Advances in Medical Instrumentation

The influence of new medical instruments is large but not always easy to interpret.

Allen K. Ream

The quality of medical practice is largely determined by the quality of patient assessment. Thus, physicians have strong incentive to master more subtle ways of discriminating differences in patient condition by making better physical measurements.

The development of medical instruments has played a crucial role in this trend, since instruments permit subtlety, consistency, and accuracy of measurement not possible by direct means. Modern medical instruments are both a key to medical practice and the enemy of the humanist, who sees loss of personal contact as loss of quality. And, because instruments also increase the capital investment necessary for medical practice, concerns have developed about their impact on the cost of medical care.

It is instructive to review the dictionary definition of an instrument. The first and oldest definition is a tool, as "the surgeon's instruments." But in modern usage the most common meaning is a measuring device, to measure the "present value" of the variable under observation. The parallel follows in medicine; tools are essential, but the most critical ingredient is often the quality of information on which therapy is based. A physician may first think of his tools if you offer to sterilize his instruments. He is more likely to think of functions related to measurement when asked to identify his most valuable instrument.

Space restraints preclude an exhaustive discussion in this article. I will concentrate on developments in measurement, because these appear to be the most important concepts influencing the cost, distribution, and quality of medical care.

The author is assistant professor of anesthesia and director of the Institute of Engineering Design in Medicine, Stanford University School of Medicine, Palo Alto, California 94305.

General Trends

In the jargon of medical practice, instruments tend to be divided into three general categories: (i) clinical laboratory instruments, which are used to assess material taken from the patient at another place (and perhaps time), such as a red cell count; (ii) diagnostic instruments, which are used to make detailed measurements on patients (at a single time) to characterize their physical status, as in the cardiac catheterization or pulmonary function laboratory; and (iii) monitoring instruments, which are connected directly to the patient and provide repeated measurements at time intervals related to the rate at which the variable that is being measured is changing. Examples include the cardiac monitor in the coronary care unit, and the fluid-filled line connecting the artery to a pressure transducer used in the measurement of blood pressure. Each of these three categories has developed as a separate area, with separate economic markets and users.

However, the distinction is largely a function of the cost, convenience, and patient risk associated with a particular instrument. For example, measurement of blood gas concentrations (for example, oxygen and carbon dioxide), essential to the care of many critically ill patients, began as a laboratory measurement. The time from requesting the measurement to obtaining the result could be measured in hours. Instruments are now available which make it possible to continuously monitor the gas tension in the patient, a much more suitable time frame for a quantity that can change significantly in seconds or minutes.

The distinction may also be based on the intended use of the information. The blood pressure cuff is used for both diagnostic measurement (as in the case of the hypertensive patient seen on a regular basis as an outpatient to ensure detection of any change in the resting blood pressure) and monitoring (as by the anesthesiologist in the operating room).

Why are these distinctions important? I would like to suggest that, although genuinely new instruments continue to come into use in medical practice and have an important impact, it is the matching of an instrumental approach to the medical need which represents most of the effort, cost, and technical skill associated with instrument development.

The most important single development in improving the value of an instrument is improving its timeliness of application. The major difference between the three categories of instrumentation mentioned above is the difference in the immediacy of the measurement to the patient. The monitoring instrument represents the most immediate application.

I do not mean to diminish the significance of new instrument development. Fundamental developments also follow an evolutionary pattern. Two developments of crucial importance to modern surgery illustrate the point. The electrocautery was described in 1911 (*1*), but widespread clinical acceptance began only after Cushing's report in 1928 (*2*). The first human cardiopulmonary bypass surgery was reported in 1951 (*3*). Yet cardiovascular surgery of the 1970's would not be possible without the electrocautery.

Similarly, the development of computerized tomography has roots going back many years (*4*). The recent flurry of implementation is based primarily on the availability of adequate computing power at an acceptable price. This pattern is identical to that in the allied basic sciences (*5*).

