OF MICE
MEN
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BY

JOHN H. HELLER

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DEDICATION

The path of the basic research man can be difficult and lonely. Many have helped me. Because of their singular contribution, I dedicate this volume to:

MY PARENTS

PROFESSOR ERNST MYLON *of Yale*

who first introduced me to molecular dimensions and to methodology.

DR. ALAN GREGG *of The Rockefeller Foundation*

who inspired and felt that one's reach should exceed one's grasp.

PROFESSOR FRANCIS BLAKE *of Yale*

who would not shrink from the novel because it was new.

PROFESSOR GEORGE DARLING *of Yale*

whose vision of the future permitted the seeding in the past.

FLORENCE SCHICK GIFFORD

who had enough faith to make the first gift.

WILLIAM A. STURGIS

whose zeal, faith and foresight gave solace and encouragement.

ROBERT T. TATE, JR.

the pillar of strength, who throughout the years, with faith and love, has been a staunch bastion and shield, who undismayed and with courage helped to fight despair, frustration, adversity, and the unholy.

SENATOR PRESCOTT BUSH

who for over a decade has remained constantly on call for any help he can render.

DR. MARJORIE KNAUTH

whose devotion and greatness can best be judged by her reply to the question: "How can one ever hope to thank you for your tremendous selflessness?" She said, "You don't. Just thank God."

DR. R. STERLING MUELLER
DR. ROBERT F. SOLLEY
DR. SCUDDER WINSLOW

The trio who have given so much of time and talent and who by their unselfish dedication provide a continuing source of inspiration and hope.

JOHN L. SENIOR, JR.

who with his family provide bedrock in a sea of uncertainty.

MY WIFE

who has unshakable faith and whose inexhaustible love has given inspiration, salved the wounds of "slings and arrows," filled the troughs of despair, and permitted the demands of the most demanding of all rivals—science.

SCIENCE: HANDMAIDEN OF FREEDOM *

"In our lifetime greater advances have probably taken place in science and technology than in all prior history. These advances and changes have also had a profound effect on government and national policy. In my public service I have found myself increasingly involved with problems and policies affected by the growth and impact of science and technology.

"Our science and technology are the cornerstone of American security, American welfare and our program for a just peace. For the government to neglect this would be folly. But the strength, growth, and vitality of our science and engineering, as in every other productive enterprise, hinge primarily upon the efforts of private individuals. Private institutions, foundations, colleges, and universities, professional societies and industry, as well as all levels of government, have a vital role to play in promoting individual leadership and in striving for excellence and the achievements of a high level of creative activity. Thus is created increased opportunity to pioneer, to initiate, and to explore untrodden areas.

* Excerpts from President Dwight D. Eisenhower's speech given at the Symposium on Basic Research in New York City—May, 1959.

"As we have long known, freedom must be earned and protected every day by every one of us. Freedom bestows on us the priceless gift of opportunity—if we neglect our opportunities we shall certainly lose our freedom.

"Basic science, of course, is the essential underpinning of applied research and development. It represents the frontier where exploration and discovery begin. Moreover, achievements in basic research, adding as they do to man's fundamental understanding, have a quality of universality that goes beyond any limited or local application or limitation of time. Eventually those discoveries benefit all mankind."

DWIGHT D. EISENHOWER

New York City
1959

INTRODUCTION

The war caused intense interest in research, in this country and in fact all over the world. It could hardly have been otherwise, with radar, guided missiles, A-bombs appearing as the applications of scientific knowledge which have been generations in building. The result has been greatly increased expenditure for research, heavily subsidized by government from tax money. Many of the results have been salutary, and, on the whole, government subsidy has been carried out with much less than many of us feared of government control and political meddling.

But the whole program has been erratic and there has been waste, the pursuit of trivial objectives, expensive support of mediocrity. This sort of thing is inevitable in a program of the magnitude that this country has pursued. It does not mask the fact that there is a great deal of sound work going on, wisely guided, and aimed at worthy ends.

The reason we have distortions is clear enough. The people of this country, and the few of the people they have chosen to represent and govern them, have, in general, an enthusiasm for research, and serious ignorance as to what it is, and how it is best furthered. Especially there is little real understanding of the difference between gadgeteering at one extreme and the painstaking search for genuinely new and relevant knowledge at the other. This latter is basic or fundamental research, and it is still far from being adequately supported. Then, too, we in this country are prone to follow fads, and we overemphasize the spectacular. As an example, let us take a cold look at the whole program on space exploration which is now costing the taxpayers some billions of dollars. It has three aspects, military, propaganda, and scientific. There is no question that we need to be energetically pushing the first aspect, in the form of long-range ballistic missiles, as long as we are confronted by a potential enemy that still aims to conquer the world. I have no criticism of this; on the contrary, I trust we are not so foolish as to neglect it. On the propaganda aspect we lost the first round, when Russia beat us to the punch and launched a sputnik. We will probably lose the next round which will possibly consist of putting a man in space. Is this race worth what it costs, for propaganda? I doubt it. But I am primarily concerned with the scientific aspect. There is no doubt of the scientific value of results already obtained, and soon to be obtained, by use of satellites. That is the trouble; just as soon as one questions the scientific program he is accused of not understanding the great value of the results. I do not question them. But I do seriously question whether they are worth what they are costing us, in dollars, in diversion of scientists and engineers from other tasks, and in the effect on the minds of youth. I question it because I see so many unsolved problems, vital but unspectacular ones, which we are simultaneously neglecting. I question it because I visualize the possible progress in critical fields of research which could be made if a fraction of the enormous effort being made on "space" were devoted to their pursuit. The lure of large funds, and of public acclaim, has warped the judgment of many scientists on relative scientific values.

We are grossly ignorant about life. Our life sciences, the biological sciences, are just at the beginning of a great surge forward. At present we grope our way in the murk; results are usually obtained empirically or by accident. Some day we will proceed with assurance and on the basis of understanding. The advances being made, and there are many of them, in understanding the complex processes by which organisms evolve and function are far more exciting to me than shooting at the moon. And they are far more important for the future health, security, and happiness of all peoples. The only reason they are not exciting to people generally is that they are not understood. It is much easier to grasp, or to believe one grasps, the functioning of a guided rocket, than the subtle mechanism by which a virus invades a bacterium, and by so doing modifies its genetic functioning. But the latter, even when grasped only feebly, has all the romance of the unknown and unfolding, and its full understanding would be a significant step toward releasing man from the terrors of virus disease which have harassed him for thousands of years.

This book opens before the layman some of the exciting vistas of basic biological research. If books such as this were multiplied, and widely read, we might then make more sense in the ways in which we direct our national research effort.

VANNEVAR BUSH

304 Marsh St.
Belmont, Mass.
29 January 1960

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AUTHOR'S PREFACE

This book is intended for the layman with no background in science. It is precisely because so many laymen have no knowledge of science that this book is written.

When the industrial revolution arrived, many individuals could afford to ignore it and got away with it. The scientific revolution in which we now find ourselves cannot be ignored with impunity. For instance, radio waves have been in great part responsible for the spread of nationalism to totally illiterate peoples. Thermonuclear bombs and radioactive fallout have become of global concern. Everything that you wear or eat has been touched by science. Whether you live or die, the diseases you and your family will have and whether or not they can be cured or prevented, your weather, your economic situation, and even your freedom will be affected by science. One need not have any scientific training to understand science adequately in order to make meaningful judgments as a citizen. A citizen must make decisions on our economic, foreign, and military policies even though he is not expert in any of these fields.

There are, without question, many institutions, individuals, research projects, foundations, corporations and the like that are meeting the challenge of the scientific revolution. However, the effort is still pitifully inadequate. In this book, I have deliberately avoided mentioning triumphs and successes. Thus, I have avoided "pointing with pride" and, for the sake of emphasis, have chosen to "view with alarm." There are many fine volumes written for aficionados of science. This is written for individuals with no background in this field. Hence, I have had to simplify considerably, and many times in the process of simplification, one must rely upon generality with the concomitant loss of precise accuracy. I have used analogy freely. Should this volume induce just a few more people to appreciate the enormous potential of basic research and the need for its adequate support, I shall be content.

JOHN H. HELLER

Ridgefield, Connecticut
1959

CHAPTER 1

THE MID-TWENTIETH-CENTURY PHYSICIAN

A good physician must have compassion. This is true not only of the modern doctor. It goes back in its concept to the pre-Christian era of the first great physician, Hippocrates. Today, as always, a physician must treat not only the ailment but the whole person. This includes the patient's mind, his fears, his hopes, and the concern of his family.

When disease strikes, concern and anxiety are almost inevitably present. In order for the physician to fulfill his great responsibility, he must be alert and able to cope with every aspect of the problem. He must intuitively know that the grunt of pain from one patient and the scream of agony from another may simply represent individual reactions to the same discomfort of two persons suffering from the same malady. The doctor must have insight—a sort of medical green thumb—so that he can determine what physical diseases are caused by disturbances of the mind in contrast to those physical symptoms which are responsible for agony of the psyche.

However, all of these requirements and virtues are part of the art of medicine. They have nothing at all to do with medicine as a science. The science of medicine, in contrast to the art, concerns itself with the "how, what, and why" of the disease. As with all sciences, it must be built on a framework of demonstrable and verifiable fact. A dearth of science is currently the greatest lack in twentieth-century medicine. This is attested to by physicians themselves, as witness the following:

Archives of Internal Medicine:

> In the modern world of busy practice, many physicians have lost the habit of reading, others have never cultivated it, and few can or will make the sacrifice of time and effort needed to know what goes on in the world they live in. They feel lucky if they can keep up with their own special interests along ever-narrowing lines. It is shocking but rarely recognized that specialists in medicine behave like bewildered laymen in other fields of medicine or science than their own. . . . We have to accept as the inevitable by-product of specialization the poison of ignorance.

Journal of the American Medical Association:

> The most urgent need of present national needs in the medical field is conceived to be expansion and improvement of medical education integrally related to research and progressive improvement of medical practice, steadily lessening the empirical nature of applications of new knowledge to medicine.

The Dean of the Vanderbilt University School of Medicine, Dr. John B. Youmans:

> Most general practitioners consider themselves too pressed by the demands of practice to undertake any responsibility for keeping in touch with new knowledge. And it is upon this contact with new knowledge that the quality of medical care offered by the practitioners depends—and the excellence of the treatment they are able to offer.

Archives of Internal Medicine:

> The emphasis on the organic, biological orientation to mental disease is singularly appropriate at a time when we see the decline of systems of belief, the mystical formulations of those who erect beautiful hypotheses but deny the possibility of testing them by the rubrics of science.

Dana Atchley, Professor of Medicine at Columbia University College of Physicians and Surgeons:

> No longer happily content with restricted diagnostic pigeonholes, he [the physician] is able and eager to understand the basic mechanisms.

This is not to say that there are no bright aspects to modern medicine. The average life span of men and women is greater than it ever has been before. We know how to reduce pain, control some anxiety, and cure a variety of heretofore incurable ailments. But a great many of the advances in the conquest of disease have come from accidental discoveries or from fundamental knowledge developed in other sciences. Let us look at a few examples.

