

ARTHUR KORNBERG, M.D.

BASIC MOTIVES OF A PROFESSIONAL LIFE

I WENT TO MEDICAL SCHOOL and then served as a house officer. I enjoyed clinical medicine and fully intended to go into practice. Then the events of 1941 forced me into unexpected circumstances. As a commissioned officer, during a tour of duty, I was ordered to do full-time research. I found I liked it and stayed with it. Yet I have always remained close to medical schools and medical problems. I have wondered many times to myself and with my students about the opportunities and responsibilities of a physician's life. I want to share some of these thoughts.

An earlier American president admonished us: "Ask not what your country can do for you but what you can do for your country." This is very fine sounding and also very misleading. Because most of the time we should and do occupy ourselves with personal interests, and we pursue national interests only when our personal and national interests happen to coincide.

I have met people in scientific research and in other professional activities who state that the prime mission in their professional lives is to help humanity. It has seemed to me that these people are either deluded or dishonest. I have worried over the years that my attitudes might be too harsh and off the mark but I was encouraged recently to find similar ideas charmingly expressed in some autobiographical notes of G. H. Hardy, the late and gifted English mathematician.

I would like to indicate what Hardy believed and what I believe to be the basic motives of a professional life, be it in mathematics, biochemistry or medicine. There are essentially three motives. These are:

First, pleasure in solving problems that provoke intellectual curiosity;

Second, pride in solving these problems with professional skill; and

Third, ambition to be creative and thereby to be an artist instead of a practitioner.

The burden of this paper will be to explain why I regard these three motivations to be the prime

components of a true professional life. But first I must consider the more usual attitude that the essence of a physician's profession is to dedicate himself to service. I assume that the physician when he performs such service for patients is primarily serving himself. He serves patients because he derives deep personal satisfaction from being of service or because he gains private wealth or most probably for both reasons. Obviously, regardless of motive, the patient's comfort or his very life depend on the services of a good physician. Sometimes physicians engage in teaching or administrative work, part time or even full time. But these are usually additional forms of community service. My appeal to students is that they consider the opportunities that training in medi-

Dr. Kornberg (ΑΩΑ, Rochester, 1941) has just completed ten years as Professor and Chairman of the Department of Biochemistry at Stanford. During this period, his Department has achieved an enviable reputation, both for its investigative productivity as well as for its stimulating teaching program for medical students and graduate students.

Dr. Kornberg, who received a Nobel Prize in 1959, based this paper on an address delivered at the Commencement exercises of the University of Utah College of Medicine in June, 1969.

cine offers for a professional life with even larger dimensions, a professional life that includes more artistic and intellectual activity. This fuller professional life, I believe, will best serve both personal as well as community interest.

What I am describing is in some sense an ideal standard, and ideal standards are shrugged off in medicine as often as they are in politics. But this does not justify one's seeking anything less. Walter Lippman said many years ago that it is "bad to shrug off ideal standards in politics . . . because it defeats us and frustrates our lives. If we do not harden ourselves by stretching ourselves to reach upward to these not wholly attainable ideals, we slump down and settle into flabbiness and footlessness and boredom."

I dedicate this paper to Dr. William S. McCann, Professor of Medicine, Emeritus, of the University of Rochester, on the occasion of his 80th birthday. I was a student and house officer in his department during the years 1939-1942. I recall with deep gratitude his generous personal concern for me and his courageous fight against bigotry, intolerance and chauvinism. AK

Now let me be specific about these three motivations in a physician's professional life that are so often lost sight of.

The first, as I have said, is the pleasure in solving problems that provoke intellectual curiosity. Hippocrates is my best example. He is cited for his Oath, which contains some highly questionable guides for modern medical etiquette. He deserves to be celebrated, rather, for being the first to reject the priestly aspects of the physician's profession and for applying his intellect instead. He urged the use of inductive reasoning in place of tradition and superstition, he made astute clinical observations, which incidentally included the use of auscultation, he carefully recorded case histories and he argued that the physician, rather than the gods, has the responsibility to interpose treatments in order to influence the course of a disease.

