library of 36,000 displays. In the coronary artery system the displays are being revised constantly as new experience is gained. These revisions, made by the computer, provide directly authoritative information necessary to make decisions on subclassification (diagnosis), prognosis, and managment for individual patients. Computer simulation of clinical cognition has introduced an important "synthesis" concept. Here the final displays do not exist in a preformed set but must be built up by appropriate combination of small modules. The computer problem is to select and apply knowledge from its stores when it is required, thus freeing the programmer from the impossible task of prior specification of all possible contingencies. This concept of synthesis is also employed in INTERNIST which combines it with elements of probabilistic computations and pathophysiologic flow charts to build and select displays. INTERNIST keeps track of and displays both explained and unexplained findings. The hepatitis data base uses the computer for simplifying text editing and updating and for convenience of storage, retrieval, and dissemination.

In this brief review of examples of some of the classes of computer systems being developed to support diagnosis, prognosis, and therapy, there is evident a clear evolution of both an increasing sophistication of systems and a progressive recognition of the complexity of the problems. Also changing is the man-machine relationship. What may have been considered earlier as an adversary relationship is evolving through greater recognition and respect for the unique capabilities of each into a synergistic collaboration. Whatever the limitations of existing systems, the data justify an optimistic view of the future of this collaboration in medicine.

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The Road from Research to New Diagnosis and Therapy

Julius H. Comroe, Jr.

My career goal was teaching—not research. When I finished my internship, I became an instructor in pharmacology at the University of Pennsylvania because it was the best teaching department in the School of Medicine and I wanted to be part of it. (It was also the best research department, but that was a secondary factor in my decision.)

One learns a great deal by teaching, especially if one has bright, inquisitive, uninhibited students. The first thing that I learned (and I learned it the first day) was that I did not know the answer to many of their questions. The second thing I learned was that, for most of their questions, no one else had good answers either. In short, the areas of ignorance were far greater than instances of solid, real knowledge. That was in the mid-1930's. We could determine the specific type of pneumonia bugs in a patient, but we could not treat the patient because we had no sulfas or penicillin. We had x-rays that could detect shadows in lungs, but except for the vital capacity test, we had no tests of the function of the lungs. We had iron lungs (even built for two) for polio patients with respiratory paralysis, but we had no vaccine to prevent the disease in the first place. We could diagnose pulmonary tuberculosis, but we had no way to cure tuberculous patients because we had no streptomycin or para-aminosalicylic acid or isoniazid. We thought we were helping (or possibly curing) patients with tuberculosis by insisting on two plus years of bed rest in sanitoriums and by pneumothorax, but we know now that we really were not. We knew when a patient was not breathing and needed resuscitation, and the Red Cross had taught everyone in the country how to use the Schafer method of prone-pressure artificial respiration—until someone made actual measurements of the volume of "good air in" and "bad air out" and found it inadequate to sustain life; only then were adequate methods devised.

We could measure high blood pressure in the systemic circulation and diagnose hypertension there, but we could not measure pulmonary arterial blood pressure and diagnose pulmonary hypertension because Cournand and Richards had not yet done their basic studies of cardiac catheterization. We had no methods at all in the mid-1930's for resuscitation of the stopped heart and no artificial pacemaker to make a too-slow heart beat at a normal rate. We could tell, by looking, when newborn babies could not breathe properly and were blue, but we did not know why and most of them died; now research has shown us what causes the respiratory distress syndrome, and knowing that, we can treat it effectively and most of these babies now live.

My father, practicing internal medicine in the mid-1930's, had a few drugs (digitalis, insulin, arsphenamine, vaccines) that improved, cured, or prevented disease, and a few more (aspirin, morphine, barbital) that relieved symptoms of disease. Mainly he provided his patients with hope, encouragement, relief of suffering, and laxatives to keep their bowels open, and he recommended excision of foci of infection (mainly tonsils) and plenty of fruit juices (he had no faith in chicken soup). I, teaching in the mid-1930's, had few honest answers to

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Table 1. Steps between a new idea and full clinical application.

