemical sensors of *p*H, partial pressure of blood gases, and glucose. Emphasis is placed on the principles and ideas used in the various devices rather than on detailed descriptions or critical discussions.

Oximetry. Oxygen saturation refers to the amount of oxygen carried by the hemoglobin in red blood cells relative to the maximum carrying capacity. Typical arterial blood is 95 percent saturated and venous blood may be 75 percent saturated. Measurements of saturation and oxygen consumption have been used to determine cardiac output. The presence of unusually high oxygen saturation in blood samples taken from the right heart may indicate congenital abnormalities of the cardiovascular anatomy. Measurement of mixed venous saturation indicates the effectiveness of the cardiopulmonary system; low saturation may indicate reduced ability of the cardiopulmonary system to deliver oxygen from the lungs, compromised cardiac output, or reduced oxygen carrying capacity of the blood.

Optical measurement of oxygen saturation depends on the difference in the absorption spectra of oxyhemoglobin and hemoglobin. The absorption coefficients are sufficiently low at wavelengths above 620 nm that sufficient light transmission through whole blood can occur over distances that are compatible with the geometric requirements of practical fiber-optic catheters. The isosbestic wavelength of 805 nm is used to compensate for the scattering properties of whole blood and to normalize the signal measured at wavelengths near 650 nm, where there is a useful difference in absorbance between hemoglobin and oxyhemoglobin.

Polanyi and Hehir (*1*) described a fiber-optic instrument for measuring local saturation and cardiac output with an injected dye, and others soon developed versions of the instrument (*2*). The first instrument required a high-power lamp, rotating filter, and red-sensitive photomultiplier tube. The expense and a lack of enthusiasm by the medical community limited demand for the device. The advent of solid-state light-emitting diodes and detectors, which work best in the red and near infrared, as well as light-conducting fibers of rugged plastic, stimulated others to continue the development of saturation instruments based on fiber-optic catheters (*3*). A good discussion of the basic research in fiber-optic oximetry to 1974 has been presented by Johnson (*4*) and Landsman (*5*). The commercial success of these instruments has been limited, but appreciation of the value of the measurement for monitoring the critically ill has grown. Continuous on-line measurements of saturation have been valuable for monitoring patients in respiratory failure who are being treated by removal of extracorporeal CO_2 (*6*). Other critically ill patients may be similarly monitored.

Dye dilution measurement of flow. While optical fibers were first being used in reflectance measurement of blood oxygenation, the same dual-wavelength optics were being used to observe the concentration of injected dye in the blood (*7–9*). Indocyanine green is commonly used. It absorbs light strongly at 805 nm, the isosbestic wavelength of the oxyhemoglobin absorption spectrum. Light of this wavelength is emitted from one fiber, scattered by the blood cells, and partially collected by the other fiber for measurement. The light is attenuated in proportion to dye concentration, but it is not affected by variations in oxyhemoglobin concentration. The transmission of light with wavelengths longer than 900 nm, which is not absorbed by the dye, is compared to compensate for the effect of flow rate on light scattering, giving the equivalent of a dual-beam ratio measurement in spectrophotometry. Instrumentation is usually designed to make the measurements at 660, 805, and above 900 nm, so that both oxyhemoglobin and dye concentration can be measured simultaneously by proper interpretation of the light signals. The time variation of dye concentration can then be used to calculate cardiac output by the usual dilution technique.