Clinical practice abounds in difficult and thought-provoking problems. If the physician has failed to ask himself penetrating questions about a disease, its basic pathogenesis and treatment, he will find that the medical literature is full of such questions and even some answers. But the busy physician doesn't have the time to think, to read, to indulge in this academic exercise. He is too busy delivering urgent service. I have a specific suggestion. The physician should find ways of being more efficient in disposing of routine service work in order to earn the leisure to use his brains. Let me cite an example.

An interesting study is in progress of the habits of pediatricians in private practice. In a rather extensive and careful survey, it was found that the pediatrician sees an equal number of sick and well children in his office. But whereas the average visit with a sick child takes about five minutes, the visit with a well child takes almost twice as long. Most of the time spent with the well baby and child is taken up with routine measurements and shots. Therefore two-thirds of the physician's time is consumed with this simple routine work, work that a trained assistant should be able to do. On the basis of these findings, each of several pediatricians engaged a nurse, and within two months trained her to take over most of the routine office functions. It has turned out that during the past year their patients have not only accepted the nurse's services but even prefer them to the doctor's, which tend to be more hurried. The patients still pay the same fees. Now that the doctor has been relieved of time-consuming, boring effort he can use these extra hours thinking and reading about and probing the intellectually provocative problems presented by his very sick patients.

If the first motivation of the truly professional physician is pleasure in solving intellectual prob-

lems, then the second motivation is pride in solving these problems with skill and style. The fine physician can justly take pride when he uses intuition and wisdom to solve an especially difficult diagnostic or therapeutic problem. But such favorable instances are not common or predictable enough. In the work-a-day practice of medicine, physicians could do far better by exploiting improved operational approaches. Some ideas occur to me from my experience in trying to solve research problems.

I want to consider first the collection and recording of data.

Despite what one hears, the successful research worker usually tackles difficult problems with a brute force approach. He makes many measurements. Important observations don't come usually from inspired ideas but rather from thorough and systematic analyses. A problem takes on entirely new directions and proportions as outgrowths from what may have seemed to be routine measurements. I think physicians would do well to collect more data. Collecting data takes time and money. I am certain we can devise more economical and efficient ways to get these analyses done. As we collect more data, we must learn how to record them so that we can use and recall them.

The keeping of clinical records has been my pet peeve since medical student days. The worst, of course, is the absence of records entirely. But nearly as bad are the usual chicken tracks of a chronicle that is scattered, incomplete and incoherent. No research student or laboratory assistant in my experience has ever kept daily records on problems of bacteria or of enzymes as undisciplined as those that fill the charts of patients in our university hospitals. It seems to me incredible that our schools and teaching hospitals have failed to demand disciplined and standardized records. Such records are crucial not only to the immediate and long-term welfare of the individual patient but are also essential to the progress of medicine as a whole. Good records will generate new insights and subtle deviations that now go unnoticed will become more explicit.

Energetic collection of data and their intelligent tabulation will solve part of the problem. But the full solution of a clinical problem includes its proper treatment. Which drug or procedure to choose and how to use it?

The problem of therapy is too large and difficult a subject for me, but I am struck by two things. On the one hand, there is extraordinary commercial and advertising promotion of drugs, and on the other hand there is a ready acceptance of these claims by the physician because he does not have the means to judge and appraise them. New drugs and clinical procedures are accepted

by the physician and used until they are proven to be toxic or without redeeming value. By contrast, the research worker regards a new technique, a new compound or a new idea as suspect until proven valid.

The story of chloramphenicol is an interesting case in point. A hematologist colleague of mine was called upon several years ago to treat a woman with aplastic anemia that arose from the use of this drug. He was later involved as a witness in litigation because the use of chloramphenicol in this case had been ill-advised. I learned from him that chloramphenicol was widely promoted and used in this country long after its potential for producing fatal anemia was well known. There were, in 1963, in California alone, 10 deaths directly attributable to the use of chloramphenicol, an incidence 13 times the general population risk of aplastic anemia. It seemed clear even then that the use of chloramphenicol was rarely warranted. It is even more clear today and still chloramphenicol is prescribed far more than it should be.

The problem of drug-induced disease has been and will always remain with us. It is a problem in which society has a collective responsibility but in which the intellectual effort of the skillful physician will always have a large and decisive role.

