Presidential Address: Stranger in a Strange Land
63rd Annual Meeting of The Endocrine Society

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The scripture reading for tonight's sermon is taken from the Old Testament, the Book of Exodus, Chapter 2, verse 22: "For he said, 'I have been a stranger in a strange land.'"

Let me hasten to assure you this reference has no implications concerning our host city. Even though this is the first time The Endocrine Society has held its annual meeting in the great state of Ohio, I, personally, am no stranger to this land. Not only did I move here when I was four and grow up within a two-hour drive of where we are tonight, but also I married a Buckeye Belle, who still thinks there is no state in the Union that can compare with the big O.

Let me also promise you readers of Robert Heinlein that I do not intend to imitate his entertaining exploitation of the same biblical passage. For our concern tonight is not with science fiction but with science fact; the cold hard fact that the organization and especially the financial support of biomedical research during the 1980's and probably the 1990's will differ substantially from that to which we have become accustomed. The trends are already evident, and unless we adapt to the changing environment, we may well find ourselves, like Moses in Egypt, strangers in a strange land.

This is not to say that, individually and collectively, we should not make our best effort to preserve that which we now have and which, in most ways, has been a highly satisfactory system for funding clinical and laboratory research in endocrinology, with a minimum of inequity and a maximum of academic freedom. I refer, of course, to the National Institutes of Health, backed up by the various private organizations and foundations with interests that impinge on endocrinology. To this end, your president, in company with Claude Migeon, Chairman of the Public Affairs Committee, Jim Murphy, our legal advisor, and several other Society members, spent May 15 in Washington conferring, in teams of two, with the staff personnel of key members of the Committees on Appropriations and on Authorizations for both the House and the Senate. Our sales pitch was "cost effectiveness": that funding for biomedical research really is not an expenditure but an investment. We cited but a few of the well known examples where a relatively small outlay for research and development has permitted the eradication or control of a disease, with enormous subsequent savings in the costs of medical services and lost productivity. Of particular concern at present is the renewed authorization for Title X, which supports the reproductive endocrinology program of the National Institute of Child Health and Human Development, and which, because it also supports family planning services, is in jeopardy of extinction at the hands of special interest groups who fail to distinguish between scientific facts and religious beliefs. I must say that the reception Bill Rosner and I received in the offices of the senators and representatives we visited was most cordial and reassuring, and I understand the other teams were also well received. But next Monday, when Jim Murphy and I testify before the House Appropriations Subcommittee, we shall see how genuine this response really is. Personally, I believe the Congress is sympathetic.

But even if rescissions are held to a minimum, we still must recognize that the actual funding for future years promises to be reduced substantially in comparison with the escalating costs of biomedical research and its increasing dependence on expensive reagents and sophisticated instrumentation. To even the most fervent optimist, it must be apparent that the era of affluence that has characterized the post-Sputnik period will soon be a thing of the past.

I certainly do not wish to imply that the NIH, NSF, or American Cancer Society are about to go out of business in the foreseeable future. What I do believe is that these and other traditional sources of funding for biomedical research, in particular for endocrinology, will not be able to provide the level of support most of us feel is required. Thus, we would do well to explore other possibilities of potential support to make up the difference between what is needed and what may be available. We might also consider what modifications might be made in the present system to permit more efficient utilization of our resources. Though time does not permit exhaustive examination of these questions, I would like to touch, at least superficially, on a few of the items I regard as especially important.

First, let us consider the grant review process now
employed by most federal and private granting agencies. This is the procedure of "Peer Review" in which an application is evaluated for scientific merit by a panel of specialists, with secondary review by a council with presumably broader interests, and assigned a priority in the competition with other projects for a given allocation of funds. Many of us would agree that, for the most part, the peer review system has worked well, with a minimum of political interference and with adequate attention to proposals from junior or unknown scientists. However, there are defects in the peer review process. While it provides an effective mechanism for the evaluation of research projects that are extensions of conventional scientific thinking, it does not deal adequately with unorthodox proposals that could lead to conceptual breakthroughs. One must realize that the heretical investigator with a truly seminal concept does not as yet have any peers in that particular area. Can you imagine the reaction of a study section in 1896 to a proposal by Sir George Beatson for funds to see what would happen if he excised the ovaries of women with breast cancer? Or even in 1941, Charles Huggins had applied for a grant to castrate men with prostatic cancer? Of course, such proposals today would not even reach the study section, for they would never pass the human subjects committee of the sponsoring institution.