Laser-Doppler velocimetry. Measurement of the velocity of flowing blood in vessels by the fiber-optic adaptation of the laser-Doppler method allows a higher degree of spatial and temporal resolution than other methods of flow measurement. The high coherence of laser light allows accurate measurement of small shifts in frequency, by the Doppler effect, of the light scattered from moving particles. The frequency shifts can be correlated with velocity, and this method has been used for noninvasive estimation of blood flow in cases where light could be transmitted through a vessel wall. Coupling optical fibers with the laser instrumentation allows the insertion of a fiber probe directly into blood vessels for observation of intraluminal velocity. Tanaka and Benedek (*10*) did this with a relatively large (diameter, 0.5 mm) single-fiber catheter in a rabbit. Recently, other researchers have described improved versions of such instrumentation along with experimental applications (*11, 12*). They used smaller fibers and demonstrated that velocity profiles could be observed with resolutions of 0.1 mm or less in position and 8 msec or shorter in time variation of velocity. A semi-invasive adaptation for measuring blood flow in muscle has been developed in which a disk sensor is placed on a muscle surface exposed by biopsy (*13*). The surface of the disk exposes the ends of two closely spaced optical fibers to the tissue. Further development of laser-Doppler velocimetry has progressed in the direction of noninvasive measurements, in which fiber optics on the surface of tissue permit high-resolution recording of microcirculatory flow (*14*).

Fluorometry. A potentially useful application of direct fiber photometry is in the observation of tissue and blood luminescence. The fluorescence of NADH in vivo has been used for many years to study the biochemistry and physiology of tissue oxidation-reduction reactions. The development of a fluorometer with a fiber-optic light guide to connect the instrument to the tissue has allowed examination of microscopic areas in many different tissue locations (*15*). Mayevsky and Chance (*16*) reviewed advances in

this field. Goldstein *et al.* (*17*) developed fiber-optic microfluorometry instrumentation and used it to measure fluorescent marker molecules in tumors and other local regions in vivo. A multiple sensor system was implanted in a mobile laboratory rat to investigate the kinetics and transport properties of tissue circulation. Single-fiber microfluoroprobes for the measurement of adriamycin in laboratory animals were used by Sepaniak *et al.* (*18*). The high peak power of a pulsed laser has made it possible to take advantage of nonlinear fluorescence excitation techniques—which provide blue-shifted emission—to decrease susceptibility to background fluorescence. A specialized application of fiber-optic microanalysis was developed for studying calcium transients in the cerebral cortex of cats (*19*). The probe combines a channel for introducing aequorin solution into the extracellular space along with an optical fiber. Introduction of the aequorin produces a light signal proportional to the calcium activity.

Physical Sensors

Physical sensors are based on the attachment of a microtransducer at the end of the optical conductor. Temperature and pressure measurement have been the fields of long-term interest.

Temperature. The development of implantable temperature sensors has been actively pursued because of the careful control of tissue heating required in the hyperthermal treatment of cancer. The sensor and its leads must not interact with the microwave field and small size is important, so an optical sensor is ideal. Various nonoptical sensors have been devised, but the fiber-optic types are likely to become most prevalent. This application requires measurement accuracy of ± 0.1°C over a range of a few degrees at multiple locations simultaneously. Cetas has discussed earlier (*20*) and more recent (*21*) developments.

One of the oldest and simplest types of temperature sensors consists of a layer of liquid crystals at the end of optical fibers, giving a variation in light scattering with temperature at a particular wavelength. A problem with "fatigue" of the liquid crystals in temperature cycling, resulting in drift of the signal (*22*), may have been solved by a system in which the change with temperature in the peak wavelength of light reflected by the liquid crystals is observed (*23, 24*). An interesting application of liquid crystal thermometry was in a catheter for blood flow measurement by the thermodilution technique (*25*).

Deficis and Priou (*26*) proposed a sensor based on the distension of a meniscus by liquid dilation with temperature; the reflection of light varies with the meniscus. The same authors have also discussed a liquid crystal sensor (*27*). An etalon sensor was developed by Christensen (*28*). A miniature optical resonator is located at the end of optical fibers, and the wavelength of light in tune with the etalon shifts as its thickness varies thermally. The device appears to be insufficiently sensitive for its purpose.