I have discussed two motivations, the pleasure a physician can derive from coping with intellectually demanding problems and the pride he can take in tackling such problems with professional vigor and method. Now I come finally to the third motivation of a professional life, the ambition to be creative and thereby to be more of an artist than a practitioner. This could be the most important aspect of a physician's life and is the most rarely realized. I would like to dwell on this subject.

Do we select students for medical school for their creative capacities? I think rather we select for general intelligence and motivation. In fact, the pressure of medical school courses and the patterns of clinical training tend to suppress creativity in the student. The redeeming and sometimes saving feature of a medical education is exposure to the magnificence of nature as it is displayed in the form and function of the human body. Who can lack the sensitivity to be awed and inspired by the fantastic intricacy and ingenuity in the operation of a cell membrane, a muscle, a reflex response? Who can be unaffected by what we know of the chemistry, physiology and anatomy of vision and how much remains to be discovered about the entire visual process that lies between the retina and the brain?

Most of us as we passed through our courses in pathology and physical diagnosis became the certain victims of some fatal disease. In my case I

succumbed to carcinoma of the bowel, an aortic aneurysm and amyotrophic lateral sclerosis, all in one semester. And as we recovered from these successive afflictions, we realized what a miracle it is to be and remain alive. Since it takes so little to upset this exquisite balance, there must be mechanisms, beyond our appreciation, that keep us in a steady state of health.

The physician has the opportunity in his daily concern with the human organism to contribute original observations about the function of the body in health and disease. Imagine the great leap forward in medicine, if each of the 300,000 physicians in the U.S. contributed one new fact in his lifetime. Some may argue that few of our 300,000 physicians have the intellect or imagination to make an original contribution, but I would emphatically deny it.

How smart does a creative scientist have to be? I recall a story told by Professor Rabi, the physicist, about a scientist who lent \$10 to a friend and after a while began to hound him for the money. The friend in irritation gave the scientist a bag full of pennies. The scientist being suspicious began counting the pennies. When he reached 500, 501, 502, he tired and said, "It's been right so far; they must all be here."

How creative are physicians? I could cite physicians who currently excel as poets, playwrights, artists, musicians, craftsmen and financiers. Yet I am not implying that physicians do creative things in everything but medicine and science. The history of medicine is studded with names of physicians who made major scientific contributions. But Jenner, Koch and Ehrlich belonged to another century and it might seem that that phase of medical history would not repeat itself. While it is true that much of modern science and medicine is highly specialized, it is also true that there are incalculable opportunities for a thoughtful, curious and determined physician to add a fact or more in his lifetime.

I met such a physician a few weeks ago. He is a 40-year-old ophthalmologist who practices in a small town in northern Minnesota. He flies his own plane to see patients within a radius of over 100 miles. He has a large practice, a large family and a large number of outdoor hobbies. He is also making an important contribution to the treatment of glaucoma. He was disturbed by the awkward and inadequate way in which his glaucoma patients had to take the required doses of pilocarpine. His patients' annoyance is shared by over 2 million people in the U.S. with glaucoma who take eye drops two to six times a day. Added to the discomfort of eye drops is the immediate miotic reaction which interferes with vision and the frequent conjunctival irritations and infections.

This physician is a thoughtful and curious man. He had heard about a new plastic which permits slow diffusion of small molecules. He obtained some of this plastic and began experimenting in his office with small drug containers, fashioned from this plastic, which could be easily placed and comfortably retained beneath the lower eyelid. He later incorporated a tiny magnetic element in the plastic container, so that a metal probe could be used to install and remove the container. He was successful in obtaining a patent and the collaboration of an outstanding pharmaceutical company. As a result there is now active research on the optimal shape, size and pilocarpine content of the container. There is a strong prospect that with proper design, the container need be replaced only once every 24 hours, that a very much lower dose of pilocarpine need be used, and that this dose will achieve a sustained and optimal drug level that will keep the intraocular pressure in the physiological range. Of course, success in this work will encourage the use of such devices for other ophthalmic drugs and beyond that the application of similar devices to therapeutic problems in other parts of the body.

