LEWIS A. CONNER MEMORIAL LECTURE

The Next 30 Years — Will the Progress Continue?

RICHARD S. ROSS, M.D.

SUMMARY Spectacular progress has occurred in cardiology during the past 30 years. The major advances that have resulted in the better methods of diagnosis and treatment of patients stem from basic research that was often unrelated to the ultimate practical application. An excellent example of this process is the evolution of the concept of β blockade from the pharmacology laboratory to practical clinical application in a variety of conditions. The sequence of discovery, translation, and application depends on many factors, but most important is the trained, dedicated investigator. If progress is to continue, a constant supply of bright young men and women must enter careers in basic research and clinical investigation. Recent studies show that the pool of biomedical scientists is shrinking and fewer young people are selecting research careers; thus, the process upon which our future depends is threatened. The socioeconomic forces that tend to turn the potential stars of the future away from research careers have been identified, and they must be counterbalanced.

For 30 years, the American Heart Association has been a leader in the conquest of heart disease through research. The faith of the Association in research must be reaffirmed. The relationship of today's basic research to the good medical care of the future must be explained to the people and to their elected representatives in words that they understand. Action must be taken to assure the continuation of the research enterprise that has been responsible for the progress of the last 30 years.

THE 1979 Conner Lecture represents a break with tradition. In recent years lecturers have described the application of science to clinical medicine: nuclear cardiology, ultrasound in the diagnosis of heart disease, and the mechanism of action of antiarrhythmic drugs have been discussed.

This year the President of the American Heart Association, Dr. Jack Eckstein, has become concerned that the process of discovery and clinical application of new science, which has been the subject of the Conner lectures, may itself be in danger, and has asked me to address this issue.

Research is important to practitioners and to those who are in academic medicine. Every day cardiologists use knowledge that did not exist a few years ago. If progress is to continue, the research establishment must remain strong and productive.

Progress may not continue at the same rate. We must examine this threat and take action. This is similar to preventive medicine. Cardiologists understand this, because we tell patients to stop smoking, or treat high blood pressure today in order to prevent complications that may be 20 years away. A similar approach to biomedical research is needed if it is to be healthy and productive 20 years from now.

Before describing the threatened malfunction, I will remind you about how the healthy process works by relating two illustrative stories of the science behind today's cardiology.

To get an overview of our field, I looked through the index of the abstracts of papers to be presented at this meeting. On the very first page of the index under the letter A, I found 31 entries under adrenergic mechanisms, adrenoceptors and similar headings. Under the letter B there are 25 entries under titles such as β agonists, β blockade, β receptors, and Beta-Blocker Heart Attack Trial. I turned to the Ps and found 19 entries for propranolol. Thus, the field of adrenergic receptors, their blockade and the application to clinical medicine accounted for 75 abstracts on this program. This is obviously an area of great practical importance.

It all began over 30 years ago in a basic science department — in the Department of Pharmacology at the University of Georgia in Augusta — with a new concept that ran contrary to contemporary thought. In describing his discovery, Raymond P. Ahlquist says, “The modern adrenoceptors were invented about
30 years ago to explain the different pharmacodynamic effects of some congeners of adrenaline. Why did phenylephrine (Neo-Synephrine) constrict blood vessels? Why did isoprenaline cause vasodilation? Why did adrenaline cause both of these effects? The simplest answer was to imagine that there were two different adrenoceptors. To demonstrate our scientific acumen we named these alpha and beta."

It took about 10 years for the new idea to gain acceptance. Cannon's concept of two transmitters, Sympathin E and Sympathin I, was widely held and Ahlquist's first paper proposing two receptors rather than two transmitters was rejected. Much later, in the late 1950s and early 1960s, the field exploded with the development of drugs that could block β receptors. Since then there has been a cascade of discoveries, each one of which triggered several others. Selective drugs have been developed, new applications in angina and hypertension have been explored, and the receptor concept has been applied to other drugs, such as serotonin and morphine.

This exciting story began in a basic science laboratory with a new idea that questioned existing doctrine and led to a torrent of clinically useful information as evidenced by the program of the American Heart Association in 1979.

