

Presidential Address

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PRESIDENTIAL ADDRESS

Keystones

ROBERT A. GOOD

The American Society for Clinical Investigation stands at the keystone of progress in American medicine. To be president of this distinguished body has been a challenging educational experience.

As members of this society we do strange things. Analysis of our behavior in light of the new ethology of Tinbergen (1) and Lorenz (2) and their interpretation by Ardrey (3) might help us understand our annual rites. Each spring on precisely a given day members of the order gather from every corner leaving, temporarily, families and activities vital to self and state and travel to familiar surroundings where a selected few display scientific accomplishments. Accepted behavior of the group demands that achievements be challenged ruthlessly, destroyed if possible, and accepted only tentatively, with a "brief word of caution," if the ground is held. On an intellectual plane how comparable to activities of more primitive forms which migrate seasonally to a stamping ground where a vital game is played (3, 4). The stakes are different . . . in the case of the Ugando Kob for example a succession of willing females seek out the proper addresses established by physical defense of a small artificial territory. Difference of reward may not be crucial. In addition to his magnificent buttocks and chin (5), man must be distinguished by complexity of his games and size and organization of cerebrum. Exalted behavior is the aim. A leader selected by previous vigor and successful defense of intellectual territories is placed in central position, given an impossible task, and then *dismissed* from the group along with aged cohorts. The dismissed become useless and are granted permission to exercise only mild and inconsequential harassment of young aspirants who year by year fight their way to the positions of leadership. Sometimes these old fellows even encourage the younger ones. Adapting to this futile role at first I struggled to the extent of thinking I might fool everyone and instead of the expected address gain 20 minutes for a paper on my latest

discoveries. In early days presidents tried this to no avail. It was not what was wanted and they were dismissed anyway.

Recent history dictates a brief moment in anticipation of oblivion which, as with certain adult insects, is used to display bold colors and form not seen during developmental stages. For the president this is the time to express feelings previously unexpressed, to make exalted exhortations, or present an analysis of the relation of behavior in the learned society to other human endeavor. Since I must play by the rules my effort will be a mixture of all three adaptations.

Our society professes to stand for excellence. To foster excellence in clinical investigation we have, just as has occurred throughout nature, used selection. We have selected for membership, for participation in program, and for publication. Within the boundaries of human fallibility we have been fair and impartial in our selections. Previous presidents have argued this case and brought forth data to prove in their swan song that in this the society has been successful. Surely we have drawn on the past and in looking to successful cultures have used old methods to achieve our goals. We have tried to create inspirational leaders, heroes, even demigods through the years.

When a distance or obstacle needs to be spanned or a firm support provided, cultures dating from antiquity have employed the arch. Neolithic man leaned stones together in a triangular arch to bridge a gap. Curved profiles for spanning distances date from the cultures of the Tigris-Euphrates valley. In a classic Roman arch there are various combinations of wedge-shaped stones. Each of the stones strategically placed is called a *vousoir*. At the apex of the arch sits the last stone to be placed; this is the *keystone*, so called because of its critical position in the arch. This stone, although of no greater value to the span than any other, has gained architectural sig-

nificance from the prominence of its key position in completing the span. Ben Johnson wrote “. . . tis the keystone which makes the arch” (Fig. 1).

Throughout history societies and cultures have used similar techniques to facilitate excellence of behavior of man. Man *can* achieve exalted behavior and seems to do best when he creates gods in his image and spans the gap from ordinary human behavior to god-like behavior through a series of voussoirs of which his heroes stand at the keystone. He creates gods in his image, not impossibly remote, and encourages acceptance of leadership to approach the keystone of heroic behavior through leadership. Could our selection of membership and development of leaders and heroes be an attempt at this traditional motivation? Another certain means to achieve excellence in culture is to assure that growth of knowledge proceeds by geometric progression. Again a view of those cultures which many believe have achieved excellence and which have made extraordinary contributions reveals the usefulness of a dialectic. At base this, the most effective form, insists that every question be answered with a question, insuring maximal rate of growth. Knowledge, then, must be considered a succession of questions and not a succession of answers. Surely in our learned society we encourage this view and worship the *question* in pursuit of scientific progress.

