APPENDICES

Appendix A

DEVELOPMENT AND DIFFUSION OF MEDICAL TECHNOLOGY

This appendix describes the process of development and diffusion of medical technology. It highlights five areas that are related to the concerns of this study, as described in chapter I.

- First, the activities that comprise the continuum from theory to practice are described and divided into four general categories: basic research, applied research and development, clinical testing, and diffusion and adoption.
- Second, the limitations of this or any other scheme of classifying R&D activities are discussed in order to make explicit problems that these limitations pose for policy makers and technology assessors.
- Third, some features unique to the development of each of the types of technology—techniques, drugs, equipment, and procedures-are enumerated.
- Fourth, some current mechanisms for funding and priority setting in biomedical R&D are examined. The role of NIH, the major Federal source of research funds, in setting priorities and allocating funds is reviewed briefly. The large investment in biomedical R&D in the private sector is described, along with the difficulties that this poses for comprehensive programs of technology assessment.
- Finally, the chapter examines evidence bearing on two converse concerns about lags in the development process—that some technologies are delayed in their development even after the necessary concepts and tools are available (so-called "bench-to-bedside" lags), while other technologies are widely adopted before they are completely developed and adequately tested.

THE PROCESS OF TECHNOLOGY DEVELOPMENT

Adoption of a new technology by the consumer can be viewed as the final step in a long sequence of activities (91, p. 64). First, a background or conceptual basis is laid by theoretical research and the sum of previous experience. Then, basic empirical research provides a framework of knowledge about the mechanisms involved, discovers points in a natural process that are susceptible to technological intervention, and suggests strategies for technological development. Applied or mission-oriented research is then directed at applying this basic knowledge to a practical purpose and demonstrating the feasibility of the proposed technology. Once feasibility 'is demonstrated, engineers, entrepreneurs, and developers, usually in the private sector, can develop goal-oriented programs. Prototypes are built and problems of transferring the technology from the laboratory to the marketplace are faced. Once the manufactured item is ready, its effectiveness and efficiency can be

assessed in a realistic way in industrial testing laboratories, in field tests, or in consultation with potential users. Finally, the technology is marketed and, if all goes well, it is adopted by the proper class of consumers, be they manufacturers or industries, public groups or institutions, or private individuals.

Such a sequence is attractive because it offers a way to understand the development process. For technologies of any type, however, this sequence represents a sociological ideal rather than a realistic description. Medical technologies, like other technologies, emerge from a process that is far less systematic than this model implies. Nevertheless, four general categories can be distinguished in the spectrum of activities that precedes the widespread acceptance of many medical innovations. They are: basic research, applied research and development, clinical testing, and diffusion (fig. 2).

Basic Research

Medical advance rests on a foundation of knowledge about the biological mechanisms that underlie the normal functioning of the human body and its malfunction in disease. This knowledge is acquired largely through basic biological research (3).

Lacking sophisticated tools, general theories, and the framework of the scientific method, early biologists were occupied with the enterprises of careful observation and extensive classification. Occasionally, general explanatory theories (for example, Darwin's theory of evolution or Harvey's theory of the circulation) emerged from the compilation of numerous observations. Most often, though, the early biologists amassed bodies of information that awaited further progress for their interpretation.

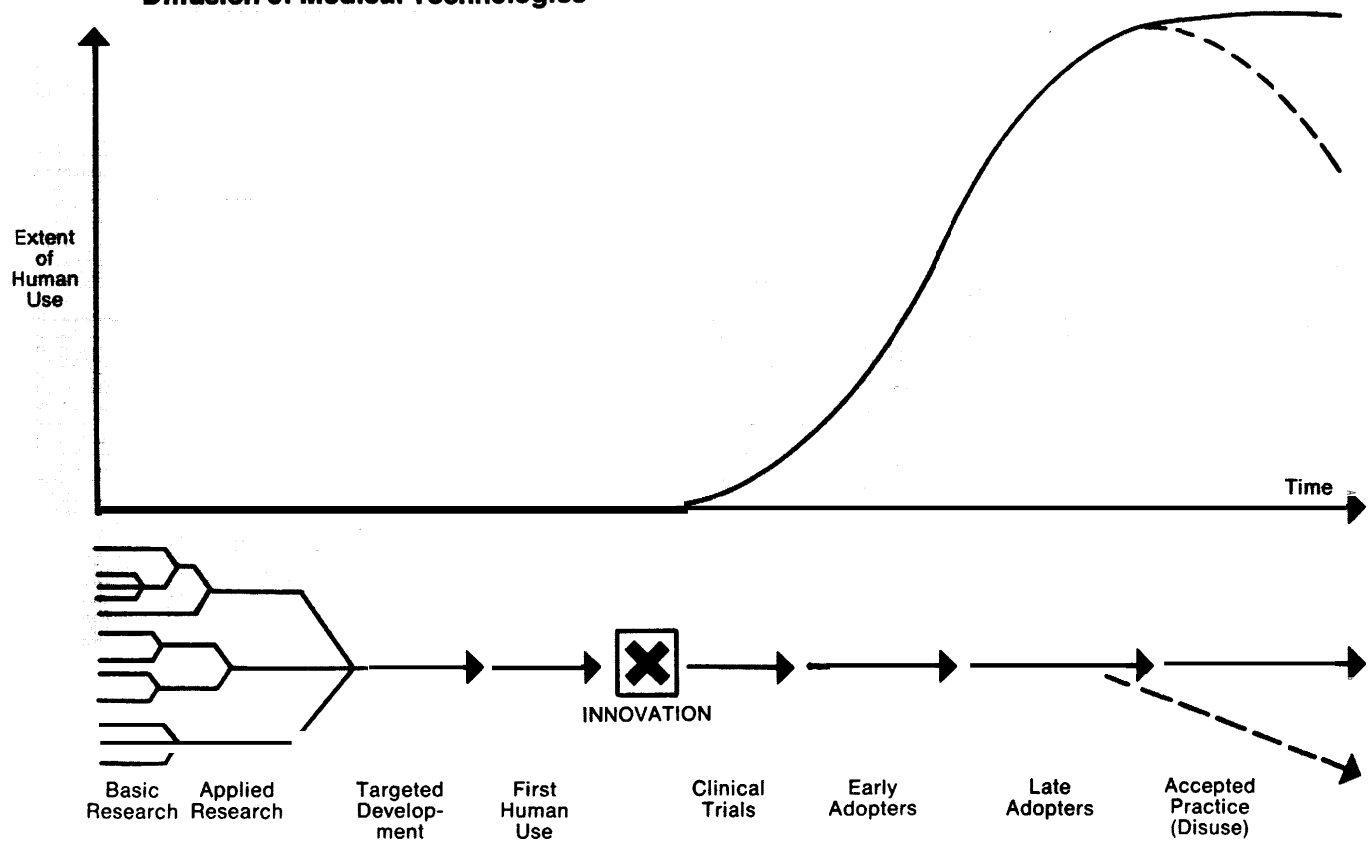
In the 20th century, biology has become a mature experimental science. Earlier detailed and reliable descriptions of whole animals or organs provided frameworks that have allowed the formulation and testing of hypotheses about the mechanisms that underlie a variety of previously described phenomena. The availability of new ideas and tools, derived largely from advances in the physical sciences, has made it possible for biologists to gain insight into many organic processes by focusing on smaller and smaller parts of the whole animal. Refinements in the techniques of microscopy and the later advent of electron microscopy have allowed examination of the cells from which tissues are built and of subcellular elements. The application of chemical theories and techniques to biological problems has made possible the study of the molecules and reactions from which all biological structures and functions are derived. The resulting progress, sometimes through spectacular breakthroughs but more often as a result of plodding, methodical work, has led to an understanding of the mechanisms that underlie a number of intuitively fascinating and practically important biological phenomena. Among the triumphs of modern biology are the discoveries of—

. The molecules and reactions responsible for the transmission of inherited characteristics from one generation to the next;

. The way in which chemical energy is transformed to mechanical energy to permit muscular contraction; and

. The ways in which large molecules called enzymes catalyze and regulate the chemical reactions that account for the body's metabolism.