The second example of the normal process of discovery, translation, and application is at a much earlier stage in development and may not reach the prominence we see for β receptors for another decade. I refer to the cardiovascular effects of the prostaglandins. There are 16 entries in the 1979 book of abstracts for prostacycline and prostaglandin, but the range of effects is spectacular and intriguing, and the titles can be viewed as harbingers of things to come. There are references to the effects on platelets, the vessel wall, the ductus arteriosus, angiotensin and myocardial cells.

The story of prostaglandin and the patent ductus is especially worthy of presentation at this meeting because this simple congenital anomaly was one of the very first to be treated by cardiac surgery. Now, 30 years later, this same condition again assumes the limelight as another new method is developed.

This story began in 1966 with the work of Coceni and Wolfe, who showed that prostaglandins required oxygen in order to exhibit an effect on contracting rat stomach. These experimental observations and those of others suggested that the prostaglandins might have a role in the functional closure of the ductus. Subsequent work by Coceni and Olley in Toronto in the early 1970s showed that the muscle of the ductus is relaxed by prostaglandins and that this effect is best seen in the absence of oxygen.

Prostaglandin infusion is now recognized to be of practical clinical value in the management of infants and children with severe cyanotic congenital heart disease. Thus, basic research on the effects of prostaglandin on rat stomach muscle has led in a very few years to the development of a better method for treating patients with congenital heart abnormalities.

This list of examples could be extended indefinitely to emphasize the importance of basic research to clinical medicine, but what we need is a careful scientific examination of the process of discovery. Fortunately, such a study was conducted in 1976 by Julius Comroe and Robert Dripps. These authors attempted to analyze the process by tracing the roots of discovery back to the beginning and asking questions about the process. First, they prepared a list of the top clinical advances in cardiovascular and pulmonary medicine and surgery of the last 30 years (fig. 1). They then moved back behind these 10 discoveries and identified the essential bodies of knowledge that had to be developed before these clinical advances could be made. They defined 137 essential bodies of knowledge that lay behind this group of 10 advances. Further research led to 4000 published articles from which a group of 529 essential or key articles were selected for careful study.

Comroe and Dripps analyzed the key articles to determine the goal of the author (fig. 2). The "bottom line" on this table is that 41% of these key articles were not clinically oriented at the time the work was done, yet they were essential to the final result which is recognized as contributing to one of the 10 major advances. Certainly the basic work of Ahlquist on adrenergic receptors was undertaken without any idea of clinical application. The same is true of the work on prostaglandin in the rat stomach, which started the chain which led to the use of this substance in the...
treatment of patients with congenital heart disease and may yet open vast new areas.

The list of 529 key articles can be further broken down to show that all kinds of research are important to the progress we are concerned with today (fig. 3). This is a profile of the process which cannot move on without all its elements. The process of discovery is a sequence, with each step depending on many others, but about two-thirds of the key articles were considered to be basic. If you were a betting person and wanted to pick a winner, you would bet on basic research.

The key papers studied by Comroe and Dripps cover a vast range of topics, but they have one property in common. They were all written by men and women with a commitment to the advancement of knowledge. These men and women used apparatus to collect data and analyzed it with computers, but the ideas behind the experiments originated in prepared and thoughtful minds. Clearly, the most important ingredient in the research enterprise is the individual human being who is dedicated to answering a question. Bright people need good equipment which may make the work go faster and life more pleasant, but many of the key observations leading to Comroe's big 10 were made in dusty laboratories with homemade equipment. The fundamental truth seems to be that bright people can be productive in any environment, but an elegant, new laboratory building cannot advance science without bright people. Consequently, if resources are limited, the priority should be placed on the selection, training, and retention of productive scientists. People before things is a good rule to remember when assigning priorities.

Bright people are required in large numbers because the process of scientific discovery is, by its very nature, inefficient. Many blind alleys must be explored for each road which leads to an important therapeutic development. It would be interesting to know how many blind alleys had to be explored before the 529 key papers cited by Comroe were produced; I would guess that the number would be 2000–5000. Blind alleys, or in the language of an energy-conscious world, dry holes, are important because negative information enhances the value of the positive. The need to explore blind alleys multiplies the number of investigators required. The number required is far greater than the number who make significant discoveries along the main line to the major advances.