In the exalted Greek and Hebrew cultures for example, magnificent heights have been reached. Participation of a high percentage of a small popu-

lation was certainly not achieved by placing limitations on the participation of large numbers of a high percentage of an aspiring population. It is on this point I often stumble as I consider our society. I agree that we should set standards; I believe we should set them very high, but having done so we must share membership with all who attain these standards. We must, I believe, as soon as possible, find means to eliminate the hazard of either a stifling or inflationary influence of an artificial number which is used to determine the numbers of men admitted to membership. Little basis, I feel, can be found to relate progress or excellence to numbers of men, numbers of their contributions, or numbers of anything.

Another question has been raised frequently in recent years . . . are we accomplishing our goals? In his introduction of *The Journal of Clinical Investigation* in 1921, A. E. Cohn (6) admonished that the aim of medicine is to understand, treat, and cure disease, and that the American Society for Clinical Investigation and its journal represent response to the call of a new spirit to develop a true science of medicine which can facilitate achievement of this goal. How well have we fared?

In a recent article in the *British Medical Journal*, Lord Platt (7) maintains that clinical investigation has failed. Particularly, he indicts the heavily financed clinical investigation of America, and he states that this discipline has contributed little to the great progress in treatment and cure of disease. Instead he attributes all progress to either basic medical sciences or pharmaceutical industry. In his audacious statement he cites numerous examples to which he attributes *no* significant role to clinical investigation. Time permitted me to research only a few of his examples, and I am afraid my bias for clinical investigation insists I express a divergent view. I will cite but a single example from Platt's own material and from that argue what I believe is the ridiculousness of his position. Platt contends that insulin was discovered in a department of physiology and, thus, gives this discovery to the basic sciences. What was the real story? It was known from the expatiative studies of Van Merring and Minkowski (8) that removal of the pancreas produced an increase of blood sugar. Excitement engendered by this discovery led to numerous attempts to extract an active principle to no avail. In 1920, Banting, a young physician, recently returned from an army post after World War I, and, apparently still having time to read, was perusing the clinical journal, *Surgery, Gynecology and Obstetrics*. He happened upon a paper written by Baron of Minneapolis (9). The focal point of Baron's paper was a single case which he as a young clinical investigator had studied at autopsy. The patient had had an apparent congenital absence of Santorini's duct and had developed a calculus in Wirsung's duct in the head of the pancreas. Behind the stone, presumably from secretory pressure, the acinar tissue had been completely destroyed, but the islets remained