1. Man has an original idea or observation, or an important modification of a current concept
2. Knowledge must already exist or be developed in one or more related or unrelated sciences (for example, biology, physics, chemistry, mathematics, engineering, social sciences) that provides the scientific base, the concepts, the techniques or apparatus necessary to test the new idea
3. Man with idea (see step 1, above) learns of existence and pertinence of requisite knowledge (see step 2)
4. Man with idea now needs funds for experimental work to test his idea
5. Man obtains data, draws conclusions, writes manuscript, and submits it to journal for publication
6. Reader response to published article (does not read it; reads it but ignores it; reads it and repeats work)
7. Confirmation with or without modification and extension, or contradiction and refutation
8. New idea enters intellectual sphere of clinicians, of drug companies, of manufacturers of instruments or apparatus
9. Initial clinical trial (phase I) after approval of Committee on Ethics and Human Investigation
10. Application to Food and Drug Administration for phase II and III clinical trials
11. Publication of clinical papers; reports of successes and shortcomings
12. Approval by Food and Drug Administration for use by physicians
13. Widespread use of new drug (or procedure) by physicians
14. Further refinements of indications for use; cataloging of undesirable effects
15. Public acceptance of value of new therapy, which replaces no therapy or previous therapy
16. Continuing search for improved drugs or procedures

student questions except "I don't know." It was then that I realized what research was all about. Research meant that the teacher did not have to say "I don't know" year after year. Research meant that a physician did not have to say, year after year, "I can't cure you" to the vast majority of his patients. In short, research meant the end of a long static period in medicine—because every one of the great advances in modern medicine and surgery has come through research.

"Delivery of Health Care"

Why this long introduction that merely repeats what surely all of you already know? Because our attitudes and thinking are governed to a great extent in 1978 by catchy Madison Avenue phrases. One of these is "delivery of health care." What does this really mean? To me, delivery means distribution of something we already have, something that is stored either in a warehouse, a drugstore, a hospital, or even a physician's head. Those who prefer longer words would speak of it as delivery of the physician's present "armamentarium." A military analogy would be: if we have atomic bombs or nuclear missiles, we can both deliver them and at the same time try to improve the delivery system. But if we do not have them at all, the world's most perfect delivery system cannot endow us with the capability for nuclear attack.

So there are two ways to improve the nation's health: one is seeing to it that we deliver what we already have in hand, and do it fairly, evenly, promptly, intelligently, and guided by the best current medical judgment; the other is to find something better to deliver—earlier diagnosis, preventive measures, more effective treatment—and to recognize that these come through research and not through Madison Avenue slogans. We have become so enamored of the new phrase "delivery of health care" that we have already forgotten that we can deliver only what we have, only what we have already learned, and only what we now know. We forget that we will never have anything better or completely new to deliver—another disease to prevent, another disorder to cure—until we discover something new, and that is what we call research.

"Health Maintenance"

Another Madison Avenue catchphrase that needs some clarification is "health maintenance." My dictionary defines health as "physical and mental well-being; freedom from defect, pain or disease." It defines maintenance as "continuing or preserving a given condition." Health maintenance therefore must mean preserving in perfect health those who are now enjoying perfect physical and mental health. Because I know very few people to whom this applies on any given day or in any one year, this highly laudable objective, by dictionary definitions, probably applies to fewer than 10 percent of our population.

But, you may argue, the ills of the other 90 percent would be fully manageable if only the unhealthy would take the simple step of consulting a physician and following his advice to the letter. Not true. In 1978 our areas of ignorance about the human body and its malfunctions still greatly outnumber our areas of complete or sufficient knowledge, and the "health industry" (really the "sickness industry") has become the largest in the country. Unfortunately, experts testifying before congressional appropriations committees believe that the best strategy by which to obtain a larger budget for health or research is to tell anecdote after anecdote about the magnificent successes of medicine rather than to relate honestly how far we still have to go. Science writers are equally to blame for headlining daily "breakthroughs"; if one of them wants to win a Pulitzer prize in journalism, all he need do is follow up each "breakthrough" reported in the press and later write an article on the state of medical breakthroughs after 10 years. If I were looking for a research problem, I would do this myself.

I could list at length what we do not know: the cause of cancer, of hypertension, of atherosclerosis, of mental disorders, or of congenital heart disease; how to relieve low back pain, allergic disorders, arthritis, or even the common cold; how to transplant organs predictably and successfully; how to deal with major or even minor viral infections. A full list would use up too much expensive paper, and *Science* is already printing some pages with margins of only 1 to 2 millimeters. You can make a list for yourself of what we do not know by looking at your recently dead or dying friends and acquaintances, and the ones who wish they were dead, the ones with chronic disorders that will not let up and the ones who reply to your casual "How are you today?" with "so-so," or "not too bad," or "miserable." Or look through the Yellow Pages in your phone book and under social services and welfare organizations; you will find the words retarded citizens, alcoholism, cancer, blind, suicide, developmentally disabled, blind babies, epilepsy, emphysema, drug abuse, cerebral palsy, crippled children, deaf, mentally retarded, leukemia, multiple sclerosis, muscular dystrophy, visually handicapped, aging, heart, lung, and mental health. Obviously, Americans think there are a lot of medical problems still unsolved; why else would they be raising money each year to solve them? And even John Knowles, president of the Rockefeller Foundation and the staunchest advocate of the individual's responsibility for preventing disease, wrote in February of this year (*1*): "The support

of fundamental biomedical research has also flagged alarmingly in the past several years. The basic biological mechanisms of our most common diseases are still not well enough known to give clear direction to preventive measures."