Figure 3—**A Scheme for Development and Diffusion of Medical Technologies**



The promise of such basic research to the public is eventual advance in the prevention, diagnosis, and treatment of diseases. Fulfillment of this promise depends on the validity of two assumptions about basic research. First, biologists assume that knowledge acquired from studies of lower animals (which are readily available, provide numerous technically advantageous features, and can ethically be subjected to experimentation) will be applicable to humans. Second, they assume that knowledge about the normal functioning of the human body will lead to an understanding of the body's malfunction in disease. As biological knowledge has accumulated, these assumptions have been confirmed. Knowledge acquired through basic biological research has led to the development of effective and beneficial medical technologies. In some cases, such understanding has allowed the development of technologies such as vaccines, which prevent disease and make expensive, risky, and incompletely .effective treatment unnecessary.

The application of basic research findings to practical ends can occur in several ways. Frequently, the immediate connection is not clear, as when medical benefit is derived from the confluence of seemingly unrelated lines of research. 4

. The invention of the microscope, done out of curiosity, was one of the advances that made modern medicine possible.

. A long history of work on ways to grow living cells outside of the body led to development of cell cultures that were used to produce polio virus for vaccines. (See Case 3 in ch. II.)

In many other cases, logical progression from basic research to its applications can be discerned retrospectively, although application might not have been predictable in advance (264).

. Biochemical studies on metabolism led to the discovery of enzymes that regulate metabolic processes, then to studies of enzyme deficiencies in disease states, and finally to the use of enzyme assays as important diagnostic tools.

Occasionally, medical advance comes serendipitously from lines of biological research far removed from the particular medical area that benefits.

. The discovery of the Rh factor in blood, which led eventually to prevention of the fatal syndrome, erythroblastosis fetalis, resulted from work on variations in the color of butterfly and moth wings (45).

• The technique of freeze drying, now widely used to preserve antibiotics and blood fractions without loss of potency, was developed in studies on the water content of liver and muscle (45).

Finally, it must be noted that basic research in physics and chemistry, as well as in biology and biomedicine, can lead to medical advances. Sometimes the application is rapid, as when Roentgen discovered X-rays while he was studying the electrical nature of matter, and quickly applied his discovery to the examination of human tissue (45). More often, the physical sciences supply background, theories, techniques, and tools that are used for doing biological research or for applying biological knowledge to practical ends.

Applied Research and Development

In its *Forward Plan for Health,* DHEW defines "applied research and development" in biomedicine as "activity drawing upon basic information to create solutions to problems in prevention, treatment, or cure of disease" **(49).** While basic research in biology seeks to understand vital processes, applied research seeks their manipulation or control.

An illustration of the difference between basic and applied research is provided by the recent work of Bruce Ames and his collaborators at the University of California at Berkeley (119). For a number of years, Ames was engaged in studies on molecular biology. He created and used mutant strains of bacteria to study the mechanisms of genetic control of metabolic processes. This work was, by any definition, basic research. At some point, Ames realized that the information he and others had gathered about genetic mechanisms, and the bacterial mutants he had created, could be used to devise a system for determining whether particular chemicals could cause mutations. This information, he realized, would be valuable because other researchers had found that most carcinogenic chemicals are mutagenic. (In fact, chemicals may cause cancer by inducing mutations.) He therefore developed such an assay and has since used it to screen a wide variety of industrial and environmental compounds for potential carcinogenicity. Ames' application of knowledge gained through his earlier work to the practical end of developing a test for carcinogens is an example of applied research.

Similarly, each of the disciplines into which "basic" biological research is organized has an "applied" counterpart. The vitality of applied research varies, however, from field to field, depending on how well developed and solid the foundation of basic knowledge in each area is. Knowledge acquired through biochemical and physiological research has been applied to the development of many medical technologies, as the cases presented in chapter II illustrate. Ames' work on the application of molecular biology to practical ends is particularly noteworthy because the field of molecular biology is so new-the discipline has existed for only a few decades.

Although further application of recently acquired knowledge can be anticipated, it is a mistake to—

> attribute to biology and medicine a much greater store of usable information than actually exists. In real life, the biomedical sciences have not yet reached the stage of general applicability to disease mechanisms. In some respects we are like the physical sciences of the early twentieth century, booming along into new territory, but without an equivalent for the engineering of that time. It is possible that we are on the verge of developing a proper applied science, but it has to be said we don't have one yet (197, p. 116).

Much of the applied research that contributes to the development of medical technologies is not, strictly speaking, biological, but rather results from the application of knowledge derived from the physical sciences to the solution of biological problems. For example, chemical engineers are engaged in developing "biomaterials" that neither damage nor are damaged by the environment of the human body, and thus can be used in invasive medical procedures or for implants. The technology of electronics has provided instruments for measuring biological parameters, which have been adapted for diagnostic uses (see cases of continuous

flow-blood analyzer and computerized axial tomography in ch. II), as well as miniaturized power sources and control elements that are eventually used in therapeutic devices (see cases of cardiac pacemaker, cortical implants, and the implantable artificial heart). Organic chemists have developed techniques and strategies for synthesizing compounds that might be used as drugs.

Although applied research of these types is, by definition, goal oriented, the development of a particular new technology is not always the immediate goal. Applied researchers in both biological and physical sciences frequently concentrate on the development of new materials, tools, or techniques that they assume will be useful for a variety of applications.

The targeted development of a particular new technology begins when knowledge derived from basic and applied research is sufficient to support the effort. Although not without risks, both human and financial, the successful outcome can be predicted with some assurance, if solid foundation has been laid by prior research. As Thomas argues,

> When you are organized to apply knowledge, set up targets, produce a usable product, you require . . . certainty from the outset. All the facts on which you base protocols must be reasonably hard facts, with unambiguous meaning. The challenge is to plan the work and organize the workers so that it will come out precisely as predicted. . . . You need the intelligible basic facts to begin with (197, p. 118).

It must be emphasized, though, that the sources of these facts are many. Workers engaged in developing new technologies, whether they be biologists, engineers, or physicians, draw on knowledge gained through basic and applied research in biological and physical sciences alike, as well as on the rich lore of industrial, experimental, and clinical experience.

Clinical Testing

At some point in their development, new medical technologies must be tested in human subjects. This area of clinical investigation and testing encompasses a range of activities from first human use to large-scale clinical trials.

The nature of first human use varies with the technology being tested. To test many noninvasive procedures or equipment, the investigator may use himself or coworkers as subjects; little risk may be involved. In other cases, only small samples of blood or tissue may be required, and these can be obtained from a number of sources including blood banks and hospitals. For invasive or particularly risky procedures, however, careful medical supervision and considerable planning are required. Furthermore, in such cases, first human use raises problems of informed consent by the subject; the individual must be aware that he is participating in an experiment and must agree to become a subject (71). Recent policies have begun to bring these activities under the control of human experimentation committees at research institutions, which review all grant and contract proposals to NIH to help insure that basic ethical standards have been met (8, 147, 149, 151).

Occasionally, the first human use of a new technology is spectacularly successful (see the case of renal dialysis in ch. II). More often it is not, and modifications in the technology must be attempted. Clinical testing frequently reveals

problems that were not—and perhaps could not have been-anticipated from prior work on animals. In some cases, considerable further research is required; at other times, minor improvements prove to be sufficient. Therefore, continued development of new technology frequently continues apace with further clinical testing.