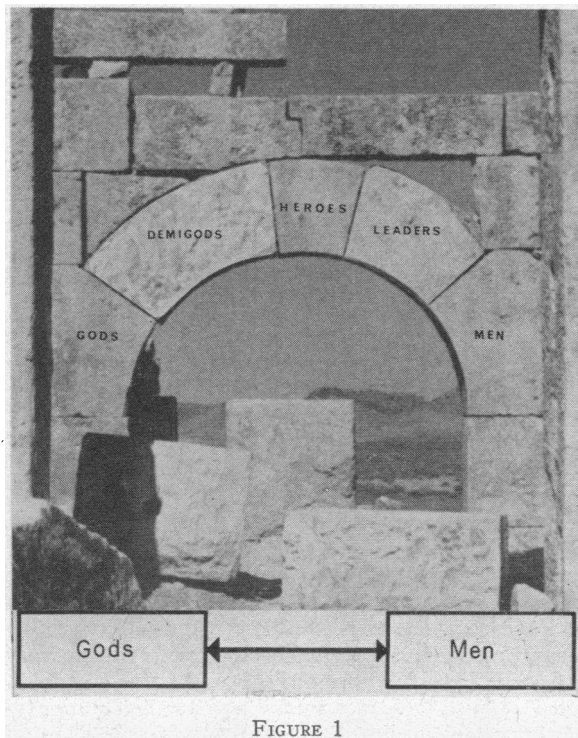


FIGURE 1

intact. The admonition from this experiment of nature was clear and the "eureka experience" of Banting so compelling that he rushed to Macleod's department of physiology in Toronto and, with great enthusiasm, presented the experimental approach to Macleod. Only then, together with the medical student Best, did he in a department of physiology proceed to execute the critical experiment. He tied off both pancreatic ducts, destroyed selectively the acinar pancreas leaving islets intact, and extracted in simple aqueous solution the internal secretion of the pancreas so much sought in numerous basic laboratories of the time. The control of pernicious anemia at about the same time was also the triumph of clinical investigation. These examples illustrate so clearly to me the concept expressed in the following arch (Fig. 2). Clinical investigation, powerful as a scientific discipline in its own right, has its greatest influence standing at the keystone of the arch to progress in medical practice. This central position is derived from the frequency with which natural experiments are encountered that result, to borrow from Koestler, in fusion of matrices (10). Such fusion relieves the anguish of a blocked matrix often unresolved by efforts toward understanding that derive from inductive experiences of the sciences basic to medicine.

Another example of how little this role of clinical investigation is understood in historical or contemporary perspective is revealed by a recent indictment of the transplantation surgeons. The indictment was directed toward the cardiovascular surgeons who electrified laity throughout the world with their heart transplantation. This leading basic physiologist focused on the failure of the cardiovascular surgeons in national and international publicity deriving from their adventure to recognize contributions from the basic sciences which to that viewer had made possible the technical contribution of heart transplantation. A number of examples were cited in which basic contributions had paved the way for heart and organ transplantation. Included were such major advances as development of the science of circulatory physiology, control of infection, development of anesthesiology, pharmacological support of cardiovascular function, technological progress permitting secure diagnosis, control of the immune rejection, and others. From my somewhat prejudicial position, I seemed to hear a dramatic recitation of example after example in which investigation had led the way, asked the critical questions, established the incisive view, or had dipped, even prematurely, into the methodology of basic and enabling sciences. Certainly the control of infection is in great measure attributable to leadership of clinical investigators. As examples one can cite Semmelweis and Holmes who independently interpreted natural clinical experiments correctly; Lister, already a clinical investigator who was alert to the earliest unestablished reports from Pasteur, and a host of clinical investigators, some still in this room,

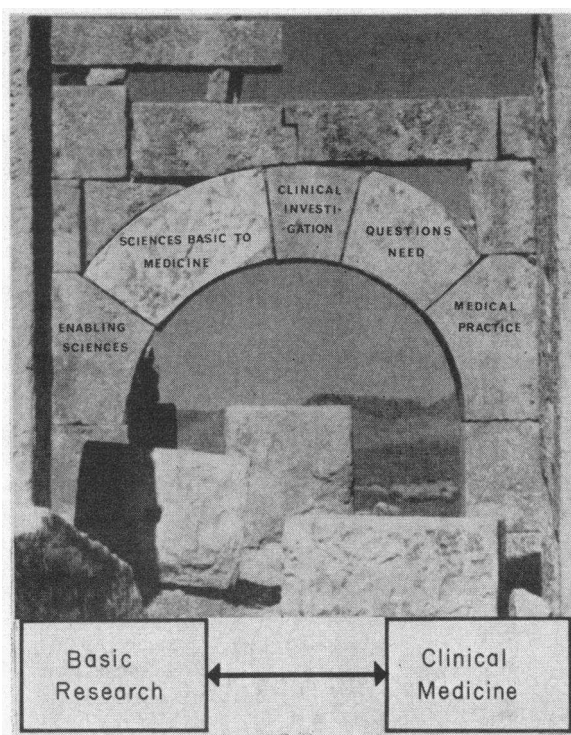


FIGURE 2

who established the safe and effective use of chemotherapeutics and antibiotics in clinical medicine.