If "health maintenance" does not refer to preserving the 10 percent in perfect health but rather to freezing our ailing population in whatever state of malfunction they now exist, and preventing its further progression, it probably involves 90 percent of our population. But it is then a phrase devoid of hope because it denies that we have the power to learn, to replace ignorance with knowledge, to cure the now incurable, to prevent the now "inevitable"—in short, it ignores the most important ingredient in achieving good health for most and then maintaining it, and that is research.

From Ignorance to Research to Application

Table 1 shows some of the steps along the road between the birth of a new idea or observation and its full clinical acceptance and proper use by physicians and patients. This is a compressed version of one road—a road for an idea that starts in a basic science laboratory, and eventually makes a fruitful connection with a clinical investigator. Omitted are the windings, the blind alleys, and the rocky and almost impassable parts. Rarely is the road shorter, because it is rare that someone takes one or two giant steps that eliminate the time-consuming problems.

Table 1 contains 16 steps. The first 7 involve basic or fundamental investigation which may or may not at that time be related to the clinical problem it is destined to solve. Steps 8 through 11 involve clinical investigation and often considerable participation by industry in research and development. Steps 13 through 16 include education of physicians, continued use of a new drug or procedure, refinement of its use, sharpening of its limitations, and acceptance of the new drug or procedure by patients who should be benefited by it.

Discovery: How to Promote It

Before discussing steps 8 through 15 in Table 1, I will summarize briefly data that Dripps and I obtained in an earlier study (*2*) of how the great clinical advances in cardiovascular-pulmonary medicine and surgery actually came about. Of 663 "key" investigations that were crucial to one of ten important clinical advances, 41.6 percent were not, at the time they were reported, related to that clinical advance, and 61.5 percent dealt with basic mechanisms of action of cells, tissues, or organs rather than with the diagnosis, prevention, or treatment of the disease itself. For each of the ten clinical advances, basic ideas, observations, or discoveries were essential either initially or later. Therefore to start a discussion of how to improve the nation's health at step 8 would leave a vital gap in understanding the processes of discovery and application and their interrelationships. To prevent this omission requires brief discussions of steps 1 through 7.

Although in our study (*2*), the crucial step was the first—the new idea, discovery, or observation—I know of no systematic, objective study by disinterested analysts on the selection, care, and feeding of those most likely to be innovative, creative, or inspirational scientists, the men or women who produce step 1. An old German recipe on how to make hasenpfeffer begins, "First you must catch the right rabbit." A modern recipe for promoting discovery would probably start, "First you must catch the right man or woman."

On the basis of my experience as director of a cardiovascular research institute for more than 16 years, I would enlarge the recipe to: "First identify individuals most likely to have completely original ideas, but give yourself 3 years to check on your judgment (that is, your talent in clairvoyancy). During this time, give your nominees facilities in which to work; provide an intellectual environment conducive to an exchange of ideas with scientists in many related and unrelated fields; shield them from nonproductive activities; relieve them from the time-consuming and nerve-wracking experiences of obtaining research support; and encourage them to develop and follow through new ideas regardless of the number or weight of their publications."

It takes experience to identify the right man or woman initially, self-restraint to let him make mistakes and go into and out of blind alleys, self-denial to create for him the freedom and intellectual environment that you would dearly love to have for yourself, and fortitude to say, after 3 years, "You're not going to be a step 1 man, but you're going to be a great step 7, 8, 9, 10, or 11 man."

What if he *is* likely to be a step 1 man? Is there any way of maintaining an ideal environment for him for all, or at least a considerable portion, of his scientific life? From the very beginning of the Rockefeller Institute for Medical Research (1901) and of the intramural laboratories of the National Institutes of Health, such an environment has existed for a limited number of scientists. It also exists for the career investigators of the American Heart Association, the lifetime research professors of the American Cancer Society, the lame-duck research career awardees of the National Institutes of Health, and for a small number of research professors supported by university endowments or private foundations or institutes. And recently some pharmaceutical companies have established the equivalent of research professorships in "pure research" laboratories.