Three types of sensors are being commercially developed, with two available now. In the Christensen sensor (Clini-Therm) (*29*), the thermal wavelength shift in the near infrared of the absorption edge of a GaAs semiconductor is a sensitive effect. The Cetas sensor (*30*) is based on the thermal variation of birefringence of $LiTaO_3$. The crystal, sandwiched between a polarizer and a dielectric reflecting surface on the crystal, in effect produces a temperature-sensitive mirror with variable reflectivity. Another sensor that has been developed is based on the luminescence of a phosphor, of which the ratio of two emission lines varies with temperature. It is available from Luxtron. Two other methods involving luminescence were presented by Samulski and colleagues. In one, temperature quenching of the luminescence of certain phosphors is used (*31*); in the other the thermal quenching is observed as a variation of luminescence lifetime. Two relaxation modes with different lifetimes and different temperature dependencies occur, so that modulation of the excitation light produces an emission with alternating- and direct-current components, the ratio of which is temperature-dependent (*32*).

Pressure. Fiber-optic transducers have been developed for monitoring intracranial and intracardiac pressure. A probe for intracranial use is commercially available (Ladd Research) (*33–36*). Intracranial hypertension resulting from injury or other causes can be monitored to assess the need for therapy and its efficacy. The probe can be located epidurally or at the anterior fontanel of an infant. The device is based on a pressure-balancing system. A cantilevered mirror is attached to a membrane located on the side of the probe; deflection of the membrane causes light emitted from a central optical fiber to be reflected differentially toward either of two light-collecting fibers on each side of the central fiber. The ratio of the light collected by the two afferent fibers is sensed by the instrument, which applies a feedback air pressure to the interior of the probe through a pneumatic connecting tube containing the optical fibers, balancing the membrane at its null position and providing a readout of the balancing pressure.

Various proposals have been made for varying a light signal with pressure in a fiber-optic sensor for intravascular use (*37, 38*). In addition, Morikawa (*39*) and Matsumoto *et al.* (*40*) have developed catheter tip sensors. All these devices can be categorized as mechanical and are based on mirrors moved by reflective membranes that distort and vary the distribution of light on sensing fibers or by a membrane that moves a slit to give variable light transmission (*41*). In 1962 Valliere (*42*) invented a catheter pressure transducer based on the enclosure of a material exhibiting pressure-variable birefringence between a reflector and a polarizer to produce a pressure-variable reflectance, in the same manner as the Cetas temperature sensor (*30*). Recently Kobayashi *et al.* (*43*) again reported the use of polarization. A "photoelastic" element is attached to the end of a single polarization fiber illuminated by linearly polarized laser light. The polarization is changed by stress on the element, and the light of altered polarization is reflected back through the fiber to a polarization analyzer calibrated for pressure. This offers the advantages of much simpler construction and smaller size. The null balance approach, used to measure static pressure with the intracranial probe, is not used for intravascular and intracardiac catheter sensors because it is desirable for them to have, in addition to small size, a good frequency response in order to follow the pressure wave forms faithfully.

Radiation. To our knowledge, only one radiation-sensing device for biomedical use has been devised (*44*). It consists simply of a NaI(Tl) crystal, surrounded by a MgO light-scattering packing, in an aluminum shell at the end of a fiber-optic bundle leading to a photomultiplier tube. The design is exploratory only.

Chemical Sensors

Chemical sensors are the most recent type of fiber-optic sensor to appear, and were originated because of the generally disappointing performance of electrodes. The basic design is shown in Fig. 1. The essential requirements are a reversible indicator system (colorimetric or fluorometric) fixed inside an appropriately permeable container at the fiber-optic end. This arrangement is attractive because so much indicator reagent chemistry is available for adaptation.

Sensor to measure p*H.* Peterson *et al.*

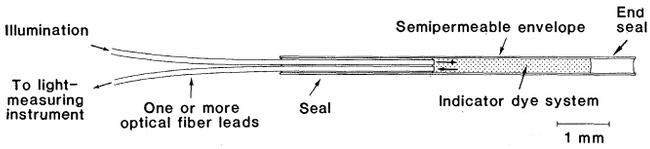

Fig. 1. Concept of the chemical fiber-optic probe.