The incentives for continuing the development process at any stage may be difficult to assess. For example, the cost may be much less for an instrument used in a remote location than for an instrument that must function in the vicinity of an individual patient, or cost may decrease but not in proportion to the increased number of instruments required. But the cost of medical care is reduced in other ways, almost by threshold effects, as the instrument moves from one category to another. (I presume that quality is preserved or enhanced, or there would be no user interest.) Measurements in the clinical laboratory have a hidden cost, the cost of transporting the sample to the laboratory and the results to the

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physician and patient, at a later time. The diagnostic laboratory permits increased efficiency because related measurements (indicated by the preliminary results) can be made at the same time, even though the analysis is not completed until after the patient's departure. Monitoring instruments are an integral part of therapy initiated during the time of measurement. But it is difficult to compare increased costs of instrumentation with avoided office visits or hospitalizations. The most significant costs may not be monetary, as delay in the treatment of a disease which can be arrested but not reversed.

Thus, the most significant recent developments in medical instrumentation are improvements in time (rapidity of response, frequency of measurement) and in scale (instruments tailored to individual needs and locations).

However, increased complexity does not always improve performance. Improvements are usually associated with increasing richness of the design concept, but this may simplify the appearance or the function. The instruments used in a cardiac catheterization laboratory in the early days often filled a large room. Equipment of similar power, used today at the bedside, can be housed in a small cabinet and newer designs are even smaller.

Perhaps a simple example, treated in more detail, can make the subtlety of this concept clear. A development necessary to modern care in the intensive care unit is the precisely controlled infusion of fluids and drugs. Early infusion apparatus utilized a drip chamber in the intravenous tubing, permitting one to measure the flow by counting the drops administered (usually per minute). But variations in drop size and the problems with gravity-fed systems led to the development of infusion pumps. Typically these pumps cost hundreds of dollars, and new versions are still being introduced. Because of their complexity and the physical abuse in typical use, they often require servicing, which substantially increases their life cycle costs. And, because they are electrically operated, batteries are required for many applications, which must be recharged from time to time and are prone to failure. The cost and small size of these pumps make inventory control a serious problem.

The most cost-effective infusion technique at present utilizes a disposable injection-molded plastic valve, with a variable orifice which delivers a constant flow, as long as the height of the bottle above the patient is not changed. When examining this technique, the accountant sees the advantage of a disposable low-cost device substituted for an expensive device which requires continuing maintenance and inventory. The user sees simplicity, convenience, and flexibility of operation (particularly when the number in use can vary enormously from one day to the next). Those concerned with instrument maintenance see a large reduction in the workload necessary to assure adequate quality control.

Perhaps the most intriguing observation regarding this product is that, although it is used for control, its primary function is measurement. I suspect (but have not been able to prove) that a significant factor in its rapid adoption is that flow rates are calibrated on a logarithmic scale. In most medical applications, dosages are changed by a percentage of the current value, rather than by a constant amount. A logarithmic scale makes a percentage change a constant change anywhere on the scale, making control easier for the user. Perhaps this is a small point, but, as instruments evolve toward the monitoring applications suggested, this kind of subtlety proves essential to effective, rapid, and error-free use.

Computers

The most critical instruments are usually used for measurement, and transmission of this information is a primary function. As our ability to detect and quantify information increases, interest is shifting to the processing and presentation of the information obtained.

A major problem for the human observer is that his capacity to assimilate and evaluate information in a given time span is limited. As instruments are improved so that more information is presented, they create a problem by stressing the observer's ability to interpret and act in a timely way. This has led to a necessary development. Proportionately more effort is being devoted to determining how to identify the information of greatest value, and how to present it most effectively.

An important concept in the effective transmission of information is human factors, the interaction of man with his instruments (*6*). An exciting development is the burgeoning interest in applying known skills in this area to medical problems, and to developing our understanding of how these constraints influence the quality of medical practice (*7*).

But one must also limit the quantity of information presented to the observer, either by restating it or by anticipating some of the thought processes required of the observer. Both of these functions may sometimes be performed by the digital computer.