I am often amazed that scientists, who insist on rigid scientific proof in their laboratories and in those of others, act on their "gut reactions" when it comes to answering questions such as how to foster discovery. It would be worthwhile to evaluate the contributions (their direct contributions and equally important indirect ones through training and inspiration of others) of American research professors (or their equivalent) since 1900 and come to a conclusion on the likely advantage to health of increasing the number of 5-year, 10-year, or lifetime research professors. I believe (gut reaction) that the advantage would be considerable, but I would like to have the facts.

Research-Research Interfaces

It was once possible to go directly from step 1 to step 13, with perhaps only a perfunctory stop at one or two intermediate steps. Withering, in discovering and using digitalis in 1785, needed little help from those in other branches of science because he himself was a botanist, clinician, mineralogist, and chemist. The interfaces in his discovery were between his own brain cells that stored information in botany, chemistry, and medicine, and these neural connections quickly enabled him to identify the foxglove as the only ingredient of a Shropshire potpourri that was likely to have potent biological activity; the century in which he lived allowed him to skip interactions with editorial boards, peer review committees, the committe on human rights, and the Food and Drug Administration.

It is rare today that one man can produce, store, recall, and relate all of the knowledge needed for a major advance in science. Let us consider the important development of open heart surgical pro-

cedures. In 1954, John Gibbon performed the first repair of a human heart while the needs of the patient's body were met by an artificial heart-lung apparatus. But many others, starting as far back as the 17th century, first had to make essential discoveries in a wide variety of fields (and Gibbon had to know and make use of these) before open heart surgery could become predictably successful (*2*). Obviously, Harvey first had to discover the circulation of the blood (1628) and Hales (1733) had to learn how to measure arterial blood pressure. For the success of ordinary blood transfusions, Landsteiner (1900) had to discover human blood groups; Hustin (1914) had to find that citrate was a satisfactory, nontoxic anticoagulant; and Rous and Turner (1916) had to learn how to preserve blood, a study that led to development of blood banks. Physiologists had to learn that a heart could be stopped and restarted ("for sure") on demand. Whole new sciences of anesthesiology, bacteriology, immunology, pharmacology, and chemotherapy had to be developed, and the principles and practice of asepsis and antisepsis had to be established and used.

Could better interdisciplinary services have brought together the knowledge required for open heart surgery 50 or 100 years earlier and permitted it in 1846, shortly after the discovery of surgical anesthesia? No, because critical, essential knowledge was unavailable until 1934. The critical factor was the need for an artificial heart-lung machine that could maintain blood flow throughout the body when the patient's own heart had to be stopped for a while to allow the surgeon to repair intricate structural defects. Some have noted that 1934 was the year in which DeBakey published the report on his roller perfusion pump. But perfunctory library research by someone who desperately needed a DeBakey-type pump earlier would have shown that details of it had been published in 1932 by Van Allen and even earlier, in 1928 (*3*), by Bayliss and Müller (who turned it over to Palmer Ltd. for manufacture) and that a man named Kelly had obtained U.S. Patent 314851 on it in 1885. The pump was obviously not a limiting factor.

A more likely critical factor was the absence of a nontoxic anticoagulant, and it is hardly accidental that Gibbon began his long research program on a heart-lung machine in 1934, the very year that heparin (a naturally occurring, nontoxic anticoagulant) became commercially available. However, the laboratory discovery of crude heparin came in 1916 and an earlier Gibbon might have forced its purification 10 to 15 years earlier than 1934. Maybe work on the heart-lung machine began in 1934 partly because the essential knowledge became available in that year, but it is more likely because Gibbon became available in that year. He had an idea and intense conviction that a pump-oxygenator could replace the natural heart and lungs for short periods; it turned out that he could not be dissuaded from his goal by the indifference, ridicule, or scoffing of his surgical colleagues. [It is important that goal-directed, mission-oriented science administrators know that Gibbon spent 13 years (1934 to 1947) trying to perfect the heart-lung machine, not for open heart surgery, but to allow time for a surgeon to remove an embolus blocking a patient's main pulmonary artery. It was only in 1947 or 1948, on the urging of Alfred Blalock (of blue-baby fame) that he switched his goal to providing an instrument that would permit repair of cardiac defects (*4*).]