(*45*) originated the concept of a fiber-optic chemical sensor in 1976 with their development of a *p*H sensor in an effort to make in vivo sensors for blood gases. The *p*H sensor is based on old-fashioned dye indicator chemistry, with a miniature spectrophotometric cell at the end of a fiber pair. The dye indicator (phenol red) is reversible and has two tautomeric forms, each with a different light absorption spectrum. The dye is a weakly ionizing acid, and the relative proportions of the base form (green-absorbing) and the acid form (blue-absorbing) vary with *p*H, with both forms at equal activity at the *p*K of the dye. In the sensor the dye is covalently bound to polyacrylamide microspheres to provide a fixed dye concentration and to form a packing for an ion-permeable cellulosic container. Green light (560 nm) and red light (600 nm) pass into the sensor from one fiber, through the packing, and back into the other fiber. Green light is absorbed by the base form of the dye as a function of *p*H, and the red light is not absorbed in relation to *p*H, so it acts as an optical reference. The light is returned to the afferent fiber to be measured either by a reflector in the sensor or by light-scattering polystyrene microspheres in the packing. The ratio R of green to red light is measured by the instrument connected to the fibers and is related to *p*H by the expression

$$R = k \times 10^{[-C/(10^{-\Delta} + 1)]}$$

where k is an optical constant of the system, C is the green optical density of the sensor when the dye is totally in its base form, and Δ is the difference between the *p*H and *p*K of the dye. This results in an S curve with an approximately linear region near *p*H = *p*K.

The original instrument design includes a tungsten lamp for fiber illumination, a rotating filter wheel to select the green and red light returning from the sensor, and signal processing instrumentation to give a *p*H output based on a linear relation with R. The system is capable of measuring *p*H in the physiological range (7.0 to 7.4) with an accuracy and precision of ±0.01 *p*H unit. The temperature coefficient of the probe is less than for an electrode, 0.017 *p*H unit per degree Celsius. The sensor is susceptible to a variation of ±0.01 *p*H unit per 11 percent change in ionic strength.

Markle *et al.* (*46*) continued development of the *p*H sensor for practical use. They designed a sensor in the form of a 25-gauge hypodermic needle with an ion-permeable side window and plastic optical fibers 0.075 mm in diameter. The sensor has a 90 percent response time of 30 seconds. With improved instrumentation and computerized signal processing to follow the curved relation (with a 3-point calibration), the range can be extended and a precision of 0.001 *p*H unit achieved. This design, with five probes for simultaneous measurement, was used in studies of the transmural *p*H gradient in canine myocardial ischemia (*47*). An evaluation in vivo of a fiber-optic *p*H probe based on the same system has also been reported (*48*).

Zhujun and Seitz (*49*) have developed a sensor of *p*H and of the partial pressure of CO_2 (PCO_2) that is based on the fluorescence of trisodium 8-hydroxy-1,3,6-pyrenetrisulfonic acid. This is ionically immobilized on an anion-exchange resin membrane, with a *p*K of 7.3 for the dye. The acid and base forms of the dye have different excitation spectra, so the *p*H can be observed as a function of the fluorescence at two different excitation wavelengths.

Sensor to measure PO_2. A sensor for measuring physiological PO_2 was recently developed by Peterson *et al.* (*50*). The device is based on the quenching of the fluorescence of a dye by oxygen. A dye was chosen for visible light excitation because available plastic fibers blocked light transmission below 450 nm and glass fibers were not considered acceptable for biomedical use. For best sensitivity, the dye must be on an adsorptive support. Inorganic adsorbents such as silica gel were used classically, but the effect was sensitive to humidity. Polymeric adsorbents are used by them to avoid the problem, although this results in sensitivity of the quenching to some volatile organic compounds.

The sensor is similar in construction to the *p*H sensor, and perpetuates the basic idea of an indicator packing in a permeable container at the end of a pair of optical fibers. A dye, perylene dibutyrate, adsorbed on macroreticular polystyrene adsorbent, is contained in a porous polypropylene envelope. This is illuminated by blue light and emits a yellow-green fluorescence, the intensity of which is dependent on PO_2. The green fluorescent light and scattered blue light are returned to the measuring instrument, and the ratio of green to blue intensity is processed in accord with the Stern-Volmer relation to provide a readout of PO_2 over the range 0 to 150 torr, with a precision of 1 torr. The developmental sensor was 0.5 mm in diameter, but it can be made much smaller. Although its response time in a gas mixture is a fraction of a second, it is slower in an aqueous system, about 1.5 minutes for a 90 percent response. The sensor has been tested in vivo but has not yet been applied experimentally.