Developments in computer applications have paralleled the schema already presented. The first were in off-line, clearly defined applications analogous to the measurements made in the clinical laboratory, such as medical records and billing. Since then, the computer has begun to be significant in diagnostic laboratory work (the modern cardiac catheterization laboratory could not function without it; this will soon be true of the pulmonary function laboratory), and its application in the fast-moving world of monitoring has been limited primarily by cost. The cost of computers has been falling at a logarithmic rate for many years. However, costs have recently entered the range where the cost increment for performance is acceptable when compared to other medical alternatives—a genuine threshold. As costs continue to decline and reliability increases, medical applications in monitoring may be expected to increase with extraordinary rapidity.

Professional experience is typical of this recent observation at a personal computer conference: "One of the nice things that the personal computer revolution has achieved for the world is computers that work when they are plugged in. . . . Among the exhibitors was much less gnashing of teeth and tearing of hair . . . than at most of the 'real' computer conventions . . ." (*8*).

As in the example of intravenous infusion, this kind of improvement may appear to be a trend toward simplicity in the eyes of the user. Microprocessors are beginning to be incorporated in monitoring instruments, permitting more flexible performance without any change in external appearance. In many cases, the number of controls can be reduced, making the instrument simpler to understand and control. Preprocessing, as in presenting heart rate from a measurement of the electrocardiogram, makes use quicker and easier. Alarm logic also stimulates more consistent responses.

Secondary factors which are economically mediated have a potential for enormous impact on medical practice. For example, the cost of monitoring equipment has been increased because virtually every purchaser wishes to specify his own aspects of performance differently from those in the catalog; these alterations require expensive hardware changes (and limit the cost control of hardware design). Many of these special requirements (as the performance of

alarms) can be programmed into a microprocessor-controlled instrument, permitting economical production of a single instrument. To change the specifications is then to change the computer memory, decreasing cost, increasing user acceptance, and increasing the rate of innovation.

Speculation on the impact of computers within a category has rarely identified developments with the significance of changes between categories (clinical lab, diagnostic, and monitoring). For example, it was suggested (*9*) that a major value of computer-assisted information processing would be to assist in mass screening of asymptomatic patients in the clinical and diagnostic laboratory. Unfortunately, the incidence of truly ill (or about to become ill) patients in this population was so low that subsequent identification and elimination of patients with false positives became an unacceptable economic burden. The screening process, including follow-up for those with positive findings, carried risk. If the incidence of disease in the population were low enough, the risk from these procedures outweighed the risk of disease. Diagnostic procedures did not materially change this picture: their increased cost and risk offset their increased specificity.

The crowning blow was the finding that for many diseases, earlier detection did not provably alter outcome. This finding is bound to change with time—the identification of illness must always precede effective treatment. But, at present, it seriously limits the practical application of this approach (*10*).

Analogous errors were committed in early attempts to apply computers to monitoring instruments. Early investigators first attempted to simply provide information more quickly and frequently. Often they were able to demonstrate the limited information-handling capacity of the human observer. The computer was then used to preprocess information in order to extract changes of interest. Efforts to use it to control therapy have begun where the principles are clearly understood (*11*).

The impact of computers on measurement is highly significant in a way that has only been dimly appreciated. A major need is to make measurements less invasively, incurring less risk and discomfort for the patient and enhancing time efficiencies. For example, it is current practice to measure blood pressure invasively in critically ill patients, because of increased precision and frequency. However, noninvasive measurement (as with the well-known arm cuff and gauge) is more convenient and carries lower risk. Recent developments suggest that the accuracy and frequency of noninvasive measurement of blood pressure can be improved by computer assistance (*12*).

A better known example is the computer-assisted axial tomography scanner (CAT scanner). This instrument has been used to substitute extensive computer analysis of x-ray information for higher risk procedures.

Indirect measurements require more links between the phenomenon of interest and the observer, and each link introduces additional measurement requirements and noise. Additional information-processing can offset these negative effects. But the magnitude of the additional processing necessary frequently requires computer assistance.

The most intriguing aspect is that, as the impact of the computer on instrumentation grows, its contribution becomes less visible. Microprocessors are often cheaper than the components they replace and thus can be used in inefficient ways and still be cost-effective. The user often sees the simplicity of the result rather than the complexity of execution that the computer permitted.

Thus the computer is of special significance because of its impact on the timeliness of information, observer limits on the rate of assimilation of information, and the need for quantified indirect measurements. Its promise is to simplify, not to complicate our professional lives.