The control of infection has been one of the greatest factors in reducing the death rate of infants and extending the life span of elderly people. But the great breakthrough in the control of infection was made by Louis Pasteur, who was a chemist, not a physician. Since Pasteur's day, the major modern advances in the control of infectious diseases have come from the sulfa drugs and the antibiotics. Both of these groups of drugs were accidental by-products of other research, and neither was directly sought for. Indeed, in both cases one can say it was better luck than management which presented medicine with two of its most powerful tools.

Many other drugs we use today have come down to us from primitive peoples. Digitalis, one of the best heart drugs we have, was given to us by a British "witch" who used it in a concoction for the prevention of dropsy; quinine and curare were used for centuries by South American Indians; the first great tranquilizer drug was "discovered" and given to our Western physicians after World War II. This "discovery" occurred when a European pharmaceutical company had the good sense to listen to some Indian physicians who kept recommending the virtues of a certain plant, Rauwolfia serpentina, which had been used in India since pre-Christian times to reduce sex drive. After two thousand years, Western medical "science" finally studied, isolated, and purified this drug, which became the first of the tranquilizer series.

An example of accidental discovery occurred recently when a pharmaceutical house, anxious to capture some of the anti-allergy market of the antihistamine drugs, developed a chemical variation of the existing antihistamines which it hoped might be effective, and began to test it in a large university clinic. The new drug turned out to be very poor for the treatment of allergy. However, an interne in the clinic pricked up his ears when a pregnant patient said that since taking the drug, though her allergy was not affected, she no longer got carsick on the trolley which brought her to the hospital. Thus a new group of effective anti-seasickness drugs was born and thousands of people are grateful for this chance observation by a young physician.

We still do not know how these anti-seasickness drugs work, nor do we understand how many other of our most effective drugs act on the human body. We have been using aspirin by the tens of thousands of tons since the nineteenth century but we have no idea why it reduces pain. We have had digitalis for centuries, and we do not know how it does what it does. We have no idea how the commonly used sleeping tablets (the barbiturates) work. We have no idea how the sex hormones do what they do. It is to the everlasting credit of physicians the world over that they have been able to capitalize upon lucky accident or chance observation and use the results so effectively, working as they must with little factual scientific knowledge but with much intuition.

It might seem bizarre that we do not know the whys and wherefores of many of the drugs which we have been using for decades or, in some cases, centuries. However, the reasons underlying this ignorance lie at the heart of medicine's problem in becoming a true science.

It is at the level of the molecule that either normalcy or disease occurs. All of us are made up of cells, trillions of them, and each cell contains millions of molecules. Until we understand how these tiny molecules within the cells function, we cannot hope to understand very much about how drugs may affect them. Actually, what this points to is that unless one understands the mechanism of normalcy, one cannot hope to understand the mechanism of abnormality or disease.

Unfortunately, most present-day physicians are not adequately trained to understand or to work with molecules. At best, they are given but a smattering of this knowledge. They know and can describe the symptoms of disease, they know what abnormalities look like under the microscope or on the autopsy table, indeed they may have some small knowledge of the chemical changes that occur in illness—but by and large they have no competency at the molecular level. On the other hand, those most competent to work with molecules, the physical scientists in physics, chemistry, electronics, or mathematics, generally know nothing of the biology of man or the abnormalities of this biology which can produce pain, suffering, and death.

One might well ask how this is possible. How can such a strange situation come about? Is there a Hippocratic iron curtain between medicine and the rest of the scientific world? Are physicians reluctant or unwilling to embrace the dramatic new developments of the other sciences in order to solve their own problems? No, none of these things is true. The physician must spend six to ten years in specialized training after graduation from college in order to be competent to treat patients and to use the drugs and tools which are at hand. The physical scientist must spend almost as long in postgraduate training to be able to master the tools of his particular specialty. There are few men willing to take the time to become proficient in both biological and physical science. The man who would bridge the gap between the medical and the molecular must spend half a lifetime in training.

I shall have much more to say about this situation and its bearing on the future of medicine in succeeding chapters, but now let us look at another aspect of present-day limitations imposed upon the medical practitioner.

If one were to look in the physician's black bag of thirty or forty years ago and compare the instruments with those of today, he would be startled to find that not one single significant new instrument has been added to his bag in all those years. In surgery we are still using some tools which were designed seventy-five years ago and have not been modified one iota to this day. Modern engineers could improve many of these implements tremendously if they understood the surgical problems; on the other hand, the surgeon seldom has training in engineering or electronics, and he must use what is available. Let us take a look at some of the procedures in use today.

As you will remember from your last physical examination, most of the procedures which the physician used depended upon his eyesight, hearing, and touch. Even with certain mechanical aids to increase the sensitivity of the physician's senses, such as the stethoscope, the abnormalities which can be picked up by such relatively crude processes tend to be rather gross. These procedures cannot hope to approach the cellular, let alone the molecular, level. The lack of adequate sensitive tools, many of which could be designed on the basis of known techniques, can be seen in the following. Take, for example, the preparation for the delivery of a child. When the physician examines a pregnant woman, he can gain a fairly good idea of the dimensions of the unborn child by measuring it through the wall of the mother's abdomen. The one other thing he needs to know is the diameter of the opening in the mother's pelvis through which the child must pass. If there is insufficient room, a Caesarean operation will be necessary. By manual examination the physician can touch with his fingertip the bony prominences on the inside diameter of the mother's pelvis. But he has no exact idea of the distance between these bony prominences, and hence the diameter of the internal opening of the pelvis, because he cannot tell how far his finger has traveled in touching first one point, then the other. In order to obtain this critical information, he often sends the mother to the X-ray man to take a series of X rays called pelvimetry. In the course of these X rays, about two and a half roentgens of X-ray dose are delivered to the unborn child and to the mother's ovaries. This amount of X-ray radiation is a major fraction of the currently established *total permissible lifetime dose* which an individual may receive from X ray without danger of leukemia or other radiation-produced diseases. And this dose of radiation is delivered to both mother and child simply because the engineering profession has not provided the physician with a device permitting him to know how far his finger travels in a routine examination.

Another example is the bronchoscope. If you have ever had a physician look down your windpipe with this instrument, you will know what I mean. This device is actually a straight tube. It is inserted in the mouth. As you can well imagine, if your head were in the normal position and a straight pipe shoved into your mouth, it would come out the back of your neck. Thus, in order that the tube go down the windpipe, or trachea, one's head must be tilted back at a weird and most uncomfortable angle. This is an experience one never forgets. However, not even this rugged procedure is adequate, for branching off from either side of the trachea are many smaller tributaries in the lung system which the physician would like to examine. These he cannot hope to view with any now-available apparatus, because none permits him to look around corners.

Actually there happens to exist now (and indeed its feasibility has been known for years) a system of tiny lightpipes which are flexible and can permit one to view directly around corners. The physician could send such a flexible tube down the trachea without the patient's having to perform neck gymnastics. Furthermore, he could then explore the numerous tributary tubes which lead off the trachea. Although the existence of this type of device has been known for many years, it is still impossible for a physician to purchase such an instrument.

Another example is the electrocardiograph. Tens of millions of electrocardiograms have been taken since the invention of this device about half a century ago. The electrocardiograph is a diagnostic aid. Whereas the electrocardiograph can give certain important diagnostic information, its capability is definitely limited to a specific range of heart abnormalities. However, since the electrocardiograph is one of the few electronic instruments available to the practitioner at present, it has received a degree of attention and veneration by instrument makers far out of proportion to any possible new information which can be squeezed from such a device by adding new electronic gimcracks to the basic machine. In spite of this, however, millions of dollars are still being expended for electrocardiographic research throughout the world. Any minute improvements which could conceivably be further wrung from this type of investigation are not, in the opinion of many, worth the price. What is really needed is new instrumentation which can permit us to measure critical bodily functions not heretofore susceptible of being measured. For instance, when a heart specialist is confronted by a patient who has had a heart attack, he can establish with the help of an electrocardiograph that a heart attack has taken place. He can give oxygen, digitalis, morphine, anticoagulants, and prayer, but he certainly cannot undo the heart attack.

He cannot do what is really most vital. He cannot predict when a heart attack is coming, or prevent it. The ability to do this probably depends on what can be learned at the molecular level. For example, some basic research now in progress at the New England Institute for Medical Research indicates that in the future it may be possible, by analyzing the changes in certain molecules in the blood involved in clotting, to spot an incipient heart attack sometime prior to its occurrence. Once this can be done, proper measures can be taken to prevent the dreaded event. If a tiny fraction of the money that instrument makers are putting into superficial improvements in the ancient electrocardiograph were instead put into fundamental research to develop an instrument that would notify the physician of an impending heart attack, this disease would no longer be regarded with fear and a sense of inevitability.

Finally, let us consider the matter of blood tests. Frequently in routine physical examinations the physician will take some blood for chemical analysis. But rarely are more than a few very simple tests made, because a syringe of blood is quickly exhausted by chemical means of testing. How many tests could be done with an unlimited amount of blood? Several hundred. How many things are there in blood which might be tested if we had the techniques? Probably over a thousand. Ideally, a physician would like to know when and if any chemical reaction in the body begins to be abnormal. The blood (and other body fluids) are probably the best single means of checking on these reactions. But, by chemical means, such exhaustive diagnostic tests are impossible because no one has the time to make so many tests; no one has the money (at five to ten dollars per test); and finally, no one has that much blood.

Thus, in terms of present techniques, the outlook would seem to be pretty bleak for thoroughgoing testing of bodily reactions by chemical means. It is bleak until we leave our present chemical approach and look to available techniques in physics. The physicist has techniques which would permit the analysis of a thousand or more different substances in one syringe of blood, for very small cost and in about fifteen minutes.

To be sure, the cost of developing a machine which could make these tests cheaply and quickly would be considerable, in terms of money, manpower, and the assembly of a development team. Such a team would have to include polymer chemists, monolayer physicists and chemists, spectroscopists, computer specialists, electronics engineers, organic chemists, biochemists, biophysicists, biologists, and physicians. But there is no question as to its feasibility, since all the basic techniques are known, and such a testing device would virtually revolutionize diagnostic medicine. Eventually it will be accomplished, but until then—as in many other areas of instrumentation—the physician will have to be content with inferior tools that greatly limit his ability. In order to obtain major new breakthroughs to obtain important new drugs and new tools for the physician, we need greatly expanded basic or fundamental research.

Perhaps the most discouraging fact of all in present-day medicine is that a pathetically small amount of all research funds is budgeted for basic research. In the next chapter the great expenditure of funds, the convenient packaging of routine development under the heading of basic research and the paucity of funds for support of fundamental investigation will be explored.

CHAPTER 2

"THE NEW MEDICINE"

The Massachusetts Institute of Technology has been offering in the last few years a course in "the new biology." The portent of "the new biology" in contrast to old or classical biology is enormous. In the biology of yesteryear, the emphasis was on simple description and cataloguing. For instance, in marine biology one might describe all the kinds of fish in a certain area, their feeding habits, anatomical differences, and so on. "The new biology" is concerned with the examination of the biological molecules—how they act and react.

The same transition from classical medicine to "the new medicine" is also occurring. There is virtually no basic difference in the change in medicine and that in biology. Although man is greater than the sum of his constituent parts, and though he has a soul as well as an incredible brain, he is still a biological species.