Another reason that the number of investigators must be large is that it is impossible to identify creative scientists with certainty before they have had an opportunity to try science. Certain approximations can be made, but the stars, like those in professional sports, emerge only after they have had an opportunity to play the game. This means that the number of young people who start on research careers must be far greater than the number who become productive scientists.

If the progress of the last 30 years is to continue, there must be a constant stream of bright young men and women entering careers in research. Without question, research manpower is the most important factor in sustaining progress and this supply is threatened. The signals are clear. The size of the research manpower pool is decreasing. In 1968, there were 15,241 physicians in the United States who listed research as their primary activity. In 1975, less than a decade later, there were only 7944. This distressing decrease of 50% occurred at a time when the faculty of U.S. medical schools increased by 160% and the number of graduates of medical schools doubled.

A good, but by no means perfect, measure of the flow of new talent into the research manpower pool is the number of young physicians seeking support for research training from the NIH. The number has fallen from approximately 4600 in 1971 to 1790 in 1977. More serious, however, is the fact that in 1977 only 70% of 2450 budgeted training positions were filled. The shortage was one of applicants, not of opportunities.

Not only is the total medical research manpower pool shrinking; it is also changing. The proportion of M.D.'s in research has fallen from 46% in 1968 to 20% in 1977, and the fraction of Ph.D.'s is increasing (fig. 4). There has also been a steady decline in the percentage of first awards of research grants to those with the M.D. degree, whether it be M.D. alone or M.D./Ph.D. (fig. 5). I do not underemphasize the importance of Ph.D.'s to the research enterprise, but I feel that we need a balanced mixture of M.D.'s and Ph.D.'s, and the balance has tipped dangerously. The shortage of M.D.'s in research will have its most serious impact on clinical investigation, that vital process of translation of basic discovery into clinical practice. Dr. James V. Warren, a Past President of the
Heart Association, upon receipt of the Herrick Award in 1976, termed the clinical investigator an "endangered species," and such he is. Dr. James Wyngaarden also spoke of the "endangered species" in his Presidential Address before the Association of American Physicians. The clinical investigator must be a good physician and much more. He must possess a thorough understanding of the scientific method and know how to design an experiment. He must be able to use statistics and epidemiology. The clinical investigator is essential to the translation of a basic observation into practical, clinical therapy. Good clinical investigation makes the health care system more cost effective because it provides the means for the differentiation of those therapies and procedures that are valuable from those that are not. The cost of supporting clinical investigation is small compared with the cost to the health care system of widespread use of treatment of no value. The M.D. training is essential for the clinical investigator. The Ph.D. may be an essential co-investigator, but cannot replace the physician-scientist.

If we are to maintain the critical mass of medical scientists engaged in research, we must attempt to influence the career decisions of young people. Decisions to enter research are usually made in medical school or during postgraduate training, but sometimes in college or even before. Let us start by considering the factors influencing the decision of the medical student.

In years past, some of the brightest members of each medical school class have chosen academic careers. Indeed, it has been said that too many have entered research and too few have elected careers in the practice of medicine, especially primary care. This may have been true in the past, but the pendulum has swung, and many believe, too far. Many forces are responsible. Some of them can be countered.

"Try it, you might like it" is a familiar invitation, applicable in many situations and one that should be extended to students considering research experience. There is no other way for a student to know whether he can be stimulated by the excitement of investigation and discovery. For many the first opportunity comes during the basic science years in medical school, where some of the teaching is conducted in the laboratory, but many schools have dropped the laboratory experience for reasons of space and economy.

Medical students' exposure to research is also limited by the smaller number of faculty who consider research to be their primary activity. This means less opportunity for elective work in research, and hence, less likelihood of a close association with a role model who is himself an investigator. The problem is not just less opportunity; there is also less interest and the competing opportunities have increased in number.

The situation is worst in the clinical departments, where increasing emphasis is placed upon clinical practice as a means of financial support. As a result, less time is available for laboratory investigation and for the scholarly consideration of a clinical problem by review of records and library study. This is especially true for the internist or pediatrician whose earnings per unit time are low. If such a faculty member must make his salary and expenses through clinical practice, there will be little time left for scholarly effort.