The discovery and application of anesthesiology, to me, also derives from interpretation of several natural experiments and conduct of critical clinical investigations. The professional physiologists have contributed much to the understanding and control of the circulation, but was not the discovery of the circulation of the blood primarily an interpretation of a clinical experiment of nature? I think so. The discovery of the foxglove, the first of the cardioactive pharmacologicals, was made as a consequence of a natural clinical experiment. Establishment of the credibility of this insight, too, was the function of a most precise clinical investigation. Finally, to me it seemed that the application of certain poorly understood antimetabolites or cancer chemotherapeutic agents for immunosuppression has launched the transplantation era. Was this not the audacious manipulation by a young clinical hematologist now a member of our society who had achieved a vector from clinical and experimental forces? We must not only understand and insist on proper support of the basic and enabling sciences, but we must insist that the fruits of clinical investigation are real. Over the past several years I have collected more than 100 striking examples from medical history and contemporary medicine in which natural experiments have contributed uniquely and in a major way to the solution of an important medical or biological problem. The ma-

jority of these examples come from clinical medicine and clinical investigation. Soon I hope to compile these into a new look at medical history.

To me the power of the clinic and clinical investigators is not only to contribute to the solution of an immediate problem, but also to provide unique questions, bases for hypotheses, and direction and purpose for investigations in the so-called basic sciences. In spite of the criticisms that have been leveled, I must keep clinical investigation at the keystone of my arch to progress in both basic science and medical practice. Fig. 3 reflects what I consider to be the essence of the power of the clinic in spanning the gap between the basic and enabling sciences and medical practice. Certainly in establishing fact it is rare if ever that scientists use a purely inductive process (10-13); although from the time of Bacon they have deluded themselves into thinking that this is their way (12). Chance and intuition often derived from distraction, unconscious mulling, or interposing experiences most frequently play a critical role. The creative experience in the science of medicine as in all other science can often be attributed to enchantment by these maidens . . . chance and intuition (11). The stories we tell and the excitement of our adventure are in large part a function of surprises. The clinic and clinical investigations have so often provided the opportunity for the chance conjunction of a natural event and the uniquely prepared mind that they represent a veritable methodology for achieving Koestler's "fusion of matrices" (Fig. 4). Intuition and chance of course are not enough, and reason