Classical biology, along with classical medicine, started many centuries ago. It started, as do most sciences, with description. Description is a necessary first step so that scientists can communicate with one another and agree upon the subject they are talking about. Without exact description there would be chaos. But once the descriptive phase is over, measurement must begin.

All scientists know that without precise measurement one cannot have a science. That, for instance, is the basic problem in psychiatry. How can one measure with numbers a person's reactions, his hate, his love, his passion? Obviously one cannot. That is why there are so many "schools" of psychiatry. If the truth were known, there would probably be only one school—the truth—but until one can measure man's mind and mood and obtain numbers, the truth must continue to elude us.

Perhaps in order to clarify the difference between the point of view of classical descriptive biology or medicine and that of the medicine of the future, which will be predicated on measurement, I may intrude a personal note.

It was not long after my coming into the field of medical research that I realized that I had no tools, in terms of my training, with which to make adequate measurements. I spent some years studying chemistry and found that not even this was adequate for my purpose. I ran into certain problems that can be solved only by the use of physics. As I was being introduced to the complexities of the physical universe, some of my colleagues on the faculty at Yale University in the Department of Physics were becoming interested in the biological universe. It was logical that we should meet and logical that we would attempt to educate one another in our respective fields. I am afraid that the physicists learned very little from my lectures except how little I really knew about the field of medicine. I, however, learned a tremendous amount about my own ignorance. A lecture session would go somewhat as follows:

I would be discussing infection and the series of biologic processes that ensued.

HELLER: Now in infection, white blood cells migrate to the infected area, and—

PHYSICIST: The white cells do what?

HELLER: They migrate.

PHYSICIST: What does that mean?

HELLER: Well, the white cells are attracted to the area.

PHYSICIST: Attracted?

HELLER: Yes.

PHYSICIST: How?

HELLER: Well, it is generally assumed that certain chemicals are produced in an infection and these chemicals attract the cells by chemotropism—

PHYSICIST: Chemo-whatism?

HELLER: Chemotropism. That is a chemical attracting force.

PHYSICIST: You mean you think that a chemical can attract something from a distance?

HELLER: Of course.

PHYSICIST: Sorry, my friend, but there are certain physical forces which can attract things at relatively long range, such as magnetic force, gravity, etc., and chemotropism sure isn't one of them.

HELLER: It isn't?

PHYSICIST: Emphatically no! That word sounds like a biologist's invention which describes something you think is happening.

HELLER: Well, isn't it possible that there is more of a chemical on one side of a cell facing the infection and less on the other side, and the cell goes towards the area of greatest concentration?

PHYSICIST: Does the cell have a brain?

HELLER: Of course not.

PHYSICIST: Does it have a nervous system?

HELLER: No.

PHYSICIST: Then how does the cell know that there is more chemical on one side than there is on the other? Then, how is this information transmitted to the cell's nonexistent brain, which then makes up the mind it doesn't have, to start all the molecules in the cell moving in one direction?

Thus, in a few minutes, they had posed basic and fundamental questions which had never bothered me before. I was still under the "descriptive" influence of medicine. The cells "go" to the infected area, and with this I had been satisfied. Now all my biological descriptive contentment was going up in smoke.

I realized that many pieces of knowledge which I had assumed were fundamental were really not answers but questions. For instance, for years we have known that adrenalin causes the smooth muscle lining the blood vessel to constrict. Since the same amount of blood must go through vessels which are now much smaller in diameter, it takes greater pressure to accomplish this. Thus, adrenalin can cause an increase in blood pressure. I had thought I knew how adrenalin causes an increase in blood pressure. The answer was simple, the adrenalin causes the smooth muscle in the blood-vessel wall to constrict. Now, all of a sudden, this was not an answer but a question. I wanted to know *why* the muscle constricted, what was occurring in molecular dimensions. I knew that the muscles in the blood-vessel wall could both contract and relax, and obviously a molecule of adrenalin must make the muscle contract. But this does not happen merely because the adrenalin molecule is nearby. Indeed, the adrenalin has to have more than simple physical contact between it and the molecule of muscle. Here is where things get complicated.

Let us liken the molecule of muscle to a door which is closed and locked. Let us further compare the contracting of the muscle molecule to the opening of this door. The molecule of adrenalin will be a key—not just any key, of course, but one that is perfectly shaped so it can fit into the lock of the door. As I said, simple physical collision of the adrenalin and the muscle is not enough, any more than throwing a key at a locked door will accomplish anything. The specially designed key must approach not just any place on the door, but the keyhole. Furthermore, the proper end of the key must go into the hole. Once we have the key in the lock, energy must be obtained from somewhere to turn the key so that the door can open. This, then, is what the basic research scientist wants to know. What is the shape of the key? What is the shape of the lock? How does the key get into the lock? Where does the energy come from to turn the key? Once all these things are known about the molecules of muscle in blood-vessel walls, we will in all probability be able to devise a cure for high blood pressure. This is a "disease" caused by unrelaxing constriction of the molecules of smooth muscles in blood vessels. It is on the level of these molecular interactions that the secret of normalcy and disease lies.

Since I have used the word "molecule" frequently, you may ask how small is a molecule? Or, indeed, what is a molecule?

This is really quite simple. A pure substance which cannot be divided any farther into constituent substances is an element. There are only a hundred-odd elements. When these elements are combined chemically they form a molecule. Thus, hydrogen is an element and so is oxygen. If they combine chemically into H_2O they form water. A single unit of chemical substance such as water is called a molecule. Even the largest molecule is minute. Thus in order to fill a glass with water it takes about 1,000,000,000,000,000,000,-000,000 water molecules. Another indication of the minuteness of molecules is the fact that a human body cell is so small that it has to be looked at through a microscope to be seen at all, and this single cell contains millions of molecules. Inside the cell, however, these millions of molecules do not exist in a haphazard manner as though they had been poured in harum-scarum. Actually, they exist in a highly organized structure.

The cells of our bodies, for instance, must make protein, one of the main building blocks of life. In order to do this, a whole chain of molecules is necessary, working in a manner not unlike the production line in a factory. In an automobile factory it is obviously vital that the machines for the production line are set up in the right order. Thus, it would be almost impossible to start with the bumpers of a car and work inward. In the tiny universe that exists within a cell the position of the molecules in relation to one another, like the order of machines in the factory, is critical. All of these many molecules must work in harmony with the millions of other molecules in the trillions of other cells in the body in order to maintain normalcy. Until we can measure how these molecules work or what happens to make them work abnormally, we cannot hope to find cures for disease except by sheer chance.

THE COMMON DENOMINATOR OF ALL SCIENCE

Not so long ago the botanist was concerned with describing and classifying flowers and plants. The astronomer scanned the heavens with a telescope. The physician worked at the bedside of a patient. Today a botanist may never look at a flower. He may be working on the secrets of chlorophyll. He is concerned with the way the molecules of chlorophyll take sunlight, carbon dioxide, and water and make oxygen and sugar. He is working on a molecular and atomic level. The astronomer today may never look through a telescope. He may be intent on radio signals emitted by atoms many light-years away from our solar system. He too is working with fundamental units of the cosmos.

The basic research investigator in medicine, like his colleagues in botany, astronomy, and a host of other sciences such as zoology, chemistry, and physics, now finds himself working with the basic units of matter, such as the atom and the molecule, and with the basic laws of energy which apply throughout the entire cosmos. At the level of basic research, the time-hallowed traditional boundaries between the sciences, which have existed for centuries, no longer apply.

The fundamental researcher in medicine now must understand many disciplines. He must know "descriptive medicine" and biochemistry in order to comprehend the dimensions of his problem. He must also understand biology, for man is a biological organism and many studies can be done far better and more easily on species other than man (see the chapters on sharks and electric eels). Finally, he must have knowledge of physics and the physical universe, including such fields as mathematics and electronics, for it is in this area that real progress in medicine will be made.

Hence these scientists from many fields, who a few years ago could not even talk with one another except on a social basis, now are working on the same level with the same units of mass and energy. Not only can they discuss their work with one another, but the discoveries of one field can be of major importance to the others. Thus, the pioneering biomedical scientist of today, irrespective of his official label, is learning, following, and applying the illimitable laws of the physical universe to gain fundamental knowledge.

This has put some enormous new demands on the medical investigator, for he must be familiar with a whole new spectrum of science and the other basic and complex fields which comprise the science of today and of tomorrow. But it also offers him a new challenge and a bright new opportunity in the conquest of disease.

WHAT IS BASIC RESEARCH?

The basic research scientist wants to go beyond the frontier and explore. He is intrigued and challenged by the unknowns in God's universe. He wants to explore the stars and galaxies and the cosmos beyond him and to peer more deeply into the tiny worlds and universe within him. He perceives great beauty, symmetry, and excitement in his exploration into the unknown. Like any frontiersman, he stands at the boundary between now and the future and eagerly wishes to plunge into the unknown to bring the light of knowledge back to his fellow men and expand the frontier. Indeed, every piece of useful knowledge which man has ever had has been preceded by exploration into the unknown. Whether it be television, rockets, radio, drugs, or automobiles, it makes no difference. All have had to be preceded by fundamental discoveries, carried out either purposefully or accidentally.

In spite of this, the distinction between fundamental research and applied research—the secondary stage in which a multitude of practical applications are developed for each basic discovery—has been poorly understood. It is so much easier to point to immediate benefits from applied research that there has been a tendency on the part of a great many people to write off basic studies of the unknown as impractical, visionary, and unlikely to produce any demonstrable returns. Let me give you a couple of examples:

The former Secretary of Defense, Charles E. Wilson, is quoted as having said: "Basic research is when you don't know what you are doing. Who cares what makes grass green or fried potatoes brown?"

Let us look at just one part of this question: "Who cares what makes grass green?" The answer: Every animal on the face of the earth, in the air above it, in the sea beneath it; and this includes all mankind. The "greenness" of grass and other plants is due to chlorophyll. This still-mysterious substance takes carbon dioxide out of the air and converts it to oxygen. Carbon dioxide is exhaled by man and animals and is produced by virtually all of man's machines. Chlorophyll in plants takes the carbon dioxide and, together with sunlight and water, produces not only oxygen but food. This greenness is man's only effective way of capturing the sun's energy. Unless this energy is captured and turned into food, every animal on the earth will die of starvation.

Thus, without this green substance there would be no oxygen and no food, and all life on this planet would perish. The secret of how chlorophyll, the most vital single substance on the face of the earth, manages this transformation is still a mystery. Once we are able to solve this riddle, it can open untold new horizons for man. When we learn by basic research the secret of chlorophyll, we can hope to duplicate it. Then we would not have to have huge prairies or grazing ranges to support livestock but would be able to *make* food for cattle at will. Such a single basic discovery could solve the food shortages which now plague the greater part of the earth's population. In countries such as Japan with huge populations and small amounts of tillable soil, one might produce livestock fodder in factories. Cattle could be raised and fattened in small pens. Indeed, many scientists feel that this may be the only way in which man may hope to keep his food supply adequate to our explosively increasing population.