The forces that come to bear on the trainee after graduation are probably even more important. In the 1970s, the importance of primary care and family practice have been emphasized. More students than ever before enter postgraduate training with primary care as their intended objective. Society has sent the
message that this is what is needed and will be rewarded. Robert H. Ebert stated this well in his foreword to Funkenstein’s book on career choices of medical students. "First of all, career choices seem to be related more to the general social atmosphere of the time than to anything that happens educationally either in college or medical school." Certainly, the general social environment favors primary care over research, but this can be changed.

Residency programs in internal medicine have been modified to eliminate research exposure during training. This change relates to changes in the requirements of the certifying boards and also tighter control of residency schedules by hospitals to ensure that the residents’ time is spent in a cost-effective manner on patient care.

The elimination of the doctor draft has also decreased the incentive for the acquisition of research experience. Many of the leaders of medical research got their first intensive exposure because their obligation for national service was discharged at the National Institutes of Health or other Federal research facilities. Those who served at the National Institutes of Health were selected because they were thought to have great promise, but the draft provided an additional push toward a research career. Some of today’s leaders might never have been exposed to research had they not been forced into it by the doctor draft.

The subspecialty clinical training programs supported by the National Institutes of Health have been criticized because young people were being paid well while training for lucrative practice situations. This was correctly viewed as an inappropriate use of public funds and clinical training programs were discontinued. This has had serious effects on the research manpower pool. The training programs that were eliminated combined research and clinical training and provided a mechanism whereby young physicians could participate in research and see if they liked it and were good at it. This was a good system despite its faults because it is impossible to identify in advance the person who will be successful in research. I could cite examples of trainees who were sure they were destined for practice who became captivated by an investigative experience during their training and continued in research. There are an equal number originally directed toward research who, after some experience, decided against this career and found happiness in practice.

Clinical training programs are now gone and only research training is supported by the NIH. Attached to research training is the so-called pay-back provision, which means that if a trainee decides that an academic career is not for him, he has to pay the government back for training by a period of obligatory service in an underserved area. On the face of it this appears reasonable, but it provides a strong deterrent to the conscientious person who is uncertain about his career but would like to try research. He may be unwilling to undertake the training if he knows that he will have to pay back those years if he decides against a career in academic medicine. This means that only those who are certain will accept a research training fellowship, and, as emphasized elsewhere, it is impossible to be certain without some exposure.

Consideration of the pay-back provision leads naturally to the other economic factors which are of great importance in providing a disincentive for a research career. Let us begin with the fact that medical school is expensive and most students graduate with a large debt. Many medical school graduates today are married and have children. Furthermore, today’s young people are impatient. They do not want to wait for the good life. Hospital schedules are less demanding and there is more time for recreation. Hospital stipends are reasonable, but with the debt, the family, the higher standard of living, and inflation, there is no surplus.

It is easy for us who are more than 40 years old to recount tales of the way it was when we were in training, but I assure you this is not a productive approach. These young people are living in today’s world and they know what they want. If we want to change the future, we have to communicate with them.

Figure 6 demonstrates the career decision facing a 28-year-old medical resident with a wife and one child, who still has a sizable medical school debt. He has been fortunate to have had some exposure to research and thinks he might like a career in academic medicine. If he goes this route he will have 3 years of training and it will be at least 5 years before he is clearly established as an independent investigator. During that 5 years he will be receiving $15,000--25,000 per year and he will have become 33 years old. He sees uncertainty in the future. Will he be any good? Will he be able to get a grant? If he decides after 2 years that research is not for him, he has a period of pay-back service before he can go into practice. He will feel that he has lost 4--6 prime years.

He compares this uncertain future in research with instant success in practice. He has tried clinical medicine and he knows that he is a good clinician and has no doubts about his ability to succeed. He can expect a much better income in practice. A recent survey in cardiology has shown that average income for those in practice 4 years after completion of fellowship is at least twice that at the same point in time for the per-

---

**FIGURE 6.** Career choices facing a medical resident.
son who chooses an academic career. He considers his own future and that of his wife and children and more often than not elects the certain course.