A further criticism of the current review system concerns the time it requires on the part of scientists, both for the preparation of their own proposals and for the evaluation of others. The problem is now exacerbated as fewer approved applications are funded, resulting either in resubmission of a revised proposal to the same agency or in simultaneous submission to multiple agencies, again increasing the demand on those who serve on review panels. With this excessive diversion of scientists' efforts to the writing desk and the committee table, there is less time available for creative thought and laboratory experimentation.

A particularly wasteful aspect of our present system is the need for an outstanding investigator, with an established track record of productivity, to reestablish, over and over, his or her credentials of investigative competence. During the past year I heard of two cases where study sections, now often composed of more junior members whose scientific memories are sometimes limited, had deferred or rejected grant proposals because not enough methodological detail was given to provide assurance that the applicant was competent to carry out the proposed study. In both instances the investigators were pioneers in their respective fields and actually had invented the methodology in question. In her perceptive presidential address of two years ago, Rosalyn Yalow discussed this problem and proposed that applications from senior investigators, with established records of performance, be judged on retrospective considerations, reserving the more time-consuming prospective review for the unproved applicant whose chief criterion for evaluation is the research proposal itself. Though this suggestion may be criticized by egalitarians, it makes a great deal of sense. For I firmly believe that an investigator's place is in the laboratory, and that writing and evaluating grant applications, though a necessary evil, should be kept to a minimum for the good of science.

If one accepts the premise that the traditional funding agencies, upon which most of us have depended in the past, will not be able to keep pace with the escalating demand for support, then it would appear that the research community should consider some alternatives. One option is that we all do less research and thereby decrease the total requirement for financial support. Another is to intensify one individual efforts to compete for the limited funds by devoting more time to the preparation and polishing of our grant proposals and also by applying to more and different agencies in the hope that, in one place or another, we may slip into the category of approval with funding. This second option overlaps the first, for, as I have pointed out already, the more time we spend writing grant applications, as well as reviewing the increasing number from our compatriots, the less time we have to do research. Personally I would reject both of these approaches in favor of a third possibility: namely, to search for new sources of support, some of which have been relatively untapped because the great father in Washington has taken such good care of all us children that, until now, we have not had a strong incentive to go out and look for other sources.

The greatest potential for new support of biomedical research, of course, is industry, in particular the pharmaceutical industry. At one time, this was the principal source of funding for research in endocrinology. We often forget that, with the exception of recent developments in neuroendocrinology, essentially all the known hormones were discovered, characterized, and, in many instances, synthesized at a time when there were no study sections, training agents, or NIH extramural programs. Much of this research was supported by the pharmaceutical industry, both in this country and abroad. During the past two decades, the relation of the federal government to the pharmaceutical industry has been a curious mixture of good news and bad news. We often hear how the FDA, with the laudable intention of protecting the public welfare but with frequent disregard for the concept of risk-benefit ratio, has markedly increased the cost and impeded the development of new therapeutic agents. On the other hand, it is less widely appreciated that, during the past twenty years, the NIH has paid the bill for much of the basic discovery, as well as the training of scientific personnel, upon which the future of the pharmaceutical...
industry depends. Now that the government no longer is able to shoulder as much of this burden as it once did, and if, as appears probable, the FDA may finally accept the reality that there is no such thing as zero risk, the pharmaceutical industry, in its own self-interest, may find it prudent to increase its support of biomedical research, especially if reduction in the tax burden can help make such funds more available. Direct funding of scientists by industry has the advantage of efficiency, for when a contribution reaches an investigator indirectly by way of the tax collector, I don't have to tell you that there may be considerable attrition along the way. So who knows? We may actually see a return to the situation of the 1920's and 30's where the pharmaceutical industry was the sugar daddy of most endocrinological research and, in return, accumulated a considerable amount of sugar for itself. All of which would illustrate the perceptive statement by Alphonse Karr in 1849: "Plus ça change, plus c'est la même chose."

Recently there have been novel developments in the industrial support of biomedical research. The most spectacular of these is the agreement between Harvard University and Farbwerke Hoechst where, in return for the right of first refusal, the company has agreed to underwrite a basic research effort at the Massachusetts General Hospital in the remarkable amount of 50 megabucks. While some may have reservations about the compatibility of such an arrangement with the traditional precepts of academic freedom, there is no question that, for the individuals involved, the opportunity for scientific discovery should be highly favorable. It will be interesting to note whether this venture will initiate a trend for similar arrangements elsewhere. It could be that the coming thing will be for academic superstars to play out their options with one owner and then declare themselves free agents, available to sign a new contract with the highest bidder.