Economic Considerations

In no other area have the discussions about the impact of developments in medical instrumentation spawned more divergent views than in the prediction of their effect on the costs of medical care. Part of the discussion centers on a clearly defined controversy: improvements in care can either be used to improve the quality of care provided to a given number of patients or to maintain the current standard of care for a larger number of patients. Given the commitment of the American physician to provide the best possible care for his own patients, it is not surprising that some economists suspect that advances in costly instrument technology are most likely to increase the costs of care by raising the standard of care. As examples, they cite the rapidly rising costs of hospitalization and the associated even more rapid rises in costs associated with high technology (instrument-oriented) areas within the hospital.

However, this argument is not as straightforward as it first appears. A few examples illustrate the difficulties that plague this kind of analysis.

Computer-assisted axial tomography (CAT scanning) has received widespread attention in the last few years, because the technique uses expensive, computer-assisted x-ray equipment and promises to supplant more dangerous procedures. Concern developed about the rapid adoption of these instruments because of the large capital investment required (typically more than $500,000), and serious attention was given to restricting institutions' privilege of purchase (*13*). The expectation was that, although these instruments would improve the quality of medical care, they might also raise costs so rapidly as to be unacceptable.

In fact, it appears that, despite the problems associated with innovation, the devices are being used in an appropriate way. A recent study (*14*) suggests that the total cost of medical care will be relatively unchanged by their use, because the high cost of the equipment and its increased use will be offset by the reduction in high-risk and high-expense diagnostic procedures, such as cerebral angiography, pneumoencephalography, and exploratory brain surgery. This study was based on the assumption that a CAT scanner would cost approximately $500,000 with depreciation over only 5 years.

However, the most significant hazard in estimating the true cost of new instrumentation does not lie in comparing its use with existing alternatives. A more subtle trap is the difficulty in estimating the cost of the instrument over the period of adoption. In the case of the scanner, for example, the cost which has been central to most discussions is $500,000. But the major part of this cost is for data-processing equipment, which is rapidly decreasing in price. In the last few months, three major companies offering scanners announced units costing $95,000 to $135,000, and the price decline appears likely to continue (*15*).

Yet another consideration that is exceedingly difficult to define is the standard for evaluating new techniques. In the case of the CAT scanner, the problem is fairly straightforward: the patient population, number of procedures, and relative cost appear definable. More often, it is not possible to directly define a simple standard of comparison.

For example, the currently most attractive commercially available computerized hospital information system was initiated by Lockheed, then developed by Technicon Corporation. It handles

chart and laboratory data, both by video screen and printed copy. The major part of the development work was performed at the El Camino Hospital, south of San Francisco. The hospital administrators were shrewd; they agreed to act as participants in the development, but their contract required that payment for the computer system be based on demonstrated cost savings.

The initial evaluation period lasted 18 months. Careful statistical analysis showed that there was a very slight decrease in length of stay, nursing hours per patient day, and nursing hours per patient admission (2 to 4 percent). The evidence became convincing, however, when an analysis of neighboring comparable hospitals showed an equivalent increase in these factors, thus doubling the difference. This evaluation took place in 1972–1973 (*16*). Similar calculations in 1975 showed even more clearly how a local comparison without a proper control can lead to misleading figures. During 1975, the nursing hours per patient day rose 1.2 percent at El Camino while rising 2.6 percent in California and 4.8 percent nationally. Without the opportunity to compare with other similar institutions, the impact of the information system on the hospital could have been completely missed.

Although in this example percentage differences are small, the dollar differences are not. For example, in the hospital studied, these data suggest that the actual savings were approximately $4.30 per patient day or $43,000/month (average census on the order of 330 patients) (*17*) or approximately $500,000 per year, enough to pay for one CAT scanner outright each year! And this analysis does not consider the professional argument: the system improved the quality of care.

There is an important difference between the two favorable examples suggested, however. In the case of the CAT scanner, the instrument is obtained (lease or purchase) by the hospital on the basis of cash flow. The fees charged patients for the use of the machine cover the financing costs and permit the short depreciation period (3 to 5 years) cited. Since these are documented costs, their reimbursement by third-party carriers (the government and insurance companies) has never been in doubt.