Linkage Between Steps 2 and 3

Those who would like to accelerate research and its application to clinical medicine would do well to think long and seriously about establishing effective linkages between steps 2 and 3 in Table 1. One can list innumerable instances in which research in medicine was speeded by connecting knowledge in one or more of five or six biological or nonbiological sciences with a difficult problem in medicine. We are today drowning in scientific literature in all fields, and I think it is time we do something other than publish more and thicker journals, more and thicker books, more and thicker review articles. A new catchphrase is "promoting the *diffusion* of scientific knowledge." Lord help us if we can't do better than let it *diffuse*. As I have noted elsewhere (*5*), diffusion is an intermingling of molecules resulting from the random movement of each. It works rapidly over short distances such as micrometers, but takes forever over long distances. Can't we pinpoint where special new knowledge should go and get it there by special delivery? The ideal instance of special delivery was the daily interaction between brother Ernest (the physicist) and brother John (the physician) Lawrence that allowed radioactive isotopes to jump directly from the cyclotron in Berkeley to clinical investigation in Berkeley. Another special instance of interaction, regarded by the participants as very exciting moments in their scientific lives, was the lunchroom at the Rockefeller Institute for Medical Research, where great scientists in many disciplines learned daily from informal conversations with others. It is too much to arrange this in very many cases. Further, there are well-recorded instances of direct suggestions, given to biological scientists by others, that were ignored, although if they had been investigated, they would have accelerated important discoveries by decades. ("You can lead a horse to water but you can't make him drink.")

I do not have answers but I do have questions: Is there a way of preparing interdisciplinary reviews that will synthesize current knowledge, emphasize important areas of ignorance, and offer thoughtful suggestions on how to learn what we need to know? Can we do all this in simple English that any scientist in any discipline can understand, and make these special reviews easily available to all without the necessity of subscribing to 30 journals? Many physical or biological and chemical scientists do now engage in interaction, but at this very moment the Federated Societies are pulling apart with biochemists meeting separately from the other bioscientists; the annual reviews in all branches of biomedical science are becoming more and more highly specialized so that they become more difficult for an outsider to read. Even *Scientific American* is becoming more technical and more of a struggle for "outsiders" to read. Can this tendency to ultranarrow, microspecialization be slowed down or reversed?

The first business of the National Academy of Sciences is a legal requirement—to advise the government on scientific matters; should not its second business be to tell all scientists in all fields of important new advances in each and how these might have important implications for their fields? The National Academy of Sciences is an interdisciplinary group elected from 23 branches of science including anthropology, astronomy, botany, chemistry, engineering, geology, geophysics, physics, psychology, and the social, economic, and political sciences in addition to ten biological sciences. Would not its *Proceedings* serve all sciences better by bringing them together instead of acting as a huge rapid-publication journal for very narrow aspects of two or three of the currently popular biological sciences?

Funds for Research and Development

A new idea can help no one unless it can be tested. A new idea when tested and confirmed cannot help patients unless it is carried further and, if possible and appropriate, brought into the sphere of clinical investigation and practice. Nowadays, all of this—which we call research and development—requires large sums of money—from federal agencies, voluntary health agencies, privately funded foundations, and institutes and industry, to name the main sources of funds.

Let us consider here only the National Institutes of Health (NIH) and its support of basic research and clinical application. Let us assume for the sake of this discussion that Congress has decided to maintain the NIH budget at its present purchasing power—that is, at its present dollar level plus allowances for overall inflation (in salaries and usual research supplies), plus allowances for the soaring costs of hospitalization that increase the price of clinical investigation year by year, plus allowances for purchase, maintenance, and replacement of now-essential, highly sophisticated, and expensive research equipment that has replaced test tubes, sealing wax, and smoked drums in basic research laboratories.

Because federal allocations of "real" dollars for biomedical research cannot increase indefinitely (unless tied by formula to increases in the gross national product), a policy that stabilizes the purchasing power of NIH dollars over a long period should solve many problems.

But one problem that it will not solve is that something more is needed than stability in congressional appropriations; the something more is a science policy and statement of priorities. Why? Because there are many ways of using funds allocated by Congress to NIH and no rules for the use of these funds. Let me give a few examples.

1) Congress divides the total NIH budget into allocations for each of its Institutes. It may also earmark a portion of an appropriation to an Institute for a specific project (such as sickle-cell anemia) or set an upper limit to a specific type of ongoing program. These actions are in a sense a congressional statement of priorities, but none carries with it more than a 1-year commitment.

2) An Institute director may divide the nonearmarked or nonrestricted part of his annual budget into funds for contracts and funds for research grants. Contracts usually pay for development of apparatus, equipment, or special research materials (much of which industry once considered to be its obligation) but they may be used also to pay for clinical trials; research grants, for the most part, pay for research on ideas and programs initiated by individuals or by small groups of scientists.