After a new technology appears to be useful in scattered clinical experiments, organized trials may be carried out; increasingly, these are controlled or randomized clinical trials. In such trials, the technology to be tested is applied to some patients and withheld from others. Patients in the "control" group, who do not receive the "experimental" treatment, are often given inactive substitutes or placebos, so that the psychological effects of "having someone do something" do not contaminate the trial's outcome. Patients are assigned to "experimental" or "control" groups by a randomizing procedure, and objective methods are devised for assessing the patients' conditions at predetermined intervals. Thus, the controlled trial at its best allows scientific evaluation of the efficacy of medical technologies.

Although the controlled clinical trial has been considered the *sine qua non* of effectiveness, some limitations in its methodology must be recognized. Controlled trials are expensive and difficult to organize. Years of trial may yield inconclusive results because the trial has not posed the proper question or used the proper methodology. (See the case of oral anticoagulants in ch. II.) Furthermore, the nature of the procedure or the seriousness of the medical problem it addresses may make organization of a controlled trial difficult. For example, a proper test of a new surgical procedure might require that some patients be given a "sham" operation; such "sham" operations may be risky to the patient and therfore raise serious ethical questions. In other cases, patients in "control" groups would be required to forgo treatments that are already available; this also raises ethical questions. In cases where no alternatives to the technology being tested are available, practitioners may feel that it is unethical to withhold a promising treatment from desperately ill patients. (See the case of radical mastectomy in ch. II.) Finally, if the natural history of a condition is well known, a controlled trial may not be necessary. (See the case of the cardiac pacemaker in ch. II.) Therefore, although the controlled clinical trial is a powerful tool, other methods for insuring efficacy are also important and necessary.

Diffusion and Adoption

The most important factors determining whether, or how rapidly, a physician will adopt a new technology are his own clinical experience and that of his colleagues (102, 183). Other sources of information, such as advertising campaigns, the technical literature, and programs of continuing education, are also important, but secondary in impact. Occasionally, if clinical trials of a new technology are promising, Government-supported demonstration projects are organized to show that a technology which is effective under controlled circumstances is also useful in the community, where socioeconomic and other factors may modify its impact (32, 152). In most cases, however, practitioners learn about new developments through less formal channels.

Although several sociological studies have examined the personal and demographic characteristics of early and late adopters of new medical technologies, comprehensive quantitative studies of diffusion in the medical area are few (80, 84, 103, 167, 173). Primarily as a result of extensive work in nonmedical areas, it has been found that the diffusion process usually describes an S-shaped or sigmoid curve, in which the rate of adoption accelerates as time goes on (171). Diffusion of some medical technologies follows this curve, as shown in figure 3A for adoption of intensive-care units by hospitals (47). The slower initial diffusion is often interpreted as indicating caution but is also consistent with poor communication between sellers and buyers or among buyers. Those who accept the new medical technology first are referred to as innovators, with early adopters and late adopters accounting for subsequent portions of the curve (171).

The diffusion of some medical technologies does not, however, follow the sigmoid curve. One major departure from the standard model occurs when diffusion reaches a high rate almost immediately after the technology becomes available, as shown in figure 3B for the case of chemotherapy for leukemia. This pattern has been referred to as the "desperation-reaction model" (209). A first phase of rapid diffusion seems to occur in the absence of evidence of efficacy because of the provider's responsibility to help a patient and their mutual desperation. Some-what later, results of clinical tests and experience begin to influence the physician's behavior. If results are positive, diffusion may continue rapidly. But if the evidence is not clear cut, there may be caution and slow diffusion. Finally, if the evidence seems to be negative, use of the technology gradually declines.

The "desperation-reaction" model points out a paradox in the diffusion of medical technologies. Faced with a desperate and sometimes life-threatening situation, each physician may be totally justified in adopting whatever technology is available. The aggregate behavior of many desperate physicians, however, may result in the extensive and premature diffusion of technologies that are incompletely developed, inefficacious, or possibly even dangerous.

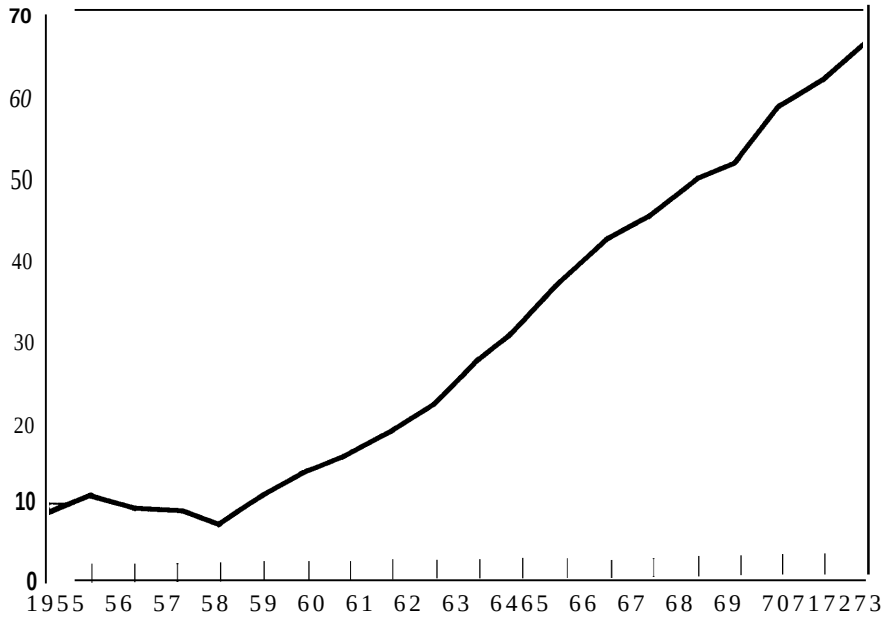
Whatever its initial pattern of diffusion, a technology may eventually be partially or completely abandoned. This can occur, as stated above, after a rapidly diffusing technology proves to be of little use clinically. Medicine is replete with examples of procedures that have fallen out of use, such as bleeding and cupping. More recent cases can also be cited. For example, a psychosurgical procedure called leucotomy or prefrontal lobotomy was widely adopted in the early 1950's and was later abandoned when its efficacy and safety were seriously challenged (fig. 3C).

A decrease in usage may also occur when a widely used technology is supplanted by one of greater efficacy or lower cost. Thomas et al. (198) have described this process for poliomyelitis, using the terms "high" and "halfway" technology. A high technology is the decisive, conclusively effective measure aimed directly at the underlying cause of the disease so that it can be terminated, reversed, or prevented. Prevention seems almost always to involve such "high" technology. "Halfway technology" refers to the measures taken to compensate for the destructive effects of diseases whose course cannot be altered, and whose biological bases are not fully understood. In the case of polio, a complex and costly halfway technology of rehabilitation centers and iron lungs was entirely supplanted almost overnight by the polio vaccine. (See the case of vaccines in ch. II.)