Turning to a more specialized area, if we knew the secret of chlorophyll the problems of space flight could be tremendously simplified. In the foreseeable future we cannot hope to carry enough oxygen for long voyages on space ships to keep the crews alive. If we had the secret of how chlorophyll works this would pose no problem, for we could take the carbon dioxide exhaled by the crew and convert it back into oxygen by the same means that plants use every day all over the earth.

These are but a few answers to the so-called "practical" man who asks, "Who cares what makes grass green?"

Let me cite another example of the tremendous and totally unanticipated impact which fundamental discoveries can have, from the field of insect hormone research.

A very small group of men, working with meager funds, have over the period of the last forty years been working to explore, isolate, and identify certain insect hormones. Had you asked any of them what good this would eventually be, none could have given you an answer. It now appears, however, that these hormones may be used as the "ultimate" insecticide. Spraying such hormones over an area would create such a series of chemical abnormalities in insects that they could not survive. These hormones have no effect upon man, wild or domestic animals, or vegetable matter. In contrast to most insecticides today, which are toxic to man and animals, they would be completely nontoxic. Hence these discoveries made over a forty-year period may provide a basic solution to a serious problem. Incidentally, individuals and corporations who successfully capitalize upon and exploit this fundamental discovery will in all probability earn a great deal of money. Most such people would have been unwilling to support the basic research which produced this knowledge because they could not have foreseen a "practical" outcome. It is easy to intrigue people with talk of an insecticide; it is remarkably difficult to interest them in insect hormones.

It may come as a surprise or a shock to most individuals who have been persuaded by stories which they see in mass communication media that huge amounts of money are being expended for research which they assume is basic in nature. This is twaddle. This is attested to by Professor Merle A. Tuve of the Carnegie Institution of Washington who stated: *

> "Huge new synchrotrons and cosmotrons and electronic computers, and polar expeditions and balloon and rocket flights and great government laboratories costing more each year than the total academic costs of many of our greatest universities —all these conspicuous aspects of our new national devotion to science are subsidiary and peripheral. They do not serve appreciably to produce or develop creative thinkers and productive investigators. At best they serve them, often in a brief or a rather incidental way, and at worst they devour them.
>
> "There is a growing conviction among my friends in academic circles that the university is no place for a scholar in science today, because a professor's life nowadays is a rat race of busyness and activity,

* Symposium on Basic Research, sponsored by The National Academy of Sciences, The American Association for the Advancement of Science, and The Alfred P. Sloan Foundation, New York City, 1959.

> managing contracts and projects, guiding teams of assistants, and bossing crews of technicians plus the distractions of numerous trips and committees for government agencies, necessary to keep the whole frenetic business from collapse.
>
> "It is important for us to recognize the relatively small size of the annual budget for . . . . basic research. The overall total probably does not reach twice what it was before the war in terms of a constant dollar. The number of . . . . men in basic research is still not too different from the prewar number of similar fully trained scientific investigators."

If you are like most people, you may still feel that basic research does not concern *you.* Nothing could be further from the truth. Basic research vitally concerns you and your family, and it concerns you in the most personal and intimate way. Here is why:

Those of you who read these words will die.

This is not a terribly original observation and I doubt that it comes as a surprise to you. There is, however, something which most people do not consider about their own death, if they think about it at all. You are unlikely to die peacefully in your bed after having lived out a normal life span.

You are far more likely to die slowly after having been riddled with cancer or after having had one of several heart attacks or heart failure. Perhaps death will come after a stroke has left you partially paralyzed and helpless for months or years. There are many unpleasant ways to die and you are far more likely to have an unpleasant form of death than an easy and painless one.

Yet you, and others like you, have it within your power in the foreseeable future to prevent much of the personal anguish and tragedy that disease now brings. This may sound strange and even incredible. However, it is true. No matter what your occupation or your influence—whether you be a housewife or a political leader—you and you alone have the power to prevent the personal tragedy caused by disease. This emancipation from the tyranny of the dread diseases lies as much within your power as it is within the domain of a free people to demand political liberty. Those of us in basic research cannot help wondering at the strange contrast of a free people insisting upon their rights to political freedom and at the same time submitting meekly to crippling physical maladies.

Each free country has some document by which the people establish their rights to freedom. The American Declaration of Independence states that it is the inalienable right of man to have life, liberty, and the pursuit of happiness. The Atlantic Charter has stressed the importance of freedom from want and freedom from fear. The free world has spent billions to try to maintain its political freedom against possible attack. Yet all of these free peoples are facing an inevitable attack of disease which will rob them of their freedom, will instill fear, can deny them their pursuit of happiness, and will most certainly take their lives.

A watchword of freedom since Biblical times has been, "Ye shall know the truth and the truth shall make you free." It was never truer than now, and it never applied more aptly than it does to the cause of basic research in medicine. It is at the level of basic research that the breakthroughs must come, if significant progress is to be made in the conquest of illness. And it can only be done if you, and millions like you, demand that support be given and the effort made.

If you seek freedom from these diseases, you must help the basic research men in their explorations. It is not enough to suspect that the world is round; one must have the ships and men to explore it. One must get to the new world and explore the mountains and jungles and deserts. Only as we learn the facts or, might we say, the truth, about the new land can we hope to find and to harness its wealth. Thus in disease we seek the truth about the unknown so that we can find and harness the rivers of life which occasionally run wild and uncontrolled, resulting in death and tragedy. It is these truths that we are after; but you must help us as Isabella helped Columbus. We are, however, not a monarchy and we have no queen to whom we can appeal. We are a nation in which the people are sovereign. It is, therefore, to you that we make our plea. Help us to know the truth, and then and only then can we all be free.

CHAPTER 3

THE NEW ENGLAND INSTITUTE FOR MEDICAL RESEARCH

The poet Robert Browning said:

> . . . a man's reach should exceed his grasp,
> Or what's a heaven for?

What does a basic research man in medicine reach for? What is his "heaven?"

He dreams about a place to work, with adequate facilities and funds to defray the cost of research. He dreams of being able to devote most of his time to basic research. He hopes to work with colleagues in his own and other fields who can stimulate and collaborate with one another. He hopes for a salary he and his family can live on.

To many, it would seem that this is a modest dream. In truth it is. But where will a medical research man find his "heaven"—in a university, in industry, in government?

Although all of these agencies do carry out basic research, the university's prime mission is to teach, that of industry to produce goods, and that of government to provide service. In relatively few places in these three institutions can our investigator find a post where he can hope to concentrate primarily and exclusively on basic research. There are basic research institutes, but, oh, so few.

Some of my colleagues and I felt that there was a real need for a research institute which would concentrate on basic research in medicine. We felt that we should staff this institute with scientists who were trained not only in biology and medicine but in the physical sciences as well. This was the genesis of the New England Institute for Medical Research in 1953. On every side we were assured that it was impossible to think of founding such an institute. There were organizations such as the Rockefeller Institute for Medical Research, but this was begun with a major endowment. We had no funds; all we had was the idea. We wanted to create an institution wherein the basic research man, trained in several sciences, could explore to his heart's content. We wanted to bring in physicists, engineers, biophysicists, physicians, biologists, bacteriologists, chemists —a whole spectrum of science—to attack fundamental problems in medicine. We wanted to give them the laboratories and equipment they needed. We wanted to match their dreams.

Expert advice was that it could not be done. Who would support such a venture? A new institution takes years to build a reputation. How can one expect any support or confidence without having a reputation of accomplishment? Perhaps if such an institute were dedicated to a single disease, it might be adopted in time and supported by some organization interested in such a disease. But just to explore into the unknown . . . !

We started off with a pledge of $12,000 from Florence

Schick Gifford of Connecticut. This pledge was contingent upon obtaining a similar amount from two or three other donors. Thus the quest began. We were aware of many of the shoals ahead; but as on any voyage into uncharted seas, there were many unknowns.

The New England Institute for Medical Research was officially chartered as a nonstock, nonprofit basic medical research institution in the State of Connecticut in 1954. It began in one room of my home. An old door on two saw-horses was the first piece of equipment. In about six weeks, owing to the generosity of another early donor, Raymond John Wean of Ohio, our pledged exchequer rose to $18,000 and we moved into the second story of a building in Ridgefield, Connecticut, in offices formerly occupied by switchboards of the telephone company. There our tiny staff began to work. Over a thousand personal letters were written to foundations, great and small. Over 80 per cent did not even bother to reply. The remaining two hundred said "No thank you." We talked with anyone to whom we could gain entree; we begged. We approached corporations, government agencies, and individuals. We never knew there were so many ways to say "No!" On a seven-day basis (days *and* evenings), we would follow up any possible lead that might provide funds. Sometimes we would receive ten dollars or even as little as one dollar. Usually we were asked: What have you discovered? The scientists could point to their individual past records, but that was not of interest. What had the New England Institute for Medical Research done? We would explain we had not even begun. We wanted the funds just to begin. The days stretched into weeks and the weeks into months. The salaries were so low as to be only token wages. Our people lived out of their meager savings. Some had to borrow. All had faith that the dream would turn into reality.

Finally, we received a major grant from a large diversified corporation and a medical-instrument manufacturer. Now we could really begin. We moved our quarters to a 125-year-old goat barn, also in Ridgefield. It was in frightful shape. One could look up from the basement through two floors and the roof and see the blue sky. We began to build laboratories. The pace seemed terribly slow. Bench by bench, partition by partition, progress inched forward. Cost was a major problem. Scientists pitched in on building, plumbing, anything they could do to help reduce cost and increase speed. We were well into 1955 by now.

Once a laboratory is completely built and equipped, it takes almost a year really to get under way. Instruments must be calibrated, procedures worked out, technicians trained, an animal colony started, and a thousand and one details attended to. A library was another major problem. A scientific library has scientific books, but this is only the smallest part of the library. Most books become outdated in a few years. The bulk of a library consists of many hundreds of scientific journals with back issues for ten to thirty or more years. This is the only possible way to keep up with what everyone in the world is doing in your field, as well as what everyone has ever done before. Thus, if an investigator finds that a certain compound or bacteria, or whatever, has suddenly become important to his work, he goes at once to the library to "read up on it in the literature." This may take several months. The investigator will go back to the first reference, which may be decades ago, and read forward through the years. When he is through, he must have a sound knowledge of what everyone has ever done before. He will learn of the mistakes and errors, the false leads, and the successes, and this search of the literature may take him into many languages, most of which he must be able to read. Those he cannot read he must have translated for him by a colleague. It is almost impossible to purchase back issues of all these journals, even if one has the money. Fortunately, there is a system whereby the national Library of Medicine makes available, for the cost of shipping, back issues of duplicate sets of journals to nonprofit, tax-exempt research institutions.

Then come the stringent demands of state and federal organizations. A nonprofit medical research laboratory such as the New England Institute for Medical Research uses ethyl alcohol, which it is entitled by the government to purchase tax-free. However, to make sure that it is a bona fide, nonprofit, tax-exempt medical institution, the Treasury investigates everything and everyone, even the board of trustees. The alcohol-tax people of the Treasury Department will not be content with the findings of the Income Tax Bureau of the Treasury Department, which determines whether an institute qualifies for tax exemption. They conduct their own investigation. Then a system of security for the alcohol must be devised and inspected, with the supply, however minute, kept secure in locked steel cabinets accessible only to certain individuals. A banking and bookkeeping system must be set up to keep track of each ounce of alcohol and its use.