3) The Institute director and his staff may further subdivide the funds allocated for research grants into those that support some large and expensive cooperative clinical trials (that clinicians in university hospitals once regarded as a normal obligation and responsibility) and those that support basic research on new ideas and their refinement. Policy on this subdivision is not necessarily consistent for the components of a single Institute and may change yearly or seasonally.

This decision-making power may work to the advantage of the scientist with a new idea (our step 1 man) or it may work against him; when Congress, the President, and the Office of Management and Budget are in a mission-oriented, "let's apply what we know" mood, it works against him.

4) Peer review of grant applications also presents a problem. A large group of nongovernmental scientist-consultants constitute regular peer review groups ("initial" review groups) that set priorities on the grant applications that are sent to them for evaluation. The regular peer review groups have received almost universal praise (in this country and abroad) and deservedly so. But not all applications for grants and none for contracts go to them for review. Those that do not are usually sent to ad hoc or standing "special" review groups. If the special review groups award higher priorities (better scores) than do regular peer review study sections that have different standards, the total review system can result in diminished support for the step 1 man with the new idea (*6*).

5) By law, the National Advisory Council to each Institute of NIH can change the priority score of the initial review group (peer review study section) so that a disapproved grant may be paid or an approved grant not paid, on the basis of the Council's scientific judgment or its assessment of "programmatic importance" to the Institute. In the absence of a national biomedical science policy, this can also diminish support for the step 1 man.

I have my own convictions on the support of research versus development; on support of undirected, basic, fundamental research versus applied, mission-oriented, goal-directed research. It is that all are important and essential and that their support should not be discussed as an either-or proposition. But a decision must be made on how much for this and how much for that, and in the interest of good, uninterrupted research, the policy decision should hold for a reasonably long term.

I believe that if we had a highly intelligent, rational, and logical visitor from a planet in outer space (say Mr. Spock of Star Trek fame, who cannot be emotional but only logical), he would give the highest priority to fattening the goose that lays the golden eggs rather than killing the goose in order to save the money required to feed her.

If I had a vote in establishing a national biomedical science policy, I would give my top priority to guaranteeing an adequate, irreducible, undivertible sum, in the form of long-term grants, for the step 1 men, and give national peer review groups the challenging responsibility for identifying step 1 men. How much is adequate is a matter for careful study and should not be an off-the-cuff decision. I would also vote that the Institute director and staff should have adequate funds to support (after peer review) research in important areas that, in their best judgment, has been neglected nationwide by the collective applications for regular research grants. And I would vote that someone would have responsibility for eliminating excessive duplication of research effort by the "me-too" researchers who drain away dollars badly needed for creative, original research.

Journal Review and Reader Response

There is not much of a problem today in getting a scientific article published. Often a scientist fails to have his article accepted by his first-choice journal, a prestigious one which also has the largest appropriate audience. Often he is maddened by orders from an editor to "cut it in half," or to eliminate speculation or suggestions for future research, or to remove what he considers essential illustrations, or by inordinate delays in publication after acceptance. But some journals have been innovative in shortening publication time, in publishing controversial articles that do not have unanimous acceptance of the editorial board (often with a cautionary editorial in the same issue), and in encouraging rather than prohibiting speculation.

Much greater problems are getting subscribers (i) to open their journals, (ii)

to read the table of contents, (iii) to read even a single abstract or summary, and (iv) to read an article itself. One journal has tested how far a reader goes into its journal by inserting a genuine $5 check in mid-journal, but I do not have the data on how many of these were discovered and cashed.

Riva-Rocci, who wrote in 1896 about his arm cuff for measuring systolic arterial blood pressure in man (*7*), apologized for not having read Rabinowitz's modification of von Basch's device until he (Riva-Rocci) had completed his work, and asked that his readers forgive him "on the score of the vastness and diffusion of the current literature on any given subject." Multiply that vastness by 1000 or 10,000 and you will see the most critical problem today in translation of results of research into clinical investigation and clinical practice, and the area in which investigators and physicians alike need most imaginative and effective help. I am convinced that scientists would learn more by speaking less, by participating in fewer symposia, by writing less, by traveling less—*if* they devoted time so saved to intensive reading of what others are doing; but reading is less glamorous and less ego-satisfying and not deductible from income taxes. (Earlier, I have given suggestions for helping the scientist learn of advances in a variety of sciences.)