Figure 3—The Diffusion of Some Medical Technologies

A. Intensive Care Units

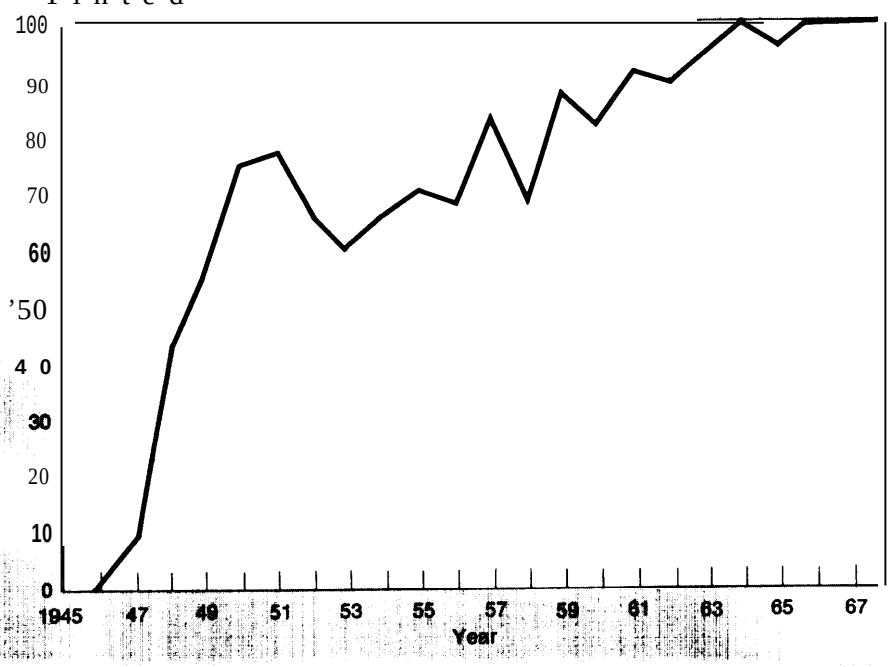
(% of Community Hospitals with Mixed ICU Units)



Source: Nnerlcen Ifosdtal Association.

B.

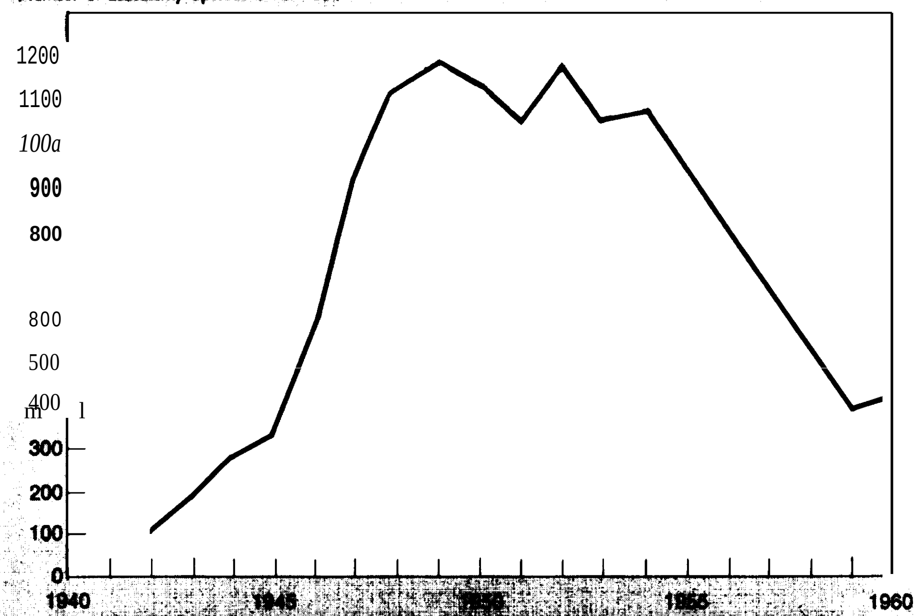
T i n t e d



Source: Reference 209.

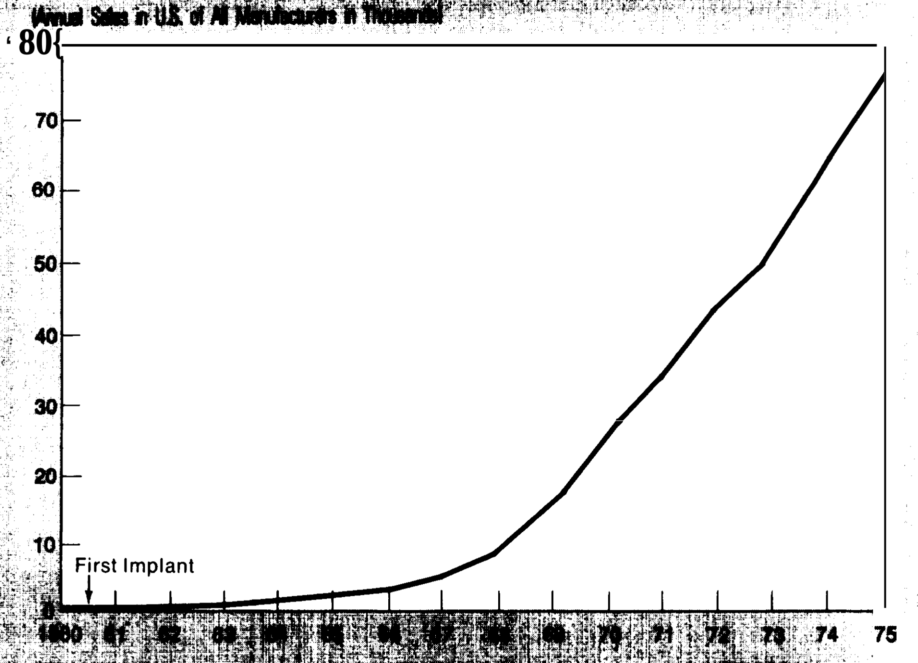
Figure 3 Continued

C. Leucotomy Operations (England and Wales)



Source: (1): G. Tooth and M. Newton, *Leucotomy in England and Wales 1942-54*, Reports on Public Health and Medical Subjects No. 104 (Ministry of Health, [illegible], London, 1961)).

D. Cardiac Pacemaker



Source: Medtronic Inc.

However, the ideal of high technology replacing halfway measures is seldom realized. Few things in medicine are as effective as polio vaccine, and prevailing technologies are regularly supplanted by somewhat more effective technologies. Furthermore, the society cannot wait for high technology to solve costly health problems, for research is slow and those threatened by diseases with unknown etiology may need expensive support systems.

COMPLEXITIES IN THE PROCESS OF TECHNOLOGY DEVELOPMENT

The categories distinguished in the previous section are adequate to classify a large number of the activities that precede widespread acceptance of a new medical technology. Categories similar to those presented here are commonly used in making decisions about resource allocation for biomedical R&D, establishing policies and priorities, and organizing institutional capabilities. It must be recognized, however, that such a classification scheme is highly idealized. If appropriate and effective programs of assessment are to be implemented, at least two severe limitations to the scheme must be considered:

First, the history of science and medicine shows that basic research, applied research, development, and even diffusion often progress simultaneously and not sequentially (29). Investigators approach the development of new technologies from many viewpoints and often independently; useful innovation most often results from the confluence of separate streams of basic, applied, and clinical research. Also, later steps in the process feed back on earlier ones—for example, new technologies may make new types of research possible, or clinical experience may suggest fruitful new research possibilities. Retrospective studies may discoverer even impose-a logical order that could not have been discerned while development was in progress. Thus, programs of assessment may aim for but not always achieve examination of the development of new medical technologies "at the earliest possible point."

Second, many programs of R&D cannot readily be fitted into one of the four categories discussed above. The boundaries between categories are indistinct, creating problems for attempting to understand the R&D process, and for attempting assessment or control. Although one can do little here to sharpen these boundaries, one can point out why and in what ways they are fuzzy.

Basic Versus Applied Research

Many types of research can easily be classified as basic, and others as applied, but there is a vast middle ground that. cannot be easily classified.

