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PRESIDENTIAL ADDRESS

THE INDIVIDUAL IN MEDICAL RESEARCH AND THE RÔLE OF THE UNIVERSITY CENTER IN HIS TRAINING

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It is the custom that there be a Presidential address. My thesis is not new. It concerns the importance of the individual in research and of the University Medical Center in his training.

This Society was established as a meeting ground for those interested in clinical investigation in its broadest aspects. If it has a fundamental objective, it is the creation and preservation of a "Heritage of Excellence" in research. The term "heritage of excellence" was coined by Alan Gregg as a penetrating expression of the abiding influence of Dr. Welch and his associates on the spirit of *creative* scholarship at the Johns Hopkins Medical Institutions.

It is important for University clinics to provide and to preserve opportunity for the training of the individual in clinical research, to promote *creative* scholarship. What does this entail? As Dr. Gregg has expressed it: "Men of superior character and capacity should have *freedom, responsibility* and *expectation.*"

There are many men on the threshold in medicine today who have the right qualities of character and ability in abundance. It is the responsibility of University Centers to maintain in full measure the opportunity for their development as investigators and teachers. Arnott has said: "It should be a basic article of faith that critical scholarship and search for new knowledge is the primary aim of the University. Not merely actual discovery, not merely even the attempt to discover, but the creation and cultivation of the spirit of discovery." This spirit should permeate the Medical Center. Granted that the combination of circumstances is such that only a *few* will achieve outstanding discoveries, everyone of us can promote such discoveries by facilitating fruitful associations with the so-called "pure scientist" and by criticism and discussion foster the spirit of inquiry.

As was pointed out from this rostrum not long ago, medical progress is in the logarithmic phase of growth. What has been the effect of this upon the ability of University Medical Centers to provide *freedom, responsibility* and *expectation* and to maintain an environment really conducive to *creative scholarship* on the part of young physicians?

I shall draw upon a crude analogy to present the situation as I see it and take as the model of a University Medical Center the Citric Acid cycle, the final common pathway for the oxidation of all three major food stuffs. It is the major source of body energy just as the University Center is the medical storage battery for the training of investigators.

The University is represented by a single active cell. Within the University are schools indicated by mitochondria, one of which is the University Medical Center. (Fig. 1, A and B.) When the intact mitochondrium is working in the presence of molecular oxygen, oxidation of food stuffs is completed, phosphorylation occurs, and ATP is formed. To carry out *its* objectives completely, the Medical Center must have molecular oxygen in the form of strong academic and financial support. The mitachondrial membrane is *selectively* permeable; only those factors essential to operation of the cycle gain entrance. In the Medical Center it is important to *select* good candidates for a career in medicine and to *select* a faculty that will foster in the student a keenness for self education and a desire to contribute to the search for new knowledge.

Let us look upon the cycle itself as the complex format for training students and investigative recruits fed into the University Medical Center. The cycle is self-perpetuating, constantly replenishing itself and constantly furnishing energy. Just as the cycle supplies 95% of the body's energy, the University Center is the major source of trained investigators for the total realm of medicine. The fat, protein and sugar feeding the cycle represent those qualities that determine selection of the prospective candidates represented by *Acetyl-CoA.*

The candidate investigators must have intelligence, integrity, a suitable personality, and ability to communi-