In the case of the hospital information system, the difference in cash outflow was accompanied by demonstrated cost savings. Since third-party carriers base their reimbursement on actual cost, they would expect the savings to be passed through to them. But this removes the incentive for the hospital to innovate in this fashion. The hospital does not share in the financial benefits, and a large capital investment is necessary to implement the system. This difference is readily apparent in the difference between the rates of adoption of the two kinds of systems, although the potential contribution of the two systems to the quality of care appears at least equal, and may favor the information system.

Thus, the current system of reimbursement to health care facilities rewards the hospital which improves care by increasing definable costs (since each increase in billing carries some associated overhead expense which increases institutional income) and penalizes the hospital which improves care by reducing operating costs (by expecting these savings to be passed through to the reimbursing agencies). This inequity is already a subject of discussion; it appears that financial incentives must be permitted to encourage applications of instrumentation which may reduce health care costs in an acceptable way (*18*).

Finally, the seeming impact of instrumentation on long-term patient care costs may also be misunderstood. This is illustrated in our third example, the monitoring of intracranial pressure in the acutely ill patient.

It has been known for many years that a rise in pressure in the brain can lead to the death of the patient by preventing adequate perfusion. If recognized and reversed, the deleterious effects of a pressure rise can be prevented. Candidates for this treatment are patients recovering from surgery for brain tumor or vascular malformations, and head injury. However, some have suggested that what in fact may happen is that patients who would otherwise die recover but are vegetative and thus require lifelong institutional care. They suggest that, if this is true, these patients may more than compensate for any economic benefit from returning other patients to adequate function.

Because care during the critical phase is intensive, it is expensive. Thus the combination of substantial short-term costs and no net long-term gain suggests that this technique may be an attractive way to increase survival only if economic costs are ignored (*19*).

It is impossible to predict such results in advance. A recently published study, involving 148 patients, is the first to address this issue. The investigators found that pressure monitoring was associated with increased patient survival. Compared with earlier studies without instrumented pressure monitoring, the size of the vegetative group did not significantly change (about 10 percent of the treated patients). The reduction in deaths (18 percent of the treated patients) was accompanied by an equivalent increase in those returning to effective function (*20*).

The technique used (the epidural hollow screw, communicating with an external pressure transducer) is not completely reliable because the dural membrane surrounding the brain can occlude the screw lumen and lead to falsely low readings. A new planar transducer promises to further reduce the risk of erroneously low readings (*21*).

My examples have been selected to demonstrate situations where the benefits of instrumentation may not be easily recognized. Admittedly, not all examples are so successful. But, because of current concerns over funding, the greater risk appears to be the rejection of new effective instrumentation rather than the implementation of ineffective instrumentation. The serious difficulties associated with evaluating the effects of instrumentation include identification of (i) procedures which it supplants, (ii) the appropriate population for comparison, and (iii) reimbursement policies, and clarification of undocumented expectations about patient outcome. The analysis of the quality of medical procedures is still in its infancy (*22*); we must be careful to avoid permitting analytic concerns to preclude an effective trial of innovation and application.

Regulatory Constraints

An effective expression of the value of instruments in medical care is the growing interest in regulatory activities. In 1976, the Food and Drug Administration (FDA) acquired jurisdiction over devices as well as drugs. This includes instruments.

Under the new law, three regulatory levels are created: (i) premarket approval (category 3), which requires treatment similar to that presently afforded drugs, (ii) standards (category 2), for less dangerous devices which are sufficiently well characterized to be controllable by a standard, and (iii) general controls (category 1), which includes minimal requirements related to record-keeping, labeling, and good manufacturing practice for devices that do not require more intensive regulatory attention. It appears clear that any instrument that can be calibrated will be in category 2, and, if significant patient risk is involved, in category 3. All instruments used in medical

care are included. The FDA has determined that "device" includes some computer software.

The law requires that existing devices be classified, a process that is just now being completed (*23*). New devices cannot be marketed without first undergoing FDA review.