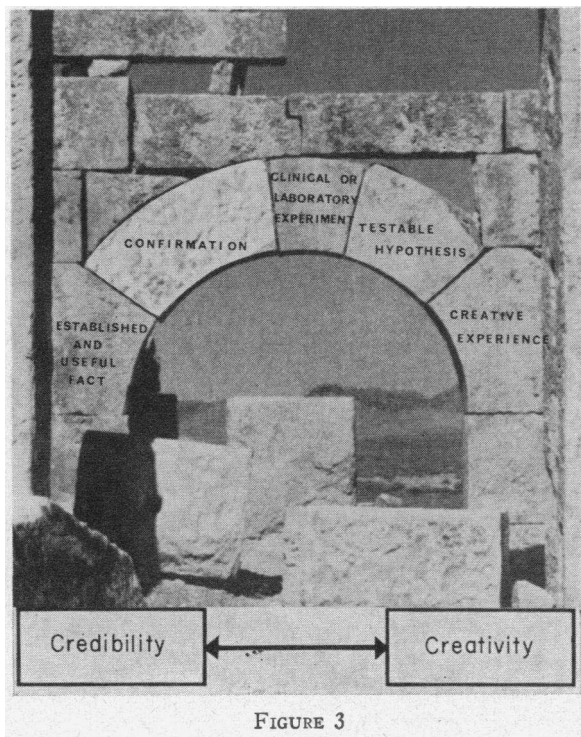


FIGURE 3

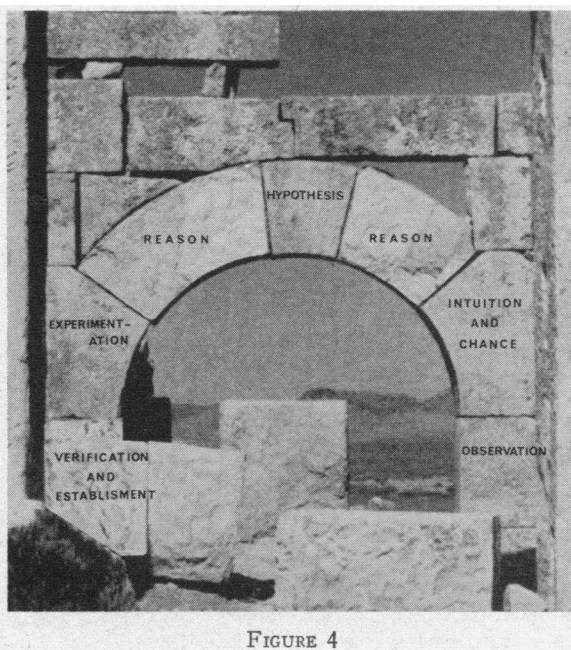


FIGURE 4

must be brought to bear to lead to construction of testable hypothesis which is followed in turn by rigid and critical experimental efforts to refute the hypothesis and thus bridge the gap from creative impulse to the establishment of useful fact. Hypotheses are not right or wrong; like classifications, they are useful or not useful.

In a most brilliant analysis, Popper (13) long ago pointed out that postulates have scientific value not as a consequence of their explanatory power but by virtue of their refutability. This characteristic is the essence of testability. Satisfactory fittings or observations which agree with an hypothesis do not in any way establish its worth or even strengthen it as a scientific instrument. It is only the hazard of refutation, the susceptibility to disproof which distinguishes a scientifically powerful and useful hypothesis from a scientifically useless one. Popper cites as examples of explanatory hypotheses which do not have scientific value the hypotheses of Marx and Freud and Adler (13). Establishing credibility of a postulate which has been derived from the creative experience is the major function of scientific analysis. The processes of creativity and establishment of credibility are, indeed, completely separate processes; they are separate types of functions (11). Both are essential to scientific progress, each is important in its own right, and each must be properly and efficiently used. Clinical investigation offers a rich complement of stimulation to creative experience. But credibility must be derived by analysis at the bench or in carefully controlled clinical experimentation. The rules of this operation in the clinical arena can be no different from those demanded in the basic biological, physiological, or biochemical laboratory. The analyses must demon-

strate reproducibility, reveal statistical force, and lead to predictability. To meet these demands of rigorous scientific demonstration is not always easy in the clinical arena. The demands, however, cannot and must not be compromised. In these spheres our society and journal stand impeccable.

The intensely emotional nature of the creative experience, I believe, accounts to some extent for what has always seemed to me a set of extraordinary incongruities in the behavior of scientists when dealing with their own brain children. From the earliest days of our introduction to science we are taught to sing popular songs about science. Science is objective; science is unemotional; science is altruistic; progress is facilitated by unreserved sharing and by freedom of communication. Nothing can give a scientist greater pleasure than to see his work as a stepping stone to progress. A scientist cannot be distressed by refutation of his hypothesis since this is the fate of all hypotheses as a consequence of progress, and progress is the goal. Even in our own group one sees over and over again, and from the most effective scientists, evidence of all human frailties . . . jealousy, hostility, selfishness, secretiveness, even surreptitiousness, and prejudice . . . these traits are most likely to leap to the fore when the intellectual territory staked out in relation to a creative experience, an original insight, a chance association is threatened by another scientist. Very few of us, none with whom I am acquainted, have entirely escaped from this hazard. Perhaps this emotional territoriality has value understandable in ethological relations to the physical territoriality of our species (3). Much study would be required to establish such a relationship, but it is an interesting thought which might be found testable.

It is, however, saddening to realize that clinical investigators and all scientists for that matter regardless of their early indoctrination remain people with all of man's difficulties. Perhaps this apparently unfortunate behavior has advantage for the species. Whatever that might be, the behavior seems from scientific perspectives destructive and useless. If scientists cannot be persuaded to exhibit behavior which transcends their animal instincts, what is to be expected of less-well educated or less thoroughly indoctrinated peoples? Perhaps like the dinosaurs we will have had it by virtue of our superspecialization as fighting beasts.