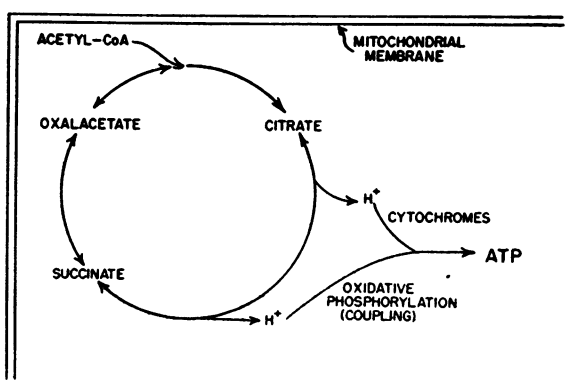

FIG. 1A

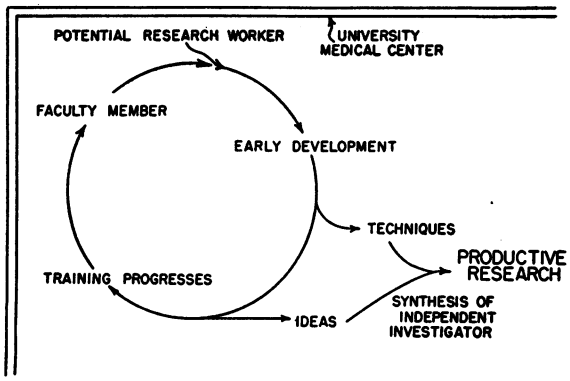

FIG. 1B

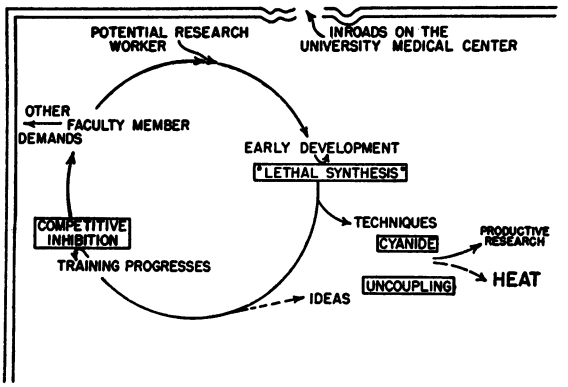

FIG. 2B

cate. Curiosity, initiative, and constructive imagination are essential. They should be resourceful and capable of self discipline. A questioning attitude to balance imaginative enthusiasm and a real measure of critical judgement complete the picture. The student or young investigator joins with the teacher (oxalacetate) and proceeds through the training cycle.

There are specific conditions which must be maintained if these integrated enzymatic reactions in the cycle are to progress optimally. Productivity requires *time* and *freedom* admixed with *responsibility—freedom* to express one's ideas, *freedom* to choose one's own research problems, and *opportunity* to teach and take *responsibility* for the care of patients without compulsion to do so at too great expense of time for research. *Freedom, responsibility* and finally *expectation;* the expectation of backing without strings, and contact with stimulating colleagues.

At several points in the cycle, electron transport to the cytochrome system occurs with oxidation and the creation of *high energy phosphate bonds.* The progress of a young investigator in developing new ideas and fostering them by well planned experiments is similarly punctuated by reports of his studies at meetings such as this one and finally culminates in a well written paper. Proper coupling is necessary for oxidative phosphorylation to occur with the greatest efficiency. The closer to optimal the conditions, the higher the P/O ratio in the cycle—the greater the amount of worthwhile research for the input of funds and facilities.

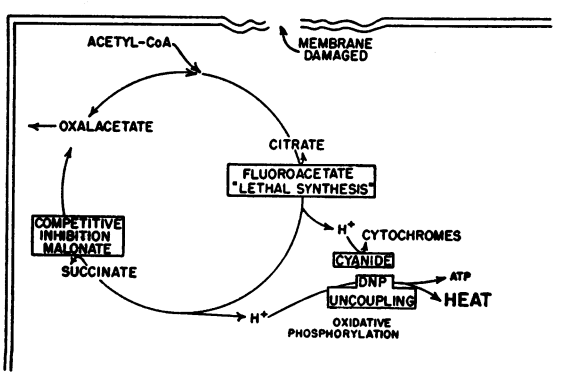

FIG. 2A

It is to be emphasized that mitochondria are the *only* elements of the cell that carry out the *complete* oxidation of carbohydrate, fat and protein just as the University Medical Center is the *only* medical environment which exists for the *complete* training of young investigators.

The ways in which the effective activity of the cycle can be blocked are many. (Fig. 2, A and B.)

The reaction rate is slowed by the removal of exalacetic acid (the teacher). The contributions of a senior staff are reduced proportionately by time spent in administration, so-called postgraduate training, society meetings, and, of course, committees.

Competitive inhibition of succinate by malonate is exemplified by the curtailment of research activities of the young investigator imposed by too many teaching or routine responsibilities necessary to supplement his remuneration. After our candidate has almost completed the cycle, the final step into a productive research career can be blocked by financial pressures to enter practice as surely and completely as cyanide can paralyze cytochrome oxidase. Furthermore, oxidation can occur without phosphorylation. Uncoupling of oxidative phosphorylation results from certain drugs such as dinitrophenol. In this circumstance there is generated unusable energy in the form of heat. Flitting from one problem to another, or taking on too many diverting functions like dinitrophenol, may produce enough heat to result in potboilers, but real research accomplishment suffers.

The recognition of these metabolic antagonists to creative scholarship is an easy matter in the gross, but there are subtle and insidious forms of inhibition that are not so obvious. *Fluoroacetate* is unusual. Its action is not like that of iodoacetate, which combines with SH groups, and no enzyme is known to be poisoned by it. Its action is one that Peters has termed *"lethal synthesis."* The non-toxic fluoroacetate is converted to fluorocitrate which blocks aconitate and the result is "jamming" of the cycle at the level of citric acid which then accumulates in the tissues. The cell fails to recognize that it is poisoning itself—too much of a good thing.

Even with good departments and a fine professional staff in a school, the production of well trained investigators can still be blocked. What are the sources of "lethal synthesis" in the Medical Center? The answers go right to the root of our research structure and affect the young investigator from his earliest medical experiences.

Common interest in the study of a given problem, with different techniques to contribute and from different points of view, that arises spontaneously from a real desire to share experiences and trade ideas, is obviously advantageous. Furthermore, the point is often reached where it is desirable and necessary to establish practical clinical applications by organized study, in patients, of experimental procedures devised in the laboratory.

When the "team" method of investigation, however, becomes a routine research activity in and of itself, the unique contributions of the individual investigator suffer a lethal blow.