Ten years ago, a market survey by Arthur D. Little indicated that only one medical device market, x-ray equipment, included companies which sold over $1 million per year in a single product. This exclusive group has since been joined by others, most notably the manufacturers of electronic monitoring equipment. But most medical devices are still sold in small quantity and made by small companies, in marked contrast to the market structure in the drug industry. Although recognizing the value of federal regulation in the interest of patient safety, users, developers, and manufacturers are very concerned about the costs and delays potentially associated with regulation in this kind of environment.

More ominous from the user's point of view is the apparent interest in regulation at the state level. In California, for example, the bureaucracy is rapidly implementing a law permitting device regulation in order to preserve separate regulatory capacity. It is not clear whether even as large a state as California can develop sufficient expertise to be effective in regulating the development of acceptable instrumentation without creating crippling jurisdictional conflicts.

The regulatory impact on innovation may be severe because of the direct impact on instrument development, as well as the marketing of commercial products. Currently, most institutions have review committees for studies involving human subjects; they are required in the case of funding by the National Institutes of Health. However, recent developments have forced the majority to require application in all cases of human study, and the rest appear ready to follow. The FDA legislation supports this approach but adds review at the federal level. The first regulations interpreting the legislation were published in the fall of 1976 but aroused a storm of protest, including negative responses by such organizations as the Association of American Medical Colleges and the National Institutes of Health. The revised proposed regulations may be in print before this article is published. Despite the much greater effort invested in the upcoming draft, further controversy seems certain. Interested readers should contact David Link, director of the Bureau of Medical Devices, FDA, Silver Spring, Maryland, to be sure they are apprised of the existence of the draft during the legally required comment period.

One problem is related to the dynamics of innovation. Studies on drug introduction reveal a phase of overenthusiastic acceptance, suggesting the need for regulatory restraint (*24*). However, device development in general has followed a slower, more costly course. Development has been slow, sometimes indirect, and often expensive. A well-publicized military study suggested that for military devices most developments came from target-oriented research. A more recent study has challenged this general conclusion, with specific reference to developments in cardiovascular and pulmonary disease (*5*). In addition, many have suggested that instrument development is primarily related to the needs of users and not manufacturers, and that direct involvement by the user is a key ingredient in successful instrument development (*25*).

This has become an even more important concern in modern medicine, where the skills of medical practice are becoming less accessible to supporting disciplines. It is unlikely that the contributions of the Renaissance men who were also physicians observed in the past [for example, Gilbert and magnetism, Young and materials, Poiseuille and flow, Helmholtz and thermodynamics (*26*)] can be as significant in the future. Collaborative effort in instrument development is essential. If the device law fosters effective collaboration, it will be an important influence for good. If it hinders that collaboration, the negative effects will be profound but not immediately evident.

Finally, the changing emphasis from measurement to interpretation carries significance for the user. Proposed FDA labeling already refers to qualified users, not necessarily all physicians. It seems clear that the classic course in pharmacology required of medical students will be joined by one in instrumentation. Unlike the rudimentary courses now offered, the primary emphasis will not be on physical devices but on physical principles and concepts of measurement. The physician needs to know how to use his instruments effectively, not (unless his commitment is to research) how to design and build them.

Summary

The effects of modern instrumentation on medical practice have been profound. There is little doubt that they have substantially altered earlier limitations on the quality of care. With the improvement in measurement skills has come the recognition that acceptable instrument function relates to time as well as physical properties. An increasing portion of effort devoted to medical instrumentation is being used to reduce time to response and to improve the associated information-processing. With these changes have come an increased emphasis on the computer and substantive threshold changes in medical practice. Interestingly, newer and better instruments may appear smaller and simpler, although the associated concepts (and perhaps construction techniques) have grown more sophisticated.

Our confidence in assessing the impact of specific instruments on the cost of medical care is still growing, and pitfalls abound. I have examined some examples to show that, where instruments permit substantive changes in the practice of medicine, it is more likely that previously acceptable evaluation techniques will be inadequate. And, the risk that an economically attractive technique will not be recognized increases because of the nature of the evaluation. Because of this concern, it appears more acceptable at present to restrict questionable devices than to prohibit them.