After this, an even more complicated procedure is initiated by the Atomic Energy Commission for radioactive isotopes. Each use of every isotope must be passed on by an isotope committee of the Institute, which must cover every minute that an isotope is within the building until the wastes are taken out to sea or disposed of by special organizations in deep pits designated by the Atomic Energy Commission. The written minutes of the isotope-committee meetings, the record of routine physical examinations of all personnel using isotopes, the "isotope bookkeeping," the weekly survey for contamination, and the rules and procedures must always be available for regular or spot checks by federal and state officials. These and scores of other comparable details are just a part of the routine work that must be taken care of before research can begin.

Another critical area and constant headache are experimental animals, such as mice. Contrary to lay opinion, a research mouse is not simply a mouse. Mice have become so important in research that some investigators have spent their whole lives breeding special strains. There are dozens of such strains whose pedigrees run back through countless generations and many decades. Each mouse and its progeny are catalogued. Each strain and substrain is identified by letters or numbers. Thus, when an investigator in the United States, England, or Australia uses a C_3H mouse, he knows he is using the exact type of mouse that his colleagues around the world are using. These mice must be kept in special stainless-steel cages which are washed and sterilized every two days. The temperature of the animal quarters must be kept constant within two degrees and the humidity strictly controlled. The temperature and air-conditioning apparatus must be versatile enough to maintain the right humidity and temperature with only one mouse in a room or a thousand. The air is never exchanged between rooms, thus avoiding the spread of infection if it should break out. Every animal room has a slightly positive air pressure to insure that when a door is opened the air blows out of the room, thus helping to prevent any bacteria which may be in the corridor from entering the animal room. No king or dictator on earth can command such tender, loving care as experimental mice receive. Sometimes, in spite of all precautions, an infection will sweep through a mouse colony—often ruining an entire year's work.

Many things which most people take for granted are major problems for the basic research man, such as water. Water is, of course, vital in any research laboratory. For investigators working at molecular levels, tap water is inadequate. They require water that is relatively pure. This may mean that distilled water or even triple-distilled water is inadequate; it must be much purer than that. It may take many months to rig an apparatus which can produce adequate amounts of water of the right degree of purity. Completely pure water is virtually beyond the capability of any laboratory. This may seem strange, but it must be borne in mind that minute contaminants can ruin experiments. Thus, an infinitely tiny amount of glass from a glass container can and will dissolve in water. Naturally, the amount is almost inconceivably small, but as long as any molecule other than H_2O is in water, it is not completely pure. For work in new frontiers, special apparatus which does not exist commercially must be especially made. For instance, we needed large numbers of special pipettes which contain only and precisely 1/30,000 of an ounce. These tubes require weeks and months of special glass-blowing techniques and calibration to produce.

Thus, slowly, from a goat barn, a modern basic research institute began to emerge. One laboratory after another was built. No two have the same requirements: biophysics, physical chemistry, microbiology, physiology, electronics, and so on. Each had to have special devices and services. Some laboratories need only regular electricity. Others need 220 volts and even 440 volts. Some need steam lines, vacuum lines, gas lines, controlled humidity, dust-free atmosphere, special precautions against highly lethal bacteria, controlled temperatures, and so on. Each new requirement is expensive, and money for basic research is still a "luxury."

But with gifts of $10, $100, and $1,000 here and there, the work of building and equipping forged ahead slowly. Real work began in 1956. The dream ship for the basic research explorer was finally a reality; a small ship, to be sure, with appallingly low salaries for its crew and a terrible and continuing shortage of funds. A ship still undermanned (it has a total staff of under thirty) for want of dollars, but a ship which can sail.

It is one of the few institutes in the United States where physical, chemical, biological, medical, mathematical, and engineering sciences all come together for the sole and common purpose of basic research in medicine. Unlike most other organizations, the Institute assigns no ranks to the members of its staff, such as instructor and assistant, associate, or full professor. We are all colleagues of equal rank, sharing facilities and knowledge and pursuing our own common problems. No one has to obtain a chief's or director's permission to follow a line of research. Advice is given but need not be followed. There are no departments with department heads. There are no laboratories or facilities commanded only by one man or one group.

The evidence of the success of this venture in basic scientific exploration can be seen in the following statement by Dr. Charles Doan, Dean of the Medical School of Ohio State University:

> The brilliant achievements of the scientists of the New England Institute for Medical Research are ample testimony to the validity of creating an in-

> stitute for basic interdisciplinary research in medicine. Scientists must be free to challenge and explore the unknown. Then and only then can major discoveries be made. The New England Institute for Medical Research is living evidence of this thesis. In but a very few years this Institute has become one of the important basic research centers in this country.

In contrast to the early days, we have now received support for research already under way from federal agencies such as the National Institutes of Health, National Science Foundation and so on. In addition, foundations have undertaken support of work which is already in progress and upon which considerable work has been done. However, it is difficult to find agencies which will support new ideas.

This was very well summed up in a recent symposium on basic research * at which Dael Wolfle, Executive Officer of the American Association for the Advancement of Science, stated:

> What the scientist needs is not always what the supporting agency wants to provide. In fact, what such donors are willing to provide may be quite inappropriate, for their thinking lags behind new scientific ideas, and often rather curiously lags behind the practical realities of the moment. They know what has been done but not what is just beginning to be thought about. During this symposium it has been pointed out that it is particularly difficult to secure support for work in new fields. Yet it is precisely in the new fields that important new knowledge will be developed.

* Symposium on Basic Research, sponsored by The National Academy of Sciences, The American Association for the Advancement of Science, and The Alfred P. Sloan Foundation, New York City, 1959.

> Committees [of foundations and Government agencies] stress the traditional and already known fields of research. They have to. But the most advanced and creative scholars are out in front of the traditional fields exploring the borders of the still unknown. There are not many such pioneers, but they have an importance out of all proportion to their numbers.

Although we receive grants and gifts from major corporations, relatively few of them are willing to give funds that are uncommitted to a specific project. Thus, the burden for support of exploration into new areas depends primarily upon individuals as well as those few corporations who are willing to give uncommitted funds. Hence, the role of private philanthropy is more important today than it ever was.

Most of the gifts and grants range from a few hundred to a few thousand dollars. Sometimes they are larger, and occasionally they are as little as $50. In contrast to applied research, basic research is still very much a stepchild with a very minuscule budget.

Research is not the only function of the staff of the New England Institute for Medical Research, although it is the primary one. Teaching is also done. There are four categories of "students." Postdoctoral, predoctoral, collegiate, and even precollegiate. The postdoctoral fellows come to broaden their horizons. Thus, an M.D. may spend his time in, say, nuclear physics or physical chemistry, learning to use the knowledge, techniques, and instruments of the other sciences. We have scant funds for such fellowships, although a few can be granted. Some fellowships are granted to scientists to work at the Institute by such organizations as the National Foundation, the William A. Sturgis Leukemia Fund and others.

Some Fellows come from abroad, sponsored by their universities, governments, or national foundations, such as the Gulbenkian Foundation in Portugal. In this respect the New England Institute for Medical Research participates in the Exchange-Visitor Program of the United States Department of State. Predoctoral fellows also come from American universities to broaden their horizons and some to do their doctoral theses.

Collegiate fellows are given the opportunity to gain an insight during the summer months into the vast and exciting frontiers of basic research. These students cannot be paid, of course, and only the best and most fertile minds are chosen. To a very few we can give summer fellowships.

Finally, a few precollegiate summer students are taken if they show great promise in intellect and an abounding curiosity. They, too, gain some insight into the fascinating unknown, with the bright promise that lies ahead in scholarship and research.

But teaching is also done for teachers. In many respects the high school or elementary school teacher of science is the forgotten man. English or French teachers merely have to go as far as the library to charge their intellectual batteries. But the science teacher has almost nowhere to go. To the individual with only a B.S. degree, the scientific journals are usually too complex and too costly. Until recently most universities have had little to offer these teachers, and if industry uses them it is primarily as technicians during the summer. Therefore, at the New England Institute for Medical Research the staff uses some of its spare time—nights and weekends—for special courses or demonstrations for science teachers of elementary and high schools.

The change in attitude which this still very small program has had on students in the surrounding school system appears to be considerable. In contrast to the national attitude of high school youths toward science and scientists, these students are enthusiasts. The national attitude has been reported in several surveys by cultural anthropologists such as Margaret Mead. In general, according to the Mead survey, most students feel that a scientist is a peculiar individual. He is thought to be a weird person who does not lead a normal life, who is inherently evil, who maltreats his family, and who, in general, is bent on some monstrous purpose. The rest of the students feel that he is not evil and that scientists do good things—such as inventing television—but there is sufficient odium to the title of scientist ("egghead") that they would never want to be one or marry one.

In the area around the New England Institute for Medical Research, where its small teaching program has been in action, the students apparently feel that a scientist may be different from many others but is a human being, primarily because he is having an enormous amount of fun probing into the unknown and doing this because he really wants to and not just for a living. Via their teachers, these students seem to sense the high adventure and challenge of pursuing knowledge for the sake of knowledge, and they dream of the unknown worlds that lie beyond, which we now can only see through a glass darkly.

Each year our Institute receives several hundreds of applications from scientists who wish to join the staff. Unfortunately, they must be turned down because the funds for the support of basic research are not available. The would-be explorers, not finding a ship, must turn to applied research or some "practical" way of earning a living. With but a few thousand dollars more each year, we could increase our staff by the addition of some of these dedicated young scientists. To reiterate the words of Dael Wolfle, "there are not many such pioneers but they have an importance out of all proportion to their numbers."

CHAPTER 4

THE RETICULOENDOTHELIAL SYSTEM

The human body is made up of cells. Trillions of them. They are minute and cannot be seen without a microscope. They come in all shapes and a variety of sizes, and each separate type usually has different functions. Each single one of these trillion cells contains millions of all kinds of molecules—each with a job to do to keep man alive and functioning. One of the most fascinating studies in science is trying to find out what is going on inside these cells.

For instance, let us take a brain cell, which can remember things such as a telephone number, the color of a dress, an odor. How can a cell "remember?" Somehow, in some fashion, a few of the molecules inside the cell are subtly changed or rearranged, and this change will carry the memory of a telephone number. This is an amazing concept. A molecule composed of carbon, hydrogen, nitrogen, oxygen, and sulfur atoms apparently makes a minute rearrangement of its constituent atoms as the telephone number is funneled into the cell. This rearrangement itself is literally a code into which the telephone number has been converted. Then the rearranged molecule sits back and waits until you need the information it has stored. When you call for it, a mysterious series of events translates the stored information in this molecular memory into digits that give commands to your eyes and fingers so that you can then dial the number. Thus each cell or group of cells possesses secrets that science is trying to unravel.

Imagine the tremendous benefit to man if we could figure out how a molecule stores memory. The giant computers which now fill several rooms, storing their memories on magnetic tape, could be reduced to miniature size and amass an almost infinite amount of information, stored in tiny molecules. If we knew how to do this, molecules could run factories and rocket ships. The secrets of the cells and their molecules are the secrets of life and all man's works.