Although, in many cases, the young investigator can profit greatly by apprenticeship in a team with full intellectual participation, he should be encouraged to tackle an independent problem right from the start, preferably a problem of his own choosing, not necessarily related to the group project. Only in this way can one assume an *alternative pathway* to guard against lethal synthesis.

There is a growing tendency for our training programs to become stereotyped—to turn out "board-eligible" products. The one way to assure that there will be no more Minots, or Peabodys is to load the formative years, when ideas and initiative should be given freedom to develop, with rigidly formal training.

In the training of house-offices, too much emphasis has been placed on programs of a relatively didactic nature. Here again practical experience in an atmosphere of good patient care, allowing the young man the maximum in responsibility is essential. As professors grow older, it seems harder for them to remember that knowledge gained by first-hand experience under skillful *guidance* is of far greater value than listening to the recapitulation of someone else's first-hand experience. The lethal synthesis of an excess of didactic exercises and meetings waste the time and sap the strength of the whole spectrum of medical personnel.

Real progress comes from new approaches, and new approaches come from men whose personal experience gives them an outlook different from the rest. It is easier to squelch such individuals at an early age than to make it possible for them to develop their own abilities. We seem to be heading this way with the long period of undergraduate preparation, the tightly packed medical curriculum, the years of prescribed postgraduate training for Boards, the unpredictable interruption of two years of Army Service, and the heavy clinical, administrative and teaching chores that are almost routinely expected of younger men in a department.

Are we not also calling on our Senior Faculty men to take on outside duties in far too great measure? The reasons for the decline in scientific effectiveness—the "investigative climacteric" which seems almost characteristic of graduation from this society—are many. Some no longer want to bother with the tribulations of personally conducted experimental studies. Administrative duties, membership on local and national committees, and the ever increasing demand to take part in additional educational exercises before local, state and national medical groups are obviously important but can also become socially acceptable excuses. A great scientific potential in the laboratory, the result of years of very expensive training, is soon lost. It is of utmost importance for the older investigator to maintain *active* contact with his laboratory. Without the continued intellectual stimulation of close association with young men, he is soon in no proper position to influence the training of investigators, even at the level of making so-called "policy."

The bulwark of defense against these and other factors which can cause a seemingly ideal environment for the creation of investigators to commit "lethal" synthesis, is sound and ample financial support of University Medical Centers. Acquisition of general funds for medical schools is easier said than done. A very discouraging statement appeared in the Lancet on January 7, 1956: "It is curious that in the United States, the wealthiest country in the world, medical schools seem to have financial troubles as great as, or greater than our own. At least half of them are said to have budget deficiencies or to need large sums to keep up their standards and yet there are immensely wealthy foundations in a position to spend money on a lavish scale. Sometimes, of course, the money given by the public can be used only in some specific direction such as cancer, psychiatry and poliomyelitis and the public does not necessarily give most generously to the most necessary purpose."

The money spent for national defense is more than 40 billions. Only 4 billions are spent for research and development of which only about 5% or 240 million goes to medical research in the broadest terms. Only about 80 million of this goes to support teaching and research in medical schools, and only a fraction pays its way in terms of overhead costs or can be used freely for the development of basic facilities.

Cutler recently gave figures from the Harvard Medical School which serve as an illustration. In 1954 there was expended from the funds of the Harvard Medical Center for research a total of $5,130,000. A fair overhead charge on this sum was about $1,500,000. But the various sources of this money for *direct* research expenses provided only $513,000 for *indirect* expenses. Accordingly, about a million dollars had to be taken from already strained general funds. As Cutler stated this is the way to commit medical research suicide. It is alternately the way to throw the burden to the young men who must fulfill some type of routine function for financial support making it difficult to attain the leisure and academic freedom necessary for his ideal development as an investigator.

There are several things that would help considerably. The Federal Government might adopt in the future an overall policy of more realistic reimbursement of overhead expense to grantees as it does to contractees of Federal research funds. A greater percentage of the

Federal money for *general* support of research and research training in University Centers and less of the total for *categorized* research is highly desirable. Large amounts of money are collected for medical purposes which is not utilized to the fullest extent desirable to meet these basic needs of the training institutions. I refer to the "special disease funds." These could go far towards correcting the situation by allotting 15–20% of their collections to independent schools as unrestricted or fluid funds. Important research in their specific areas of interest, far from suffering, would be enhanced by such a policy. If this practice became general, the funds might be pooled and administered under a sound formula set up by a non-partisan body such as the National Research Council.

Finally, it is to be emphasized that research is only a part of the entire medical structure. As Means put it: In serving the ultimate purposes of medicine, *research, education,* and *practice* must be sweetly blended. Within this triad there is mutual stimulation in all directions. For this reason, an optimum location for medical research and medical research training is the medical school and its affiliated teaching hospitals. It is here that the basic opportunity unfettered by regulations on research money should be provided. *The medical schools must be gotten out of their relative poverty in the midst of plenty.*

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