The regulatory agencies are taking note of potential instrument problems and are expanding their legal authority to impose controls. Existing legislation already permits enormous influence over the innovative process. Whether this influence becomes a serious impediment to future innovation remains to be seen.

A sign of the maturing influence of instrumentation on medical practice is the increasing emphasis on abstract skills in data processing. User education must increase and must include more basic principles.

In a review Klopsteg noted ". . . among the 138 Nobel laureates in physics and chemistry from 1901 through 1960 . . . recognition was accorded 112 . . . for research in which instruments were dominant . . ." (*27*, p. 1913). I believe we have reached an analogous condition in both medical research and practice.

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Behavioral Neurochemistry: Neuroregulators and Behavioral States

Jack D. Barchas, Huda Akil, Glen R. Elliott
R. Bruce Holman, Stanley J. Watson

Summary. There is compelling evidence that behavioral events alter neurochemical function and that altered neurochemical function can change behavior. Such processes have been related both to neurotransmitters and to neuromodulators, together termed neuroregulators. Available research tools and theoretical constructs have begun to permit studies of certain types of behavior, primarily those related to emotional states and drives. This work is changing long-held concepts about severe mental disorders and the treatment of them.

Preparing a general review of behavioral neurochemistry is a striking experience. Only two decades ago, no such discipline existed; and yet today it addresses topics that range from biochemical aspects of behavioral mechanisms to severe neurochemical abnormalities that have behavioral sequellae, including psychiatric disorders and mental retardation. The field is concerned with relationships of behavior to levels of neuronal organization ranging from nerve networks to cytoplasmic and nuclear events; it makes use of many disciplines, including biochemistry, analytical chemistry, neuropharmacology, neurophysiology, histology, neuroanatomy, physiological psychology, and psychiatry. Basic investigation has enhanced our understanding of biochemical aspects of brain function, provided new insights into certain basic behavioral processes, produced testable hypotheses about the causes of several severe mental disorders, and yielded effective pharmacological treatments for these illnesses.

The field of behavioral neurochemistry deals with a wide range of behaviors and related neuronal processes. For purposes of this article, we have chosen to focus our discussion on the relation of neuroregulators in mammalian systems to emotional states and drives. Our purpose is to demonstrate the multiple ways in which information regarding neuroregulators has developed and has affected the general concepts and approaches in behavioral neurochemistry. We give examples of some problems, substances, and hypotheses which have received particular attention. We consider clinical problems with which neuroregulators have been linked. Some of the recent work dealing with opiate-like substances in the brain, which may function as neuroregulators, is considered as a case that demonstrates the rapid advances within the general field. Finally, we will touch upon some general considerations related to health maintenance problems.

Neuroregulators: Neurotransmitters and Neuromodulators

An underlying assumption in behavioral neurochemistry is that certain substances, neuroregulators, play a key role in communication among nerve cells. These compounds may be subdivided into those which convey information between adjacent nerve cells (neurotransmitters) and those which amplify or dampen neuronal activity (neuromodulators). Table 1 presents a partial list of some of the compounds which are known or hypothesized to be present in brain and may function as neuroregulators (*1*). The idea of chemicals being involved in neuronal communication is usually credited to T. R. Elliott, a Cambridge graduate student who, in 1904, suggested that stimulation of peripheral autonomic nerves might release small amounts of a chemical substance to produce effects on the target organ (*2*). However, Loewi's (*3*) 1921 demonstration of the release of *vagusstoff* following vagal stimulation provided the first compelling evidence for chemical neurotransmission. That same year Cannon and Uridil (*4*) described the properties of "sympathin," a substance released from the liver on stimulation of sympathetic nerves. These compounds subsequently were identified as acetylcholine and norepinephrine, respectively, the first two neurotransmitters to receive extensive investigation.

Early suggestions that chemical neurotransmission might occur in the central nervous system (CNS) generally were

Dr. Barchas is Nancy Friend Pritzker Professor in the Department of Psychiatry and Behavioral Sciences at Stanford University School of Medicine, Stanford, California 94305, and is director of the Nancy Pritzker Laboratory of Behavioral Neurochemistry in which Dr. Akil, Dr. Elliott, Dr. Holman, and Dr. Watson are senior staff members.

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