Scientists with a general interest in cells may become particularly interested in a certain cell or a special group of cells. This chapter concerns itself with a group of cells whose existence has been known for virtually half a century. These cells have piqued the curiosity of many. Indeed, almost 5,000 scientific papers have been written about them. One might think that this enormous effort would have produced a comparably enormous amount of information. Unfortunately, this is not the case. More misinformation than fact has resulted from many of these studies. The great limiting factor has been that such systems cannot be either studied or understood unless one can draw from a host of disciplines ranging from the physical sciences through biology. It has been only in the last decade, when a transdisciplinary attack was mounted, that the barriers of the unknown began to crumble.

At the New England Institute for Medical Research, where a study of the system of cells in question is under way, it is taxing the creativity and ingenuity of a whole group of scientists from electronics engineers to physicians. The story now unfolding is extraordinarily exciting and filled with promise.

This group of cells is called the reticuloendothelial system. The long Latin names which are affixed to so many things in medicine go back to the early descriptive days, and the names, in themselves, are descriptive. Later knowledge frequently makes them obsolete; but as so often happens, once something is named it is difficult to change it. However, even in medicine, which abounds with long names, the reticuloendothelial system is rather a jawbreaker, and has been abbreviated to "RES." The cells which compromise this system are known as RE cells.

A good deal of the interest in the RE cells stems from the fact that they are guardian cells, without which man would soon succumb to his enemies. They are responsible for the state of man's resistance against disease. Indeed, they may be likened to defense forces which include sentries, shock troops, mobile reinforcements, and troops in fixed heavy-defensive positions. Like any army, they have a variety of weapons for different purposes. Furthermore, an army must be supplied, and therefore the RES has factories that produce some of its armament. This army keeps us alive in a world where we are surrounded at all times by aggressor forces. Whether we live or die will depend upon the outcome of the constant battle between the aggressors and our defensive army. It is obvious, therefore, why investigators want to learn about this defensive army and how it works. They want to be able to devise methods of helping and reinforcing troops if the battle is going in favor of the aggressor. In the event of any weakness in defending forces they want to be able to bolster the defense system to prevent invasion. Let us now look at what little we have found out about our army—that is, the RES.

One of man's primary foes on earth is germs—or bacteria, viruses, and other microorganisms. We live in a world populated by far more germs than people. We are outnumbered. They are in the air we breathe, in our nose, mouth, throat, lungs, intestinal tract, and on our skin. Thus, each of us is actually surrounded at all times by would-be invaders. If this were a military situation, we would first have to have sentries everywhere, on watch for a breakthrough of the enemy. We would have mobile troops ready to reinforce any part of the perimeter if the enemy should break through in force. This is exactly how the RE cells are deployed. Throughout the body, tucked away among skin cells, in the throat, around the intestines, literally everywhere, there are individual RE cells on guard. If bacteria invade through a scratch, the RE cell goes into action. Its first job is to capture the enemy. We can see what this cell does, but we still do not understand how it does it. As the bacteria attempt to pass the RE cell they are firmly gripped to the surface of the cell by some force not as yet clearly understood. Next, the RE cell manages to pull the bacteria through the cell wall into the interior of the cell, where well-trained molecules begin to tear the invader apart.

If too many bacteria invade for the individual sentry to cope with, an emergency call is sent out and mobile RE cells rush to the scene. They will try to wall off the area, and shoulder to shoulder, will advance to capture and destroy the aggressors. If, by some misfortune, the bacteria manage to break through the outer defenses and get into the blood stream, the heavy artillery is brought into play. Huge numbers of RE cells in certain organs such as the liver and the spleen mark the big fixed fortifications, and smaller outposts can be found in blood vessels everywhere. As the blood stream sweeps the bacteria through the liver, enormous numbers of RE cells lining the blood vessels in this organ attempt, and usually succeed, in picking up and destroying virtually all the intruders. Experimentally, one can take a healthy rabbit and inject a million bacteria directly into its blood stream. In five minutes not a single invader will be found floating in the blood. All will have been taken into the RE cells.

However, in addition to the blood stream, man has another system of pipes filled with fluid. This is known as the lymphatic system. The fluid which fills it is called lymph, and comes from cells and tissues. Every so often these lymphatic channels broaden and flow through a network made of RE cells. These networks are called lymph nodes. The layman usually calls them "glands." Thus, if you have "swollen glands" in your neck or armpits, it is usually due to the fact that bacteria have invaded, gotten into lymph channels, and flowed until they hit a lymph node. The swelling of the node is evidence of the battle which is being waged by the RE cells in the node against the invader. The watchword is, "They shall not pass."

Thus, when the defensive army is strong and well-deployed, man stays healthy. If it weakens locally or generally, invasion or infection take place. The antibiotics, of course, are helpful to the defensive forces, but they don't win battles by themselves. Penicillin, for instance, works by slowing down the multiplication of bacteria until the RES army reserves can come into action and mop up. If the RES is knocked out, one can pump in penicillin with a garden hose and the patient will still die.

Thus far we have mentioned only the first line of defense of the RES. A good general will want defense-in-depth. If he finds that his lines have been breached by an aggressor with certain specific characteristics, he will try to build into his general defense system certain traps to foil any future invaders who manifest the same characteristics. This is exactly what the RES does. As was mentioned previously, once the aggressor is inside the RE cell, trained molecules tear him apart. For the sake of simplicity, let us pretend that these molecules are little human beings and the bacteria are also men armed with specific weapons. The "weapons" of bacteria are usually poisonous molecules called toxins. For the sake of our analogy, we will assume that the different toxins of bacteria are different weapons —rifles, howitzers, swords, spears, and so on.

The scene is inside an RE cell. Two different enemy soldiers have just been captured. One has a sword and the other has a howitzer. The defense scientists are the molecules which have disarmed the soldiers and are examining their weapons. These scientists, realizing that they are confronted by rather nasty weapons, decide to work out a plan of defense against future invaders. They decide to make blueprints of the weapons and then design something from the blueprints to render the weapons harmless. For instance, in the case of the sword they design a scabbard. They reason that if enough such scabbards are available, by the time another enemy comes along armed with similar swords a scabbard can simply be placed over each sword. Without a point and a cutting edge, the swords will be harmless. For the howitzer, they design a plug which can be jammed down the muzzle. The blueprints are duly made and sent to the factory (another kind of RE cell). Once in the factory, the production line is set up and begins to turn out scabbards and howitzer plugs. As soon as adequate amounts of both items are made, they are sent into the blood stream, where they can instantly be used on any further swords or howitzers. In the meantime, the blueprints are stored away (molecular memory) in the event that the same enemy with the same weapons tries to invade again sometime in the future. If that happens, the blueprints and the production line are all set to go into action at once, without having to wait as they did the first time to draw up plans and set up a production line. They are poured into the blood almost instantly and the invader is rendered impotent.

In actuality, since the weapons or toxins of the enemy are really molecules, the scabbards and howitzer plugs are really antimolecules. These antimolecules are called antibodies. Furthermore, like a scabbard made to fit a sword of a certain size and shape, these antibodies are highly specific. Obviously, if one made a scabbard for a long, straight, double-edged sword, and then tried to slip it onto the blade of a shorter, curved saber, it would not fit. Thus specificity is one of the primary characteristics of antibodies. Vaccines, whether against smallpox or infantile paralysis, work by inducing the RES to make appropriate antibodies. A vaccine is usually made by treating bacteria or viruses in such a way that they are relatively harmless when injected into the human body. Going back to our military analogy, the treatment of the vaccine (before injection into man) is like tying soldiers up hand and foot. Therefore, even though he has the weapons that the RES can use for blueprints, the enemy cannot wield them. The initial problem with the Salk polio vaccine arose from the fact that not all of the soldiers were tied up tightly enough.

It was mentioned that antibodies are highly specific. They are. But everyone can visualize a scabbard made for one sword fitting onto another if the other sword is sufficiently similar to the first. Thus a patient is vaccinated with cowpox to protect him against smallpox. The scabbards (antibodies) that fit the swords of cowpox also fit beautifully on the slightly different weapons of smallpox.

These are some of the things that science knows about the RES. There are innumerable things we don't know, and some we know only imperfectly. For instance, how does a cell—which has no brain or nervous system—identify an invader? This we have discovered in part. The RE cell really cannot identify a bacterium as such. It will, however, grab and engulf any tiny particle which has a negative electrical charge on its surface. Virtually all bacteria have such a charge, so things work out well for man. But how does the RE cell identify this charge? We don't know. How does it "pull" a bacterium through its wall? We don't know. Which molecules make the blueprint and how do they do it? We don't know. How is the blueprint information in one type of RE cell communicated to another type of RE cell so that the second one can turn out the right kind of antibodies? We don't know. How do these "factory" cells know when the same invader appears years later so that they can go into production? How do sentry cells which are being overwhelmed send out a call for reserves? We know none of these answers. We are trying to find out.

What can we do with the knowledge which we have gleaned so far or, to paraphrase, what good is this basic research?

An enormously useful clue was obtained when it was determined that RE cells can identify invaders by electrical surface charge. Up to that time we had no idea how to measure whether resistance to disease was normal, below normal, or better than normal. Obviously, one could give a man a serious infection. If he lived, one could conclude that his RES was in good shape. If he died, his RES was not up to snuff. Not only would such a procedure be somewhat unpopular, but as was stated earlier, to make progress in science, we have to be able to measure things and get numbers. The problem then was to measure the state of defense or resistance and obtain a numerical value which would indicate whether it was good, bad, or indifferent. Unless we could measure resistance, we would have no index of how successful we were in trying to increase that resistance. Therefore the following scheme was devised. If the RE cells could only identify bacteria by their electrical surface charge, why not design "artificial bacteria" which would have the same surface charge? This would be extremely advantageous. First, these artificial bacteria would be completely inert and harmless, that is, inert soldiers or mannequins without any weapons. Therefore, no harm could come to the animal or man who was injected with these artificial invaders. Next, it stood to reason that if the RES was on its toes it would be able to capture, let us say, a million of these pseudo-invaders in five minutes. We could determine this by injecting a million of these artificial bacteria into an animal's blood stream and then checking a drop of blood every minute to see how many invaders were still there. If it took eight, ten, or twenty minutes to do the job, there would be something wrong with the RES. Furthermore, if we took some experimental animals with a poor RES (in the twenty-minute range) and treated them in such a way as to stimulate the RES, we should get back to the five-minute value. In this way, a quantitative method was worked out to measure RES function.

A variety of artificial bacteria have been devised by various research men. One type consists of tiny (as small as real bacteria) plastic spheres. Another is especially prepared carbon particles—about as small as the carbon particles in a puff of cigarette smoke. Making such particles requires the special skills and talents of the organic, polymer, physical, and colloid chemists. To prepare the particles for injection and to measure how many are still left in the blood at any particular moment requires still other specialists, including a biochemist, biophysicist, and physiologist.

However, this technique has more possibilities than just measuring the RES. For instance, it is thought that certain viruses and other microorganisms which succeed in making man ill are able to do so because they do not have the appropriate electrical surface charge or in some other way elude the cells of the RES, and antibody production is therefore poor. At the New England Institute for Medical Research, experiments are now under way to attach some of these elusive aggressors to the carbon particles. Thus, the aggressors would become piggy-back riders, compelled to go to the RE cells whether they will or not. If such experiments work, we may look forward to being able to develop good antibody production or immunity to a host of diseases to which man is not now immune.