The physician I have told you about is unusual but not unique. When I examine the experiences of a number of physicians like him who have made significant original contributions, I am impressed by two things. They have concentrated on a single subject or better still on a single facet of a single subject. Secondly, this sharp focus on a subject has not limited but rather enlarged their general stature as a physician. The same can be said for a laboratory research worker. He concentrates on a single question and probes it from many angles. Invariably, clarification of any facet of a problem opens new fields to his vision, offers him fresh alternatives for his further studies and thus enlarges his horizons of science.

My own research experience has included both clinical and chemical work. It started as a medical student, when I developed jaundice and tried to figure out why. Incidentally, that diagnosis involved a chemical measurement of my bilirubin level and it was real. Thereafter, for three years, I made as many measurements of bilirubin levels and bilirubin clearances as time and access to people's veins would allow me. From this work we learned something about the incidence and significance of a not uncommon dysfunction of bilirubin excretion.

As for chemical or laboratory research, I had no special interest in it in medical school. Enzymes were hardly mentioned in my biochemistry course in 1937. My fascination with enzymes in general began ten years later and with one enzyme, in particular, DNA polymerase, in 1955.

This enzyme is remarkable because it can copy long stretches of DNA, the genetic material, without error. It can synthesize viral DNA which is fully infective. From this we infer that the genes in the chromosome of a virus are replicated faithfully.

But how does this remarkable enzyme do its job? We were in the doldrums regarding this question for many years. The problem was not advanced by inspiration but by time-consuming and back-breaking work. We learned how to streamline the preparation of the enzyme from *Escherichia coli* so that we could work up 200 pounds of bacterial cell paste and thereby obtain half a gram of pure enzyme. Previously we had had only a few milligrams at any one time.

Having these large amounts of pure enzyme in hand radically changed our approach. We could afford for the first time to make routine but necessary measurements of the size and composition of the enzyme and to determine its capacity to bind DNA and the nucleoside triphosphates that serve as building blocks in synthesis. These were not novel experiments but they yielded new data and raised novel questions. For the first time we began to develop a comprehensive picture of the working center of this enzyme molecule.

From this picture we came to realize that the enzyme can work not only as a sewing machine to make DNA, but under certain circumstances can also cut out sections of DNA. It occurred to us that this ability of the enzyme to cut out sections of DNA might enable it to excise distorted regions of DNA such as lesions produced by ultraviolet light (UV) irradiation. Such a lesion in DNA prevents it from being copied and can therefore be lethal. However, we know that all cells, bacterial and animal, possess the capacity to excise such a UV lesion and patch the area from which the section is removed, thus restoring the DNA to its original state. In fact, very recently investigators at the University of California Medical School in San Francisco have shown that patients suffering from Xeroderma pigmentosa, a disease in which there is extraordinary sensitivity to sunlight and a disposition to skin cancer, lack the ability to excise UV-induced lesions from DNA. When we tested DNA polymerase in the test tube, it proved to have a great facility for excising UV-induced lesions and for patching the section of DNA from which the lesion was excised.

At this point we don't really know whether DNA polymerase repairs UV-induced lesions in the cell as it does in the test tube. If it does, then the cellular operations may be as follows: First, there is a special enzyme which patrols the chromosome and upon finding a distortion in the double helix introduces a cut next to or near the

lesion. Thereupon, DNA polymerase excises this section of DNA at the same time replacing it with new DNA. Finally another enzyme, called DNA ligase, whose function it is to seal cuts in DNA, then restores the chromosome to a fully intact double helix.

I have cited these recent experiences of a Minnesota physician and some current work from my laboratory to illustrate the opportunities in biology for inquiries which, if sustained, inevitably lead to new information. Medicine is full of these opportunities. What medicine can do for each physician in his lifetime is to let him use his mind as well as his heart. In addition, medicine offers him the splendid opportunity to use that artistic

combination of mind and heart which leads to creative effort.

There is a statement attributed to Aristotle, who was the son of a physician, was trained by his father and influenced by Hippocrates, and who is said to have practiced medicine early in his career. This is a statement which means a great deal to me and with which I shall close. He said: "The search for Truth is in one way hard and in another easy. For it is evident that no one can master it fully nor miss it wholly. But each adds a little to our knowledge of Nature, and from all the facts assembled there arises a certain grandeur."