One problem in defining basic and applied research on biological systems can be illustrated by comparing biology with the physical sciences. Physics and chemistry are both sufficiently mature to support "theoretical" enterprises, which deal entirely with abstractions, usually mathematically.

Biological processes, on the other hand, have not yet been adequately described and cataloged in preparation for the creation of a firm, predictive theoretical base. This is not to say that biological principles of great generality have not been discovered; they have. With few exceptions, however, biologists are still experimentalists; they are not theoreticians.

Biology and the physical sciences differ at the other end of the R&D spectrum as well. Often, massive pieces of capital equipment are developed by engineers from a base of knowledge in chemistry and physics. Prototypes must be built in industrial laboratories and often require organization and resources on an industrial scale. Medical technologies are, however, usually small enough to be built with limited resources and by small groups of workers. Workable developmental models of most medical technologies can be created in the laboratory or at the medical center; pilot plants are seldom required. Development of medical technologies may of course be enormously expensive, but the physical scale is limited.

Thus, many research activities in the physical sciences are theoretical and therefore indisputably basic, or are industrial in scale and therefore clearly applied. In biology, nearly all research activities fall into a middle ground where classification is more difficult.

There are other problems of classification as well. Basic research is usually defined as an attempt to understand nature, while applied research is seen as an attempt to control nature. However, the aims of a particular project and its outcomes may be significantly different. Basic researchers sometimes acquire knowledge or devise techniques that have immediately applicable practical ends; applied researchers frequently make discoveries that lead to new understanding. Furthermore, the very concept of experimental science runs contrary to the distinction between understanding and control. Basic researchers must devise ways to manipulate nature if they are to perform experiments. The techniques they develop may have immediate practical as well as experimental utility.

Several attempts have been made to formulate characteristics that can adequately distinguish between basic and applied research. Lewis Thomas, for example, has claimed that "surprise is what makes the difference." He contends that basic research requires "a high degree of uncertainty; otherwise it isn't likely to be an important problem." Applied research, he feels, requires "a high degree of certainty from the outset" (197, p. 118). Although appealing, this distinction may not be practically useful. It does not completely describe either the basic researcher, who is not working in a vacuum and may be quite certain of what he hopes to achieve, or the applied researcher, whose activities are also creative, intellectually challenging and, in fact, sometimes quite uncertain.

Comroe and Dripps, in a study of the sources of knowledge that lead to medical innovation, make the distinction between "clinically oriented" and "nonclinically oriented" research (46). However, since funding agencies stress clinical relevance in their application forms, and since all biological research is potentially relevant, the purported orientation of a research project or publication does not seem to be practically useful in devising a meaningful distinction. A study by the Battelle Columbus Laboratories, with aims similar to the work of Comroe and Dripps, distinguishes between "mission-oriented" and "nonmission-oriented" research (10). This distinction, which is sometimes used by the NIH in describing its programs, is subject to the same caveats as that of Comroe and Dripps.

Thus, although many research programs can easily be classified as "basic" or "applied," there are some activities that defy categorization. This fuzzy line creates great problems for those contemplating assessment. On one hand, "basic" research can masquerade as "applied" research to compete for funding in an increasingly goal-oriented system; on the other hand, "applied" research can masquerade as

"basic" research to escape the pressures of social accountability that increase as one gets closer to practical application of knowledge.

Applied Research Versus Clinical Testing

Applied research performed in vitro (outside of the body) or using animals raises fundamentally different problems from clinical testing on humans, and different forms of assessment are appropriate for these two activities. Ideally, applied research and development of new medical technologies would depend on tests in animals, with clinical testing on humans occurring only when development is thought to be complete. However, some testing on humans is occasionally required well before a new technology has been completely developed. In some cases, work on animals cannot anticipate the special problems that human anatomy and physiology pose. In other cases, the uniquely human ability to respond verbally is required to assess the success of a new technology and to determine the directions that further developmental effort should take. Finally, some technologies are developed by practitioners who have patients available to them, but have neither the facilities nor the expertise for work on animals. For these reasons, activities of applied research and clinical testing are often inextricably linked.

Clinical Testing Versus Clinical Use

Finally, it is not even possible to separate the processes of research and development from those of diffusion and adoption when considering medical innovations. "Experimental" use of new technologies can involve rather extensive diffusion, and because this often occurs in university-affiliated medical centers to which physicians and the public look for guidance, such use can materially enhance pressure for widespread adoption. Also, scientific assessment of medical technology for safety and efficacy requires people, sometimes large populations. This rather wide diffusion before clinical proof inverts the expected order of testing and then diffusion.

The blurred distinction between development (or experimental use) and practice (or therapeutic use) is illustrated by the case of mitral valve surgery (192). The mitral valve of the heart can become constricted as a result of rheumatic fever. Brunton, a British cardiologist, proposed a surgical technique for reopening the valve in 1902. After preliminary tests on animals had been completed, surgery was carried out on 10 human patients between 1923 and 1928. Results were discouraging, and a period of 20 years elapsed before human use was again attempted and eventually proved successful.

As a result of this informal "clinical moratorium," the early trials can be classified retrospectively as "experimental," but the distinction was not clearly made at the time. It is often impossible to regard developing or newly developed procedures as either purely experimental or purely therapeutic. It is more realistic to think in terms of a process, with an experimental procedure at one end of a spectrum, a therapeutic procedure at the other end, and many steps in between.

A current example of this dilemma is the renal transplant, still hampered by problems of graft rejection. Research physicians acknowledge that renal grafting still provides a "fertile area for clinical investigation," meaning it is still experimental. On the other hand, transplants are gradually becoming clinically accepted and therefore more "therapy" than "experiment" (69, p. 73).

Presently, an informal evaluation by each physician is the primary method of classifying new procedures as "experimental" or "therapeutic." Of course, as indicated, there are many forces acting on the individual physician in making such a decision. In particular, one can highlight the "desperation-reaction model" discussed above: a clinical fervor to do something for desperately ill patients, at the same time producing a medical advance. Furthermore, some third-party payers will not reimburse for procedures that are designated as "experimental. " Formal criteria for distinguishing between experimental and therapeutic use have been proposed (106, p. 237) (114), but current medical practice does not permit a clear distinction in many cases.

DEVELOPMENT OF DIFFERENT TYPES OF MEDICAL TECHNOLOGY

Different types of medical technology are developed in different places and in different ways. These variations pose problems for assessors and must be considered if programs of assessment are to be realistic and effective. The following paragraphs describe some features unique to the development of the four categories of medical technology that were distinguished in chapter II: drugs, equipment, technique, and procedure.

Drugs

The link between basic biomedical research and drug development is often clear. Drugs develop from a basic knowledge of organic chemistry, pharmacology, and human pathophysiology. Occasionally, knowledge is sufficient to permit the rational design of new drugs. For example, the development of polio vaccines, which are classified as drugs for purposes of this report, was based on a solid foundation of knowledge derived from basic research. (See the case of vaccines inch. II.) Basic research in biochemistry and bacteriology has also permitted prediction of successful strategies for synthesizing some antibiotics. In many other cases, basic research has led to the development of new drugs even without complete knowledge of their mechanisms of action.

Some drug companies maintain institutes for and support work in biochemistry and pharmacology. However, much of the basic research that precedes the development of new drugs is supported by Federal agencies, especially NIH, and takes place in universities and medical centers. A study of 68 pharmaceutical innovations showed that over half were made possible by discoveries made outside of the drug industry, in universities, hospitals, and research institutes (129, p. 185). Although some applied research targeted to the development of new drugs is funded by NIH, most is supported by private industry.