Since this chapter was begun, the first experiments were started. They have been successful, and the promise of this technique is bright. Furthermore, since RE cells are also involved in the problem of allergy, such a procedure may be able to avert or even cure many of the annoying and sometimes serious manifestations of allergic conditions.

If these were the only activities of the RES it would obviously be an important system. It apparently has many additional functions. One of these is the capture and destruction of excess cholesterol in the blood. Cholesterol is the fat which gets into blood-vessel walls, and if it localizes in the blood vessels of the heart it can cause a coronary thrombosis, or heart attack. There are two sources of cholesterol. One source comes from certain foods we eat, and the other source is synthesized by the cells of the human body. We still do not know which of these sources is responsible for the cholesterol in arteries, and indeed, it may be a little of both. It has been established that at least the cholesterol which comes from food is picked up and apparently destroyed by the RES. It is further known that someone with a protracted high level of cholesterol in his blood is more apt to have an early coronary thrombosis than the average man.

Another interesting observation is that women are practically immune to coronary thrombosis prior to menopause. The question arises, therefore, can female sex hormones have an effect on the RES and hence on blood cholesterol levels? Actually, female sex hormones have been given to men with too much cholesterol in their blood. Whereas this type of treatment gives some evidence of being effective, large amounts of female sex hormones in a man begin to produce all kinds of feminine characteristics in him, including marked enlargement of the breasts. Most men refuse to continue with this type of treatment because of sexual side effects.

Scientists at the New England Institute began to wonder if it might not be possible to make synthetic female sex hormones and change the chemical structure of the hormone ever so slightly. The change would be designed to rid the hormone of its power to produce femininity, but still retain its stimulatory effect on the RES. Two years of research went into this project and several hormones were developed which met the specifications. The hormones were studied in mice. The success of the experiments elated the scientists until they found that the hormones which were active in mice had no effect of any kind in rats. This is one of the constant pitfalls which confront the investigator. He must work at first with laboratory animals before he can try a drug in man. Many substances which work in a mouse will work in rats, rabbits, guinea pigs, and man. Every so often, however, one animal species will show certain effects from a drug that no others, or only a few others, will show, owing to differences in body chemistry. This is to be expected, for, after all, one cannot hope to keep a tiger alive on the same diet as a chipmunk.

Hopes for the synthetic hormones were raised again when it was found that although they were ineffective in rats, they were partially effective in rabbits, and that the stimulation of the RES resulted in a significant reduction in blood cholesterol. Will these or similar hormones work in man? More research and time will tell.

Another major function of certain cells of the RES is to make new red and white blood cells. Both red and white blood cells age and die. Thus there must be a constant source of new cells. Without a healthy RES to produce new cells, no animal can live. It is this function of the RES which is so sensitive to radiation. Thus, in a lethal dose of, say, X ray, death is produced by knocking out this critical blood-cell-producing part of the RES, which is located primarily in the bone marrow. During the last several years, investigators have found that they can save the lives of animals that have received a lethal dose of radiation. This is done by the injection of new RE cells from another animal. These RE cells from a normal animal will take up residence in the otherwise-doomed irradiated animal and begin to produce new blood cells in adequate amounts to permit the recipient to return to relative normalcy. As a result of this basic research, physicians began to wonder if they might not have a new approach to the cure of leukemia. In leukemia, for some unknown reason, the so-called stem cells of the RES in the bone marrow begin to turn out faulty white blood cells. The cells which do this keep multiplying until all the normal RES in the marrow has been crowded out. Without a supply of normal blood cells, death is inevitable. Since radiation can knock out or kill RE cells, either normal or leukemic, it was thought worth trying to give patients with leukemia a fatal dose of X ray. Then, before they died of the radiation, one could inject normal marrow RE cells from a normal individual who would donate cells in the same way that a blood donor donates blood.

This is a startling concept. Take a patient with a fatal disease. Then give him a fatal dose of radiation in order to kill the disease. Then rescue the patient from death by the injection of new RE cells. Can it be done? We don't know. It is being tried as these words are read. There are all kinds of problems. As previously mentioned, just because a mouse reacts in a certain way, there is no guarantee that man will do the same. We know how much radiation to give the mouse in order to knock out his marrow RE cells. We don't know how much to give man to produce the same result. Too little will permit the leukemia to recur. Too much may produce lethal effects on systems other than the RES. How many new RE cells should be given? From a single or from several donors? These are but a few of the questions. About fifty patients have been treated in various hospitals in the United States thus far. None has lived. But with each failure, a little more is learned. Perhaps soon there will be enough knowledge to effect a cure. A lethal treatment for a fatal disease and then, perhaps, out of death—life.

As the clinicians work with these new tools put into their hands by basic research, the basic research man races on as fast as funds and hands will permit to provide new answers to new, as well as old, problems. For instance, is there an RES hormone which can stimulate the formation of new RE cells? We think there might be. If we could find it and isolate it, we would have a tremendously powerful tool—not only in the leukemia problem but in all kinds of disease.

However, basic research men working with the RES do not only try to stimulate this system. There is another problem confronting us which if solved will—all by itself—revolutionize medicine. Today, except in the case of identical twins, we cannot surgically transplant skin or an organ from one individual to the next. There are only three exceptions, which will be mentioned shortly. The only factor which prevents successful transplantation is the RES. No two individuals have the same fingerprints. There is apparently the same degree of individuality (except in twins) in certain of the protein molecules in the cells of the human body. Therefore, if one person's skin is transplanted to someone else, the recipient's RES will be able to detect the difference. The RES is a defensive army with orders to fight any invaders. The transplanted skin cells with somewhat different proteins are duly noted by the defense forces. They are identified as foreign and hence are aggressors. They must be killed. The antibody factories are put into high gear. As soon as enough antibodies to these foreign cells are produced, the transplanted skin will die. In surgical terms, the graft will be rejected and will slough off. The three exceptions to this rule are the cornea of the eye, pieces of artery, and bone. Of these three, the cornea is really the only true exception. When grafted from one person's eye to that of another it will grow, owing to a peculiar set of anatomical conditions which prevent the RES from getting at the transplant. When bone or pieces of blood vessel are transplanted, they are not expected to live and they don't. They are primarily used as a temporary structural framework to fill an accidental or a surgically-induced gap in a bone or blood vessel. Bone and blood vessel grafts merely provide a temporary bridge until normal tissue can grow in from either side.

Hence, if we could persuade the RES not to be so defensive about grafted cells, we could transplant not only skin, but kidneys, livers, hearts, and so on. There is no question but that in time, as a result of basic research, if a man has a bad heart he can go to a surgeon and get a new one. The surgical techniques are far enough advanced to make this technically feasible. Only the RES stands in the way. Physicians have considered and occasionally tried knocking out the RES by X ray before attempting a transplant. Since the RES when badly damaged by radiation cannot make antibodies, this is a possible approach. However, in such a case, in addition to the transplanted organ, there must be a new transplanted RES.

It is only because the antibody-producing ability of the RES is knocked out by X ray that "foreign" RE cells can grow in the irradiated individual. A further problem that arises in knocking out or seriously damaging the RES is that bacteria and other aggressors can invade at the same time. Ideally, we have to provide a way to stop the RES from attacking "foreign" transplants, while ensuring at the same time that it does its regular job against real aggressors.

A final complication in this already knotty problem lies in the fact that a transplanted organ will inevitably have some of its own RE cells in it. These transplanted RE cells will attempt to make antibodies against the proteins of the body into which they have been transplanted.

It is easily seen that whereas transplanting organs may be considered a surgical problem, the removal of the road-blocks in its way to success requires the joint efforts of a host of basic research scientists, including immunologists, chemists, biophysicists, and physiologists.

The problem of "foreign" protein molecules and the RES challenges the ingenuity, creativity, and versatility of scientists throughout the world. This is by no means all there is to the RES story. The RES apparently plays an important function in the way the body handles and disposes of drugs such as alcohol and barbiturates. Indeed, some have suggested that the solution to the problem of alcoholism lies in the RES. This system is apparently also involved in cancer.

As transdisciplinary study provided new methods of quantitative measurement for the RES, the system began to be less of a mystery. New methods gave scientists new tools for investigation. As a result, there was a quickening of interest throughout the scientific community. The interest became so great that in 1954 a new scientific society was created, devoted to the study of the RES. Its members, from all over the world, represent the broad spectrum of fields to which this system is of interest. Surgeons, blood specialists, bacteriologists, internists, radiobiologists, and scientists in many other fields are represented. Thus a transdisciplinary research attack upon a system whose functions cross disciplinary lines has fused together into a single society many specialities heretofore often thought to be remote from one another. Headquarters of the society are at the New England Institute for Medical Research, which through a new scientific journal serves as a clearing house for new information from scientists throughout the world.

It is suspected that we are just at the beginning of the list of functions for which this intriguing group of cells is responsible. Further knowledge must await more transdisciplinary basic research.

CHAPTER 5

SHARKS

If the average individual catches a glimpse of a man with mask, fins, and underwater-diving apparatus chasing after man-eating sharks, he may logically draw two conclusions. The underwater character is either a skin diver who has lost his mind or a marine biologist doing something rather dangerous.

In previous chapters we mentioned the rapidly dwindling barriers between different sciences, so it should not come as a surprise that the individual chasing these sharks is actually a physician doing research on man.

Scientists at the New England Institute for Medical Research became interested in sharks in the course of their work on cholesterol in man. Cholesterol is a fat. Man eats it in eggs, cream, and other dairy products, and as animal fat. There are also a large variety of cells in the human body capable of making or synthesizing this chemical. Cholesterol has its uses in man, but it is also a potentially dangerous substance—indeed, it is frequently a killer. For some reason still unknown to science, cholesterol will occasionally become deposited under the innermost lining of arteries, causing a small bump to be raised. In a large artery this bump is usually not too significant. However, if such a bump appears in the vital coronary artery of the heart, it can set up a chain of events in that artery which will cause a clot. This is coronary thrombosis. Cholesterol deposited in the arteries of the brain can have similar disastrous consequences. Thus for years medical science has been trying to determine the following: Where does this cholesterol come from? Why does it go where it goes? Can it be stopped? Can one get the cholesterol out of an artery wall once it has previously been deposited?

As mentioned before, cholesterol can come from the food we eat or it can be made in our own bodies. We can synthesize cholesterol in the laboratory and make one of its carbon atoms radioactive, so that if we feed it to an animal we can trace where the cholesterol goes once it leaves the intestinal tract. As mentioned in the preceding chapter, it looks as though the cholesterol which we eat and which then goes into the circulating blood is picked up primarily by the cells of the reticuloendothelial system and destroyed by them. We can trace this process because the cholesterol is tagged with a radioactive isotope. But how can we tag the cholesterol that is synthesized in the body in order to find out whether this is the culprit we are after? We can't just shoot radioactive carbon into the body, because almost every molecule in the body contains carbon. Thus, if every type of body molecule were tagged with radioactivity, we could not possibly hope to know which one was the cholesterol we are after. Therefore, it became necessary to take a closer look at the way the body synthesizes cholesterol. Such a process in the body, like the making of protein that was mentioned earlier, is much like the assembly-line production of a car.