From the Laboratory to the Clinic

Occasionally the same man produced or purified a new drug and was also the first to use it clinically (Florey and Chain, penicillin; Banting and Best, insulin; Withering, digitalis); no interaction or transfer from laboratory to clinic was involved. Occasionally a clinical investigator was constantly in the wings, fully prepared to test a promising new compound developed in a basic science laboratory (Feldman and Hinshaw were at work testing streptomycin in mice with experimentally produced tuberculosis within a month or two after publication of Waksman's first preliminary report on their new antibiotic agent). Very often the same man who constructed new equipment was also the first to use it clinically (Zoll, the defibrillator and cardiac pacemaker; Gibbon, the pump oxygenator; Drinker, the body respirator); again, no interaction or translation was involved.

I know of no complete study of how many clinically useful drugs (i) originated in nonprofit research laboratories and were then purified, put into proper form, and marketed by pharmaceutical companies, as opposed to drugs that (ii) originated in research laboratories of the pharmaceutical laboratories, were then tested by clinical investigators elsewhere, and were finally marketed by the company whose staff initially discovered, purified, or synthesized them. In our study of key advances necessary for modern treatment of cardiovascular-pulmonary diseases (*2*), we found that industry had a remarkably good record in supporting basic chemical and pharmacological studies that led to clinically important drugs; about half of 50 such drugs came entirely from the efforts of scientists in industry (for instance, oral diuretics, sulfanilamide, numerous antibiotics, propranolol). The drug industry has also had a good record in supporting basic research of not-for-profit groups, in supporting clinical investigations of new drugs, and in supplying nonprofit groups with countless modifications of a parent compound in the hope that one might be clinically useful.

Dealt with elsewhere in this issue are the ethical and moral considerations that a clinical investigator faces when he first uses a new drug in volunteers or patients, the requirements of the Food and Drug Administration that must be met before it approves a drug for use generally by physicians, and the necessary delays involved in compliance with these. The exemption from regulation of new surgical procedures, or modifications of old ones, is another matter that I will not discuss, although it is an important issue.

In our study, the record of manufacturers of equipment and apparatus was not an impressive one. Of 65 new types of equipment needed for advances in cardiovascular-pulmonary medicine and surgery, the basic principles, prototype, and early modifications came from university or other nonindustrial laboratories in 55 cases; only ten came from initial research and development in industries' own laboratories. Lags of at least several years occurred before private industry decided to produce items of equipment that had been generated in not-for-profit laboratories and make them widely available. On the other hand, when the president of a company took a personal interest in developing a new product (for instance, IBM's Watson and Gibbon's pump oxygenator), progress was rapid.

It appears that the nonpharmaceutical industries are not well prepared to judge the potential value of new biomedical instruments and apparatus or prefer not to become involved until satisfactory sales and profits are assured, or both. How to shorten delays caused by industry's caution is a complex problem which has been the subject of several studies.

Continuing Education of Physicians

Few medical students, interns, or residents receive formal training in critical evaluation of medical literature, yet they are expected to continue their own education for their professional lifetime. There is no dearth of medical journals that publish new scientific work in medicine and surgery and there is certainly no lack of attractive advertising designed to introduce to physicians the uses and advantages of new drugs and procedures. What physicians need more of is easy-to-read, short, authoritative articles giving the best medical judgment on the value and limitations of new scientific work. Medical magazines supported by advertising rather than by subscription fees were the first to recognize this need and fill it. Some of the more prestigious medical journals have recently begun to evaluate new reports critically and to publish side by side both aspects of controversial issues.

I believe that periodic reaccreditation of practicing physicians presents the best hope of solving the "keeping-up-to-date" problem. It is obviously going to create a huge new industry. If it does its job well, it will have some advantages over journal scanning. First, continuing education will challenge existing teachers in universities and the new industry that deals with learning techniques to devise ways of presenting medical science clearly and succinctly to busy practitioners. Second, in many instances, it will bring the faculty and "students" into direct contact and so permit immediate clarification of difficult presentations. Third, it will bring unusual clinical problems of practicing physicians to the attention of faculty trained in clinical investigation and this can direct the attention of the latter to matters that merit serious investigation. (The burgeoning new industry of medical information systems is discussed elsewhere in this issue.)

Public Acceptance and Responsibility

Many of the public are or want to be well informed on medical matters, but few are prepared to cope with medical jargon or with completely contradictory opinions from two "highly authoritative" physicians or scientists. The jargon problem can be solved only by editors

with supersensitive jargon-detectors and complete authority to eliminate jargon and gobbledegook from all written or spoken material directed to the lay public. The problem of controversy and what to do when authorities disagree must be presented squarely to the public, and the public must learn that medical scientists believe that certain things are currently "for sure," that they are presently in disagreement on others, and that they have at the moment little secure knowledge on still others.