Before marketing, new drugs must meet standards for safety and efficacy that are set and administered by the Food and Drug Administration. These regulations, mandated by the Food and Drug Act Amendments of 1962, constitute almost the only legal standards that new technologies must meet **(164). New** techniques and procedures are not at present similarly regulated. Some of the testing that precedes certification can be done on animals in the laboratory. Tests on human subjects are also required, and drug companies sponsor tests on volunteers in a variety of settings, including prisons. Ethical standards for clinical tests of drugs, long left largely to the discretion of developers, are currently being reviewed by the National Commission for the Protection of Human Subjects.

Once marketed, drugs are often accepted rapidly by practitioners, as seen in the adoption of new chemotherapeutic drugs for the treatment of leukemia (fig. 32?) (209). Adoption is speeded by a number of factors, including the low cost of drugs compared to many other technologies and the massive advertising campaigns frequently mounted by the pharmaceutical industry. A study of a new antibiotic showed that 60 percent of physicians had adopted it within 8 months of its release (39).

Equipment

Research in biomedical sciences such as physiology and anatomy provides knowledge that permits development of devices that can be used for diagnostic, preventive, and therapeutic purposes. However, much of the basic research that leads eventually to the development of equipment is performed outside the biomedical research sector in such fields as physics, chemistry, and electronics.

The successful development of equipment requires a combination of expertise in both the biological and the physical sciences. The application of the tools of mathematics and the physical sciences to biological and medical problems is called biomedical engineering (157). Biomedical engineers have achieved spectacular successes in recent years, but numerous difficulties beset their work. One is that most physicians are not trained to collaborate effectively with engineers to solve problems, or even to recognize that a technological solution might be feasible. Few individuals have sufficient training in both biology (or medicine) and engineering to work alone (82). Also, in a marketplace oriented to profits, medical equipment manufacturers may develop and overproduce equipment of questionable utility or fail to support the development of types of equipment that are needed (204). Additionally, engineers are trained to think in terms of physical performance characteristics and technical precision but often fail to evaluate new technologies on the basis of how they affect the health of populations or individuals. Finally, many feel that Federal health agencies are reluctant to fund private companies to do research or to develop new medical technologies that might return profits to those companies.

In the area of medical equipment, funding for applied research and development is largely private. There are some Federal programs to facilitate research and development of certain devices (94, 128). They are often fragmented, however, as shown by the complex pattern of Federal investment in the development of medical diagnostic ultrasound (table 1). Furthermore; it is frequently difficult to document these diverse sources of funds, and compilations such as that shown in table 1 are rare.

Once developed, medical equipment is tested in a variety of locales. Many items can be adequately tested in the laboratory, using healthy volunteers or small samples of blood or tissue. For equipment that is risky or requires invasive procedures for its operation, testing usually occurs in hospitals. Tests of safety or efficacy have not been legally required before new equipment can be marketed. However, the failure of some devices (76, 77) has led to the formulation of a medical devices bill that was recently enacted (P. L. 94–295) and will require premarket demonstrations of safety and efficacy for some medical devices (55, 56, 68).

Recent studies have begun to shed some light on how large pieces of capital equipment are acquired by hospitals. Diffusion may follow the S-shaped curve for

Table 1.—Funding for Research and Development in Ultrasonic Imaging Diagnostic Instrumentation by Federal Agency, 1975 (2)*

National Bureau of Standards	$100,000
Department of Defense:	
Army	120,000
Navy	285,535
Energy Research and Development Administration	80,000
Department of Health, Education, and Welfare:	
Food and Drug Administration.	841,459
Health Resources Administration	25,000
National institutes of Health:	
National Cancer Institute	418,514
National Heart and Lung Institute	2,851,165
National Institute of General Medical Sciences	1,530,166
National Institute of Arthritis, Metabolic and Digestive Diseases	118,964
National Eye Institute	439,297
National institute of Necrologic and Communicative Disorders and Stroke...	379,905
Division of Research Resources	20,000
Division of Research Services	50,000
Social and Rehabilitation Service	24,851
National Aeronautics and Space Administration	360,000
National Science Foundation	818,850
Veterans' Administration	20,500
Total	8,484,206

● Doesnot include all intramural programs, which are considerable.

some expensive technologies, as was the case for adoption of the intensive-care unit (fig_. 3A) (47). The large initial investment required may compel cautious adoption. On the other hand, there is evidence that hospitals may sometimes adopt large and highly visible types of equipment for purposes of prestige, without sufficient consideration of medical utility. Little is known about the diffusion of less costly types of equipment.

Technique

Medical techniques develop largely from knowledge gained through clinical experience. The spectrum of research and testing activities is difficult to separate. Testing for efficacy maybe minimal and informal. These developments depend on creative clinicians and probably encompass thousands of small incremental changes in medical practice, which diffuse in unstudied ways. There are special problems in assessing this part of medical practice because the steps in development and diffusion are so informal and ill-defined.

Procedure

A procedure is the combination of technique with drugs and/or equipment. Its development is correspondingly complex and depends on research and development in several different fields. The many bodies of knowledge and lines of research that led to the development of one complex procedure, cardiac pacemaker implantation, are indicated diagrammatically in chapter II (fig. 1).

New procedures are often tested in university-affiliated hospitals. Some tests are supported by Federal research funds and private funds. Considerable funding also comes from service funds (such as private insurance and Government financing programs), especially in cases where the distinction between experimental and therapeutic use is not clearly made. Some medical procedures have been submitted to formal clinical trial, but this is probably more common for new procedures than for existing ones.

There are presently few formal mechanisms to prevent unsafe and useless procedures from being used in medical practice (9, 17, 112, 130, 155). As noted, clinical trials are not often done. Hospital tissue committees, which screen operative results to assure that operations have been appropriately done, can sometimes assess the merits of new procedures, albeit in nonquantitative ways. Collegial standards and the growing threat of malpractice litigation provide strong but nonsystematic deterrents to the widespread use of procedures whose efficacy has not been demonstrated.

FUNDING AND PRIORITY SETTING FOR RESEARCH AND DEVELOPMENT

Biomedical research and the development of medical technology account for about 4 percent of the expenditures in the health area in the United States, or an estimated $4.5 billion per year (144). Federal obligations for health research and development were about $2.8 billion in 1974, or 62 percent of the total. State and local governments invest $284 million. The remaining $1.4 billion is derived from the private sector: $227 million emanates from private nonprofit agencies, and approximately $1.2 billion from industry. Sources of support for biomedical research and technology development are summarized in figure 4.

At the Federal Government level, the sources of health research support are myriad. Table 2 shows the Federal health research budget for 1975, indicating that the Department of Health, Education, and Welfare (HEW) controls more than 75 percent of the total, with the National Institutes of Health (NIH) predominant in HEW. NIH alone controls 63 percent of the Federal expenditure for health research.