Another development, resulting from the explosion in recombinant DNA technology, has been a proliferation of bioengineering companies, founded and controlled by members of the research community. Although academic scientists for years have had varying degrees of participation in applied ventures originating either from their own basic discoveries or from those of others, these biogenetic enterprises are on an unprecedented scale. Whether, in the long run, this will be good or bad for basic science remains to be seen, but in any case, one result of all these endeavors will be more private money flowing into biomedical research and development.

I realize that few of us are going to have either the opportunity or the desire to establish our own companies, or to be the proteges of corporate patrons. But for many of us there is a possibility for "self-help" that often has been neglected in the past, partly because, in an era of abundant government support, we didn't need to think about it and partly because of the attitude, until recently, of many universities including my own that there is something immoral and degrading about patents. Consequently there have been discoveries by endocrinologists that had potential commercial application and might have brought financial return to the institution of origin, but did not. In this area of self-help, the University of Wisconsin through the Wisconsin Alumni Research Foundation, established originally with the respective discoveries of the dicoumarol-type of anticoagulants and of vitamin-D production by irradiating milk, has been way ahead of the game. Only now are other universities trying to emulate this kind of arrangement by which the fruits of today's discoveries can be used to pay for the basic research of tomorrow.

These are but some of the alternatives that merit consideration as we enter a period of inadequate funding from traditional sources. I don't mean to imply that each of us will be in a position to exploit all or even any of these possibilities, but we, as well as our institutions, should be alert to perceive such opportunities when they exist. If enough new private support can be generated as a supplement to the federal funds still available, the total, if equitably distributed, should be sufficient to insure that research in endocrinology will continue unabated.

In a time of austerity, one should ask not only "Where can we obtain additional support?" but also "How can we use our current assets to their best advantage?" In my message in the March Newsletter, of which this presentation is really an extension, I mentioned how the ready availability of research funds we have enjoyed in the past has fostered disregard for conservation. I suggested some possibilities for economy, which include 1) the sharing of experimental animals when different research groups in the same institution are studying different tissues or organs; 2) foregoing the dubious luxury of our plethora of scientific meetings with redundant published proceedings; and 3) consultation with biostatisticians to insure that experiments are designed with a maximum potential for significant results.

In the area of experimental design there are certain basic considerations that, in some instances, can mean the difference between "high-information" and "low-information" experiments. As I discussed in a philosophical article, published 1969 in Perspectives in Biology and Medicine and entitled "The Science of Science," most biological experiments are designed to provide facts or information from which conclusions can be drawn by deductive logic. I mentioned John Platt's contention that some areas of molecular biology have enjoyed unusually rapid progress because they made extensive use of inductive reasoning or what he calls "strong inference." This involves setting up alternative hypotheses and devising
definitive experiments to exclude one or more of these possibilities. Wider use of inductive reasoning, where applicable, could enhance scientific progress without additional cost.

Investigators would do well to go back and read or reread some of the perceptive discussions of research principles, such as *The Way of an Investigator* by Walter B. Cannon, *The Art of Scientific Investigation* by W. I. B. Beveridge, and *Principles of Research in Biology and Medicine* by our own Dwight Ingle. These authors describe several types of errors that can creep into a scientist’s experiments and limit the significance of the conclusions. Of these, time permits me to mention only three, which, unfortunately, occur all too often in research today. These are the failure to include completely adequate controls, the failure to recognize multiple causes of a phenomenon, and, what is most common, the drawing of conclusions that are not completely warranted by the data. To this sophisticated audience there is no need to elaborate on these fallacies except to point out that, in the case of unwarranted conclusions, how easy it is for even a thoughtful investigator to fall into a trap.

Cannon tells the story about Dr. Eliot, a former president of Harvard University, who on leaving a social function was amazed to see the doorman select his hat from a large number of others and hand it to him. “How did you know that was my hat?” Eliot asked. To which the doorman replied, “I didn’t know it was your hat, Sir. I only know it is the one you gave me when you came in.”

In conclusion, the outlook for continued funding for biomedical research from traditional sources at our accustomed level is not promising. Although we must strive to preserve what we can, at the same time we must search for new sources of revenue and make more effective use of our present resources, including both time and substance. Let me emphasize: the take home message is not despair but hope. I am optimistic, for I have confidence in our collective ingenuity as we adjust to meet the challenge of a strange land. As Ella Wheeler Wilcox put it so well:

One ship drives east and another drives west
With the selfsame winds that blow.
‘Tis the set of the sails and not the gales
Which tells us the way to go.