The public also deserves to be told the difference between factors that directly and with certainty cause (or prevent) disease, and risk factors that do not cause disease with certainty but do increase the risk that a disease will occur or become more severe. Then the public also deserves to be fully informed about causative factors and risk factors and (i) what the chances are (such as 9 in 10, 1 in 10, 1 in 1000, 1 in 1,000,000) that continuing to take the risk will result in earlier death or disability, and (ii) what the chances are that following a prescribed program will prevent disease, prolong life, and improve the quality of life.

The statement has often been made that more than 20 million people in this country have hypertension, that half of these do not know they have it, and that half of those who know they have it are inadequately treated, often because patients elect to discontinue treatment. Because hypertension by itself may produce no symptoms if mild and of recent origin, but increases the risk that the individual will acquire coronary artery disease or stroke, the National Heart and Lung Institute has conducted a Hypertension Information and Education program for several years. Its goal is to identify the 10 million individuals who are believed to have hypertension but do not know it, and to inform all of the 20 million with hypertension of the availability of drug treatment.

Considerable criticism has been directed against the public for not seeking diagnosis or, once a diagnosis has been made, for not following a recommended drug or dietary regime. It appears that we are approaching a national debate over compulsory diagnosis, treatment, and prevention of noncommunicable diseases (to eliminate hospital costs and unemployment caused by preventable or treatable illness) versus the right of an individual to know the risk factors involved and then be free to decide whether he prefers the treatment to the risk in no treatment. The historical point of view teaches us that much of what we once knew "for sure" was later disproved and suggests that some of what we now know "for sure" will one day be proved wrong (such as, regular exercise prolongs life, cancer of the bowel is caused by the food we put in it). It also suggests that in the long run a well-educated, well-informed citizenry will more often than not make the right decison. With physician education and public education going hand in hand, issues such as that discussed above may well be solved without first repeating the mistake of the prohibition amendment (which made one medical risk factor illegal but still available at a price).

References and Notes

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3. J. H. Comroe, Jr., *Retrospectroscope: Insights into Medical Discovery* (Von Gehr Press, P.O. Box 7654 Menlo Park, Calif. 94025, 1977), p. 18.
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6. A 12-member team, headed by R. Kirschstein, recently carried out a comprehensive evaluation of the peer review system for evaluating NIH research grant applications. It was completed in January 1977, and on 8 February 1978 the NIH director issued his decisions based on the Kirschstein report. He approved 42 of their recommendations. Among these were: "Special efforts must be made by reviewers and staff to identify unique or unorthodox research. The need to be alert to unique ideas should be stressed in the orientation of new members of initial review groups and councils and in the Guide for new members. . . . The responsible officials and staffs of the various initial review groups or Advisory Councils/Boards [shall] hold annual orientation sessions for their new members in order to place peer review in perspective and to inform reviewers of their functions, duties and responsibilities. . . . The peer review system must remain alert to innovation. . . . Training curricula [shall] be developed by NIH for extramural program and review staff in order to provide orientation and to refresh and reiterate principles concerning the philosophy, objectives, and procedures for peer review. . . . *Initial Review* Groups [shall] be requested to identify applications they consider to be especially creative or innovative."
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Surgical Innovation and Its Evaluation

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Many observers have called attention to the inconsistency of controls and regulations governing the introduction of new therapies in the United States (*1, 2*). New drugs are introduced in a manner conforming to strict federal regulations that require rigorous testing in animals according to careful experimental designs, followed by carefully controlled testing in humans with appropriate protocols and follow-up observation. In contrast, new surgical operations may or may not be tested in animals, may be introduced as human therapy with or without review by a human experimentation committee and with or without a formal experimental design, and may or may not be evaluated by long-term follow-up observation.

The question is asked: Why should operations not be subjected to testing and controls that are as timely and no less rigorous than those required for drugs? In an effort to answer this question, and to suggest solutions for problems found, we have reviewed the process by which four relatively new operations were introduced and evaluated. Three of the four were subjected to randomized clinical trials (RCT's), but only after the passage of much time and many procedures, and it was apparent that earlier trials would have speeded the process of evaluation in each case. Shortcomings in the evaluation process also included lack of systematic and comprehensive collection and reporting of clinical experience. Early clinical surveillance could have facilitated the design and early implementation of RCT's when necessary. Of

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