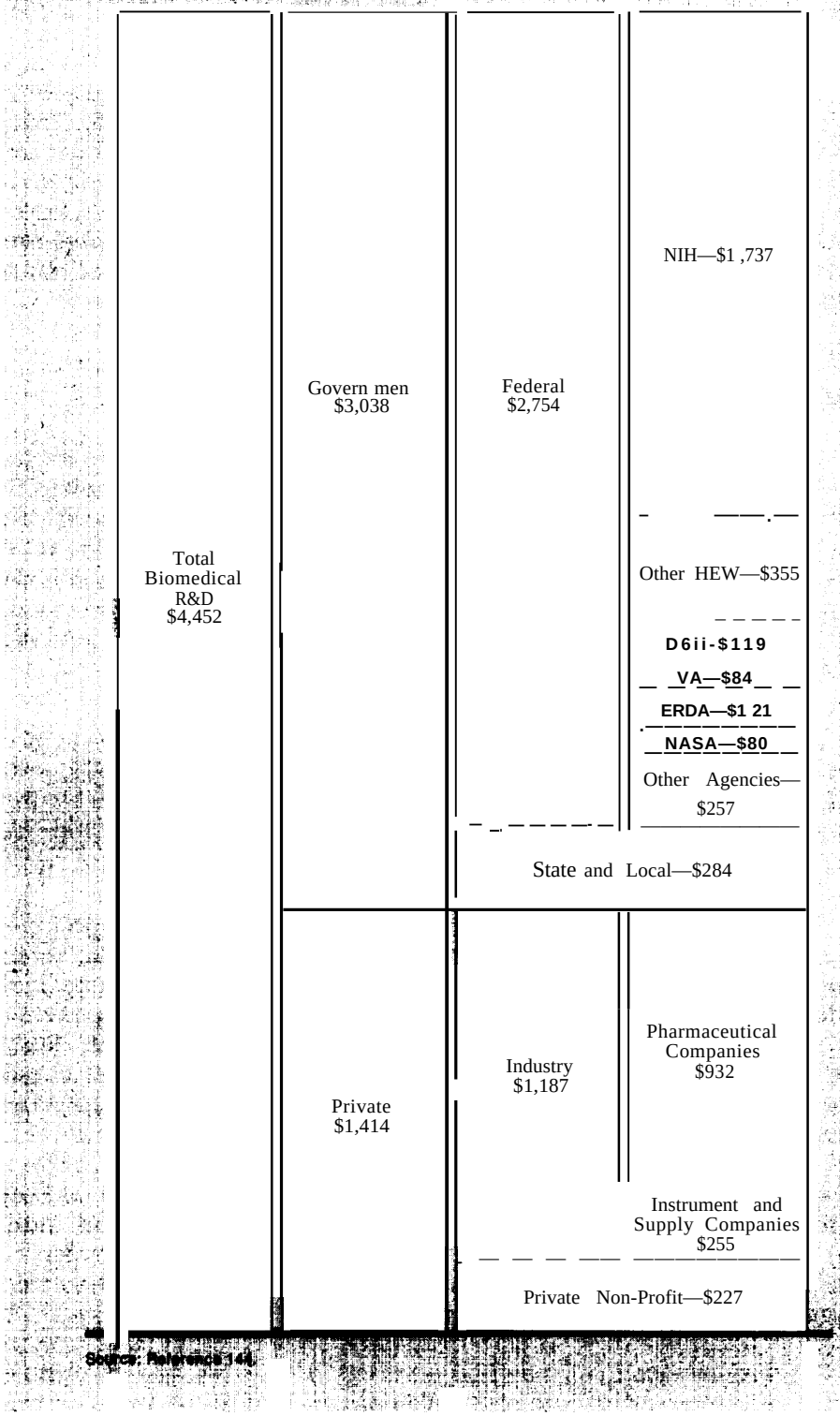
In the private sector, the industry figure includes $932 million invested by the 135 members of the Pharmaceutical Manufacturers Association, which includes some nondrug manufacturers (186, p. 26). An estimated 1,500 firms produce medical devices and instrumentation (55); companies manufacturing medical supplies and instruments invest an estimated $144 million in health R&D, and the electronics industry and the nonprescription drug industry invest an estimated $91 million in health R&D (144). The industry R&D is conducted largely “in-house” in research laboratories.

Basic research is largely funded by the Federal Government, although some is funded by private foundations, voluntary health agencies, and industry. Drug companies invest an estimated $90 million a year in basic research (186, p. 24). Other industries spend little on basic research (129, p. 20). A high percentage of the Federal investment in basic health research comes from NIH.

Applied research is funded by a variety of sources. Much of the support for applied research and technology development is derived from private industry.

Figure 4—[illegible]

(Millions of Dollars)



Source: Reference 144

Table 2.+ Federal Outlays for Health Research by Agency, 1975*

[Dollars in millions]

Department of Health, Education, and Welfare (total)		**$1,867**
Health Services Administration	9	
Health Resources Administration	58	
Alcohol, Drug Abuse, and Mental Health Administration	114	
Center for Disease Control	42	
National institutes of Health	1,598	
Food and Drug Administration	27	
Assistant Secretary for Health	4	
Social Security Administration	—	
Social and Rehabilitation Service	2	
Other HEW	13	
Department of Defense		**104**
Veterans Administration		**93**
Department of Housing and Urban Development		**—**
Department of Agriculture		**47**
Environmental Protection Agency		**20**
National Aeronautics and Space Administration		**59**
Energy Research and Development Administration		**143**
Department of Labor		**1**
Department of State		**—**
National Science Foundation		**44**
Department of the Interior		**35**
Department of Transportation		**15**
Department of Justice		**—**
Other agencies		**31**
Agency contributions to employee health funds		**—**
Total outlays for health, 1975		**2,459**

● **Because obligations and expenditures are calculated separately, the figures in this table differ somewhat from those in fig. 4.**

Source: **Table K-28 in** *Special Analyses, Budget of the Uniled States Government, 1977.* **Washington, D.C.: U.S. Governmen tPrintingOffice, 1976, p. 215.**

Most of the industrial R&D budget is spent on applied research and technology development with priorities usually determined by the perceived potential for profit (129, p.20).

Government investment in technology development is also considerable, although fragmented and largely undocumented. Research conducted or supported by Federal agencies such as NIH is often aimed directly at the development of new medical technologies. (See the case of the implantable artificial heart in ch. II.) Another important role of the Federal Government is in cooperation with private industry, through incentive or procurement programs. For example, the Veterans Administration and the Department of Commerce have been active in encouraging development through procurement programs (137). The National Science Foundation, in cooperation with the Veterans Administration and the Department of Commerce, has developed incentive programs. These programs generally are not coordinated among Federal agencies.

The mechanisms of NIH are organized to recognize the hazy line between basic and applied research. NIH's mission is to advance the health and well-being of man by—

- Enlarging knowledge and understanding of the normal and pathological processes of the human body; and
- Developing ways in which the providers of medical care can safely and effectively intervene to prevent, treat, or cure diseases and disabilities (146).

NIH has classically pursued this mission through supporting— "

- Biomedical research and development, including, in some instances, demonstration and control programs,
- Research training,
- Development of research resources, and
- Communication of research results (146).

These responsibilities are carried out through 11 categorical institutes, each of which awards grants and contracts, as well as carrying out "intramural" research (on the grounds of NIH).1 Each categorical institute is charged with supporting research aimed at eventual understanding and amelioration of a particular class of diseases.

Allocation of funds at NIH occurs at three levels:

1. From an overall budget, appropriations are made to each of the institutes. This is done by Congress: each institute is funded through separate appropriations.
2. Within each institute, funds are divided among various areas with competing claims to scientific, social, and medical importance. Each institute has a national advisory council, which is responsible for approving or disapproving grant awards and is supposed to consider such factors as potential importance of proposed research. Other decisions about allocation of funds within each institute are made by the administration of the institute, by the Director of NIH, and by Congress through special provisions in authorization or appropriation bills.
3. Awards are made to investigators or teams who compete for research funds. Funds are disbursed in the form of grants or contracts.

There are several important differences between grants and contracts. Grant proposals may be submitted on any topic that a researcher feels is relevant to the mission of NIH. The proposals are reviewed by 52 "study sections" at NIH, groups of outside scientists organized by discipline or scientific area. These study sections, or peer review groups, assess proposals for scientific merit, and assign them priority scores. The proposals are then referred to the appropriate institute, where the national advisory council ranks them, generally following closely the order determined by the study sections. NIH awards the funds based on this ranking. Grants may be awarded only to nonprofitmaking entities.