But science goes on, and biology and clinical medicine have made such great strides that as enterprises they threaten the very ecological niche which man must inhabit. I relish the opportunity to talk with students of all ages. Recently I spoke to a group of 250 of the brightest high school seniors in our five-state area trying to picture for them our glimpse into the transplantation era. I had finished talking of logarithmic growth of scientific and medical knowledge. I had stressed the impact of our growing understanding with ultimate control of certain forms of

aging, prevention and treatment of cancer, treatment of kidney disease, heart disease, chronic and recurrent infection, to say nothing of license for allogeneic and xenogeneic transplantation which might derive from manipulatable understanding of the lymphoid system and immunological capacity. One of the youngsters asked: "Dr. Good, doesn't your logarithmic curve extrapolate into an impossible world?" . . . Ladies and gentlemen, it does. So does our understanding of declining energy resources of our solar system, increasing knowledge of physics, chemistry, or genetics. This question brings me to my final keystone which I have derived from reflections on Rene Dubos' recent look into the incredible future.¹ Fig. 5 indicates the polarity of technocracy and humanity and represents my effort to span this gap with a final arch. As scientists we must be the servants of our culture, the very slaves of our artists, our poets, and our philosophers. Our science must be hard-nosed and critical unto itself, but it must be at the same time sensitive to needs of our cultures and peoples. Nowhere in science is it so natural to develop and express this sensitivity as in clinical investigation. As the diseases and distresses of people change, so must, of necessity, a change occur in our science. Clinical investigation must continuously take on new challenges and provide new solutions and new understanding for new kinds of problems.

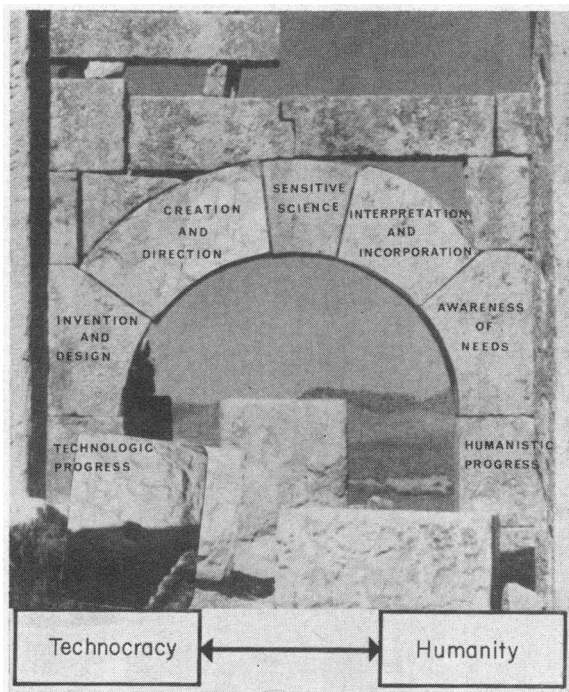


FIGURE 5

¹Dubos, R. New York Academy of Science Sesquicentennial Celebration. December 1967.

As a society and as individuals we must be sensitive to the needs not only of our science but also of changing needs and changing diseases of man. We can begin by standing ready to admit to program, publication, and membership scientists who are approaching behavioral problems with refutable hypotheses; we must include those scientists working in new or less well-developed facets of clinical investigation who are enjoying and critically interpreting questions derived from natural experiments. We must not let our learned society become simply a society for selection of professors of academic internal medicine but should insist on the vigor that will continue to derive from welcoming the clinical developmental biologists and those obstetricians and surgeons who worship clinical investigation as a primary function. We must listen to those of our group who, like Rutstein (14), become concerned with the delivery of the fruits of our sciences with maximal efficiency. Personally, I would like to see a scientific explanation of the challenging clinical observation that infant mortality is higher in some American ghettos than it is in Peru. Why?

I think in some respects our society and our journal have developed a threatening conservatism. If we are to survive and thrive as a learned society, we must make an increasing effort to develop the resources of youth. More and more exciting young people are available, and the best should be recruited to clinical investigation. We must listen with greater sensitivity than we have to the creative impulse and provide for its expression, we must be more prepared to set aside our cherished views and to change the objects of our analyses, and we must develop deeper awareness to the cries of our fellows who demand humanization of scientific progress. We must not reject mission-oriented research in which the mission demands we face new problems and new questions with proved strength. We must respond to the chang-

ing medical problems of our people with a sensitive science of clinical investigation at the keystone.

ACKNOWLEDGMENTS

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