There are many other factors that are essential to the continuation of progress, but in my opinion manpower is the most important and the one upon which the Heart Association should concentrate.

The problem is not new. Leaders in medicine have discussed this point before learned professional societies, but none of these groups has the potential for action inherent in the unique structure of the American Heart Association, with its representation from the health-concerned lay community as well as from the profession. The Heart Association must take action in several areas.

First, the people and their elected representatives must become aware of the problem. Never miss an opportunity in your local community to explain why research is important to the health of the public. Physicians have great influence. Make sure that your patients, many who have positions of power, know that research is important to you and therefore important to them. We all have a stake in research. You must sell research to the public.

Our objective is to interest more physicians in a career in research. Funkenstein has told us that the social climate of our time is more important than anything else in influencing career choice. The Heart Association has the power to change the social climate.

Combat the anti-intellectualism of some physicians who look on research as something medical school faculty members do for entertainment. Emphasize the relationship between today's research and tomorrow's therapy. Correct those who ridicule the scientist or academic physician for not "doing anything useful." Explain that research is a slow process and the rewards may not be immediately apparent. Broaden your horizons and those of your colleagues and friends. Do not be satisfied with the medicine you practice in 1979. There are still many problems and medicine will improve as solutions are found. Reflect on the changes that have occurred in medicine since you started and assume responsibility for tomorrow.

We know that many career choices are made before the student enters medical school and therefore this decision point is beyond the reach of medical school faculty, but your influence can be decisive. When young people come to you for career advice, make sure that they are aware of the satisfaction that may be found in a research career, especially in clinical investigation with which you are all familiar. Practitioners may be the only role models they know in medicine. You must show them that there is something else. Take a bright young student with you to visit a medical center and meet a colleague who is doing research. Tell your young friends about the great medical scientists of the modern era. Bring them to this meeting. Make them as familiar with the scientists who won the Nobel Prize as with the teams which won the World Series and the Super Bowl.

When dealing with medical students as friends or teachers encourage them to ask questions and seek answers through experiment. Advise them to spend an elective period in research. There will be plenty of time to learn how to read ECGs but medical school provides the last opportunity some of them will ever have to savor research and it should not be missed.

The specialty boards should be encouraged to make it possible for some research experience to count toward certification. This will provide an opportunity for much needed exposure.

The Heart Association should use its collective power and the power of its individual members, both physician and nonphysician, to eliminate the disincentives for research careers and provide incentives. Research stipends need to be raised. The National Institutes of Health recently did this.

There is also some action directed at encouraging medical students to try research. On October 1, the National Institutes of Health announced a new program known as the National Research Service Awards for Short-Term Training of Students in Professional Schools. This program will provide up to 3 months of experience for students with the Institution's best investigators.

The private sector must take leadership roles. The Heart Association has done this with the Clinical Scientist Award. Private foundations and industry should develop similar programs to encourage physicians to enter research careers.

Heart Association funds must be wisely spent, both nationally and locally, to get the maximal benefit. Affiliate allocations for research should be increased and the applications should have rigorous peer review. Heart Association funds are especially useful as a source of support for the first year, when the prospective investigator can try research and decide whether he wishes to enter into a 2- or 3-year training program supported by the Institute and hence, subject to the pay-back provision. Heart Association money is especially precious because of its flexibility.

Finally, unless we can maintain and even increase the number of scientists doing biomedical research, the progress will not continue. If, on the other hand, the trend can be reversed and bright young people are encouraged to enter research careers, the advances of the next 30 years may outshine those of the past.

References
1975: How They Came About (Government Printing Office, Washington, D.C. 1976), two volumes. Single copies are available upon request from the Public Inquiries and Reports Branch, National Heart, Lung and Blood Institute, NIH, Building 31, Room 5A03, Bethesda, Maryland 20014.


The next 30 years--will the progress continue?
R S Ross

Circulation. 1980;62:1-7
doi: 10.1161/01.CIR.62.1.1

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1980 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on
the World Wide Web at:
http://circ.ahajournals.org/content/62/1/1.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally
published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the
Editorial Office. Once the online version of the published article for which permission is being requested is
located, click Request Permissions in the middle column of the Web page under Services. Further
information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/