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[1]The National institute of General Medical Sciences has no intramural program.

Contracts are usually used for support of research and development when one or more of the following considerations exist (149):

- The awarding institute or division has identified a need for certain research work to accomplish its mission and has determined that the work must be done outside its own facilities. This is sometimes referred to as targeted research, and the philosophy is that the NIH staff should look at the field of biomedical science and target funds to areas that need further development or are ready for development. . .
- Funds are awarded to profitmaking institutions. Under current regulations, grants cannot be awarded to such organizations.
- The objective is the acquisition of a specified service or end product.
- The collaboration of a number of institutions must be obtained and work must be coordinated or carried out in a comparable manner by all so that the data collected can be combined for statistical analysis, such as in clinical trials.

Contracts are awarded at the initiative of the bureaus, institutes, divisions, the Clinical Center, and the Office of the Director of NIH. When a contract is to be awarded, a Request for Proposal (RFP) is developed by NIH staff based on a perceived need. These RFP's are published and distributed, and the proposals received are reviewed by special groups of outside scientists assembled for that purpose. National advisory councils usually are not involved in the awarding of contracts but are kept informed of contractual activities of the institute they serve. The awarding unit participates in the direction and control of the contracted work to the degree necessary to accomplish its mission.

In 1974, $765 million was distributed by NIH in the form of regular grants, $335 million as contracts, and $246 million as center grants (144). About 10 percent of the NIH budget supported the intramural research program. The Director of NIH has estimated that 27 percent of NIH dollars supports basic research (70).

Clinical testing is funded by a variety of sources. Private industries, particularly drug companies, sponsor a large amount of clinical testing of new technologies, including some formal clinical trials. Federal agencies also support clinical testing. In **1974,** for example, NIH supported 1,080 clinical trials at a cost of approximately $168 million; 65 percent of these were controlled trials (148). NIH also supports testing of new technologies through grants to medical centers in which clinical testing is a major activity. For example, NIH now funds centers in which heart transplants are carried out. NIH also funds significant demonstration and control programs in communities around the Nation, especially in cancer control and heart disease control.

Some clinical testing is also supported by service funds—that is, money appropriated for health-care delivery. For example, an insurance company may not cover a procedure that is clearly experimental (such as a heart transplant), but it will pay for the use of the operating room or for the cost of hospitalization. Furthermore, some technologies that are in fact being developed or tested are not formally classified as experimental and are thus eligible for reimbursement from insurance companies or Federal programs such as Medicare.

The present pattern of support for biomedical R&D raises several problem~ that must be considered if developing medical technologies are to be properly

assessed. First, Federal support for biomedical R&D is administered through a bewildering variety of agencies. Compilation of the budgets and agenda of these agencies, a formidable task, is a necessary prerequisite to comprehensive programs of assessment. More information about the effect of Federal programs on private investment is needed if the results of assessment are to be useful. As discussed in a report prepared by the Rand Corp. (29), Government funds administered in different ways can encourage, discourage, or displace private investment in R&D. If assessment of Government programs results in altered allocations, the effects of these alterations on industrial expenditure must be considered. Finally, most of the targeted development of medical technology currently proceeds in the private sector, supported by industry, and motivated by the quest for profit (129, p. 20). Programs of assessment aimed specifically at Federal agencies will inevitably be incomplete.

LENGTH OF TIME FOR THE DEVELOPMENT AND DIFFUSION PROCESS

There are, inevitably, lags between the time when an idea or innovation is conceived and the time when a technology is introduced into practice. The lag should be neither too short nor too long. If too short, it may be that the technology was not completely developed or tested before it was introduced. If too long, patients who might benefit might be needlessly deprived of appropriate therapy.

On the question of long lags, Peltzman (164) has calculated the costs that would have accrued had appropriate therapies for tuberculosis (antibiotics) and mental illness (tranquilizers), and preventive measures for polio (vaccine) been delayed for 2 years. The purely monetary costs, in terms of lost productivity, would range in the billions of dollars; social or human costs are incalculable. Although no detailed analysis has appeared, one might imagine that costs of premature introduction of inefficacious therapies are also enormous.

Unfortunately, there is no reason to think that lags could be shortened appreciably without sacrificing caution. Comroe (44) and a study by Battelle Columbus Laboratories (10, 11) have calculated duration of lags in development of 186 innovations and have analyzed reasons for those lags. In both studies, median lags from "conception" to availability were 10 years or less.

In another study, lags from discovery to innovation were compared for various nonmedical technologies and pharmaceutical innovations. While all technologies had lags averaging 14 years, and technologies in the petroleum industry had lags that averaged 11 years, new drugs were introduced only 5±4 (mean ± standard deviation) years after the time of the discovery that made innovation possible (129, p. 181).

In most cases studied, reasons for long lags were limitations of knowledge or lack of supporting technology. This seems to indicate that the lag has been wrongly defined, since the application was impossible for scientific technical reasons. For example, Battelle considers that there was a long lag between conception and clinical application of the idea of kidney transplantation. However, immunosuppressive therapy, a necessary prerequisite to clinical success, was not available until shortly before human kidney transplants were attempted. Apparent lags can also result from delayed adoption of available techniques. Studies of the quality of

medical care indicate that the most appropriate diagnostic or therapeutic procedures are often not used in medical practice; however, these cannot properly be considered lags.

One cause for lags pointed out by Comroe and by Battelle is a failure of communication: loss and subsequent rediscovery of important ideas, resistance to innovation by uninformed physicians, or academic skepticism to challenging new ideas. Some ameliorative measures might be applied in this area.

The Overview Cluster of the President's Biomedical Research Panel (198) has also examined the question of whether excessively long lags have occurred. Examining a representative list of the therapeutic and diagnostic advances of the past 25 years, the report concludes that the progress from discovery to application appears to have occurred in a reasonably timely and orderly fashion. This does not mean that in some cases lags might not have been shortened by applied research or targeted programs, but evidence that this might be true is lacking.

On the other hand, there is the question of lags that are too short. There are great social, economic, and human costs attached to prematurely accepting technology. In the present medical system, development and testing are often not completed before a new technology is introduced; examination of social impacts is almost never done.

The reason for this lies in the present system of health-care delivery (29, 72, 83, 208). The medical market is not a free market, with private consumers buying from those willing to supply the technology at the market price. In fact, there are numerous deviations from the free-market model. There are few sellers of either service or technology and many barriers to entry in the form of educational requirements and licensing. Regulation of firms, which is increasing, is another barrier to entry. Sellers, especially physicians, cooperate with each other and do not compete for the lowest price. The public is ignorant of what is available and is unlikely to become educated, given the unclear goals of the system and the complexity of medical care. Physicians also have no incentive to hold down costs in a system where almost the entire population has insurance coverage for hospitalization and surgery. Externalities such as controlling epidemics or improving the economy complicate the medical market further. And finally, the position of the physician is remarkable. The hospital administrators depend on his expertise and follow his advice in purchasing. He also makes most of the decisions for the patient, especially when these involve expensive diagnostic or therapeutic procedures. The physician, trained to deal with crises and to be instrumental, wants to provide everything possible for his patient (195).

These features of the medical market all combine to produce incentives for premature acceptance of incompletely developed or tested technologies. Premature acceptance may have occurred in such cases as radical mastectomy and anticoagulants for myocardial infarction (see ch. II).

Thus, attempts at assessing the development of biomedical R&D must take account both of the possibility that some medical technologies are delayed in their development and the certainty that other technologies are diffused prematurely, before they are completely developed (84). It must be recognized that many of the "pressures for premature acceptance arise in the health service system and therefore that assessment of R&D, while undeniably important, may fail to deal with many of the fundamental problems that motivate this report.