Sensor to measure PCO_2. Development of the fiber-optic *p*H sensor led Vurek and colleagues (*51*) to devise the fiber-optic PCO_2 probe. The *p*H of a bicarbonate solution depends on the PCO_2 with which it is in equilibrium. Colorimetric or fluorescent *p*H indicators such as fluorescein can be used to estimate local PCO_2 (*52*). Instead of coupling the *p*H indicator dye to an insoluble matrix, a simple isotonic solution of salt, bicarbonate, and dye is used, with a gas-permeable, ion-impermeable silicone container membrane separating the indicator solution from its surroundings. With the appropriate dye concentration and an effective length of the optical path, transmittance through the solution is linearly (within 5 percent) related to PCO_2 over the range 20 to 80 torr. This makes for a degree of instrumental simplicity, although modern data-processing techniques can extend the useful range economically. The sensor's performance was demonstrated in vivo.

Sensor to measure glucose. A glucose sensor was developed by Schultz *et al.* (*53*). This is of particular interest because the design idea has broad applicability to biochemical measurements. The principle of competitive binding is used, with the analyte (glucose) competing for binding sites on a substrate (concanavalin A) with a fluorescence-tagged indicator (fluorescein isothiocyanate and dextran). The sensor is arranged so that the substrate is fixed in a position out of the optical path of the fiber end. It is bound to the inner wall of a glucose-permeable hollow fiber fastened to the end of an optical fiber. The hollow fiber acts as the container and is impermeable to the large molecules of the indicator. The optical field that extends from the fiber sees only the unbound indicator in solution inside the hollow fiber. Excitation light passes through the fiber and into the solution, fluorescing the unbound indicator, and the fluorescent light passes back along the same fiber to a measuring system. The fluorescent indicator and the glucose are in competitive binding equilibrium with the substrate. The inte-

rior glucose concentration equilibrates with the concentration exterior to the probe. If the glucose concentration increases, indicator is driven off the substrate to increase the concentration of indicator in solution. Thus fluorescence intensity as seen by the optical fiber follows the glucose concentration. This principle can be applied to any analytical problem for which a specific competitive binding system can be devised.

Conclusion

Fiber-optic sensors are mostly in a developmental stage, having achieved little penetration into the general field of biomedical sensors. There is substantial interest in the development of new sensors for various clinical and research applications. In the case of biochemical fiber-optic sensors, the principal competition involves field-effect devices, which had an early start. There have been difficulties with these devices, but they have great potential. Although fiber-optic technology may lead to improvements in traditional sensors, its most important application could be in the development of entirely new devices.

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Scientists and Congress

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Congress is a body that is expert in one thing—politics. Among the members of Congress are acknowledged experts in one field or another, but on the whole Congress is an aggregation of laymen. We are often asked to judge issues on which we are admittedly not expert, somewhat in the same way that a jury that is not a body of handwriting experts may be asked to judge the conflicting opinions of witnesses who are in fact handwriting experts. Our problem as legislators is like that of jurors in a court of law—we have to resolve claims that are in conflict, and we face an array of more or less persuasive fact and opinion on both sides. It is up to us to make a decision on one side of the issue. To put it another way, our problem is not necessarily a lack of information but resolving the conflicting claims that are put before us. The resolution of conflict, in one arena or another, is the essence of politics and also the essence of legislation.

In the realm of scientific research, Congress plays a role of tremendous importance and makes decisions that are often based on little real knowledge of the facts and less knowledge about the consequences. The federal government spends about $45 billion a year on scientific efforts of one kind or another. It is impossible for any member of Congress to review all of this research, let alone reach any sound conclusions about its entire range. We attempt to find some areas of general focus through our own in-house agencies, the most important being the Office of Technology Assess-

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