The molecules in a cell, like the machines in a factory, cannot be thrown together in a random manner, but must begin with basic raw materials and gradually and in proper sequence build up a production line which will finally produce the molecule which this tiny cellular factory is equipped to turn out. In the case of cholesterol, the cell usually begins with a very few carbon and hydrogen atoms and then begins to add on various other atoms in a step-by-step manner.

To carry the analogy a little further, let us return to the automobile factory. If we assumed that all General Motors cars used the same type of plate-glass window, and we placed a piece of plate glass in the middle of the General Motors complex, this window might be taken for any one of the many different types of cars they produce. Hence, if we placed a marker on this piece of glass in order to trace a certain Cadillac, it would be a rather futile procedure because we would have no assurance that this window would ever be put in a Cadillac. This is an analogy not unsimilar to what would happen if we just injected radioactive carbon into man or another mammal. We would have no assurance that it would go where we wanted.

However, if we take a look at this in a different light, we may be able to devise a way whereby we can tag a specific car so that we can trace it.

Let us assume the automobile we are after can be tagged by a scratch, a nick, or an initial so that we can find out what happens to it. Further, let us assume that we wish to do this to a Cadillac rather than any of the other cars which General Motors makes.

Let us assume that the last step in assembling a car on the production line is the addition of the bumpers. Let us further assume that we will make an initialed, labeled, or tagged Cadillac in a foreign country, complete except for the bumpers. Now, if we placed this slightly unfinished car into the middle of the General Motors Corporation, the unfinished car would obviously be turned over to the Cadillac factory and placed in the production line for completion. It would not be turned over to the Chevrolet or Buick factories, because it is unquestionably and without a doubt a "pre-Cadillac." In this manner, we would have "persuaded" General Motors to make a tagged Cadillac that we could follow through its sale and eventual fate.

We planned to do the same thing with cholesterol. We wanted to find the step just before the final one in the body's production line. We would have to put our radioactive tagging atom into our "pre-Cadillac" or, in this case, our pre-cholesterol molecule. Then we could inject our pre-cholesterol molecule into the body. Like the pre-Cadillac, it inevitably would fall into the proper production line for the addition of the last item. It would be too long a story to go into the history of the identification of the pre-cholesterol molecule. Suffice it to say that it is called squalene, and that it was identified by biochemists as one of the fatty substances in the livers of the giant basking sharks, which are found in several places in the world. The name comes from the Latin word for "shark," *squalus*. The biggest batch of squalene ever collected was the work of a whaling ship that had returned from the Antarctic after a very unsuccessful trip. In Monterey Bay on the West Coast of the United States the whalers saw a large school of basking sharks. They thought they might recoup some of the losses of their unsuccessful trip by harpooning these sharks and taking their livers in order to extract the oil. Shark-liver oil, much like cod-liver oil, contains many useful ingredients, such as vitamins A and D, and can be sold. When the whalers unloaded the shark-liver oil, they found a second oil, quite light, floating on top of it. This was tentatively identified by the biochemists as squalene.

A big chemical company that is usually interested in out-of-the-ordinary chemicals heard of the squalene and offered to buy it. Apparently they thought they would receive a few quarts. When an entire railroad tank car showed up, there was a group of slightly shocked chemists. Not knowing what in the world to do with a tank car full of squalene, the company ran an advertisement in several scientific journals telling the story of how they had been stuck with it. The advertisement ended with the plaintive question: "Squalene, anyone?" There were enough curious scientists so that the entire tankful disappeared in short order.

Squalene is the pre-cholesterol form that is made in the human cells which are producing cholesterol. The production line moves so fast, however, that it is virtually impossible to obtain a significant amount of squalene from any mammal, including man. If we had been able to synthesize squalene in the laboratory at this time, we could have inserted a radioactive atom some place along the line and then injected the tagged squalene into man. Synthesis was beyond our capabilities, however. Therefore, the suggestion was made that we might take some radioactive carbon and inject this into sharks. Of course, virtually every molecule in the shark contains carbon, just as in man. Thus we could expect all compounds which the shark synthesized after the radioactive carbon injection to be tagged. However, a shark liver is so large that it is sometimes one-seventh the weight of the whole shark, and in the liver of the basking shark there is a tremendous amount of squalene. Thus, even though the carbon would go everywhere in the shark, enough of it presumably would wind up in the squalene and give us our radioactive pre-cholesterol, which we could then inject into mammals to find out what we wanted to know. Squalene is removed relatively easily from shark liver.

Since squalene had been found in basking sharks, we initially decided we would get a basking shark in order to perform this experiment. When we realized the smallest of these sharks that we would be likely to find would be between thirty and forty feet long, the problem arose as to how anyone could hold a monster of such size in order to inject him. It became obvious that we would have to try to get a somewhat less gigantic species in order to try the experiment.

Did all other sharks have squalene in their livers? No one knew. Some reports in Japanese scientific literature indicated that probably not all sharks had squalene. Which sharks did? Again, no one knew. It had never been determined.

This, then, became the first order of business, for it obviously had to be ascertained before we could begin, and it took two years of work to determine the answer. It is astonishing how important nonhuman aspects of biology have become to the study of man, and this is just one instance. However, going after different kinds of sharks in order to determine which have squalene and which do not is not a job that can be done by amateurs. The identification of various species of sharks is sometimes difficult, even for the marine biologist. Of course, anyone can identify a hammerhead shark because of his special shape, or a tiger shark because of the stripes on his sides. However, many other types are very similar, and a specialist can have difficulty in making the identification. Thus the first step was to learn about sharks. The second step was to go out and find them. They would have to be caught, brought aboard, and killed; then various lobes of their livers must be cut out, and the oil extracted and identified in order to determine the presence of squalene. We did not know whether there would be a difference between male and female, young or old, or whether squalene might be present in one season and not in another. Actually, no one has the foggiest notion why any sharks have squalene or what they do with it after they have made it.

The search began. We covered great areas of ocean in the Atlantic, the Caribbean, and the Gulf of Mexico. In the course of this search we secured the collaboration of two marine biologists who were particularly interested in sharks for other reasons. One of them was Doctor Eugenie Clark, Director of the Cape Haze Marine Laboratory in Florida. The Cape Haze Laboratory and the New England Institute for Medical Research are affiliated for problems of mutual interest. Dr. Clark is a splendid collaborator and went far out of her way to make equipment, facilities, boats, lines, and her very considerable knowledge available to us for our project.

Catching sharks is not easy. For sports fishermen or commercial fishermen who don't want and can't use sharks, the ocean frequently seems full of nothing else. They take the sport fisherman's bait and they foul up and tear the commercial fisherman's nets. But let someone go out with the avowed purpose of catching sharks and they seem to disappear from the ocean. A classical example of this happened in World War II after scientists developed what they thought was a good shark repellent. In order to test it, they had to find sharks. They chased all over several oceans and seas for almost a year before they found a heavy enough concentration of sharks really to put the repellent to a test. We found that we were no exceptions. Whenever we heard that a particular portion of a sea or ocean was heavily infested with sharks, we would immediately go to the spot—only to find that they seemed to have disappeared just about the time we arrived. Sharks appear and disappear for reasons best known to themselves. It is true that many seem to follow migratory fish schools and others tend to collect around places in the ocean where garbage or waste meat products are being disposed of. However, one cannot count on this, as we found out time and time again.

Finally, after we had collected enough representative species and analyzed their livers for squalene, we found to our dismay that the only sharks with large amounts of squalene were those which lived at a hundred fathoms or below. Inevitably the fish would die when they were pulled to the lesser pressure of the surface. This did not serve our purpose at all. We obviously had to have sharks which we could capture alive, inject the carbon, and keep alive for a week or more so they could synthesize carbon-tagged squalene for us.

It was apparent we would have to use sharks that could live near the surface, which meant that we would have to try to make do with species which produced small amounts of squalene. We decided to make our main base of operations at the Cape Haze Laboratory, which is on the Gulf of Mexico. This worked out quite well because Dr. Clark was also interested in sharks, although from another scientific aspect. Thus each shark which was caught and which could be kept alive served several purposes.

As we learned more about sharks, we began to realize how nasty and vicious these fish could be. I have frequently been disturbed by the many articles written by amateurs describing which sharks are safe and which sharks are dangerous, as well as what one should do in the water to avoid being bitten. Most of these articles are sheer claptrap. The skin diver who has not been bitten assumes that he was not attacked because he did what he did. The people you don't hear from are those who may have performed the same antics underwater and never lived to tell the tale. Sharks are nothing if not perverse. Sometimes you can say "boo" and they will turn tail and swim away. Sometimes you can even hit them and they will flee. At other times, with the same species, it doesn't make any difference what you do, you will probably not live to tell about it.

No one has any idea why a certain species will attack at one time and run away the next. Even so-called harmless three-foot sharks with relatively small mouths can and have, under appropriate circumstances, taken a good-sized chunk out of a man. Some sharks will bite at anything, for reasons that are very difficult to determine. I have found in the stomach of a tiger shark the cellophane wrapping from a cigarette package, stones, and pieces of rubber. Others have found tin cans and a great variety of similarly improbable and certainly tasteless objects.

The upper and lower jaws of a shark have many rows of teeth. They are not teeth such as man has in terms of structure, but are actually modified scales. Depending upon the species and size, the teeth can be one, two, or more inches long and razor sharp. Some are saw-toothed, and there can be nine to fourteen rows of them. A shark does not have to worry how many teeth he may break off, for he always grows more. Strangely enough, despite their teeth and viciousness and incredibly tough hides, sharks are fragile. "Fragile" seems a peculiar word to apply to a sixteen-foot undersea monster that can snap a man in two with a single bite. However, when one tries to capture a shark and keep him alive, his fragility becomes quite apparent.

One of the virtues of the site of the Cape Haze Marine

Laboratory is that it is close to a spot which has an amazing density of sharks per acre of ocean. As far as we know, there are very few other places that can compare to this area in terms of its rich variety and number of sharks the year round.

For our shark fishing we used a three-hundred-foot, one-inch Manila rope, anchored to the ocean floor and marked with a buoy so that we could find it when we went out again. From the rope dangled fifteen to eighteen chains with half-inch steel hooks specially made for this work. In choosing bait for the hooks we were faced with the problem of the trout fisherman who tries to figure out what fly the trout will rise to. Just as the fisherman might open the stomach of the first trout he catches to see what it has been eating, we do the same with sharks. Sometimes they will strike at mullet, sometimes at shark meat, sometimes at horse meat, and often at nothing. We would bait the hooks, return to the dock, wait several hours or overnight, and then go out again. We would cut the motors, haul up the line, and then manhandle the boat down the line to see what we had caught. There is always a period of excitement as this line comes up. There may be a shark or a surprise such as a three-hundred-pound jewfish or a giant sting ray. On one occasion the half-inch steel hook had been straightened out. It is hard even to dream of the size of shark which could have done that! Often a shark would be dead or close to it, having fought the line to the point of exhaustion and death. Sometimes they would come swimming to the surface, mad clear through. If the shark seemed lively and in good shape, we would detach the chain from the line and hook it on a cleat in order to tow him home. One shark was so strong that he pulled the cleat entirely out of the boat. On another excursion a large tiger shark decided that the boat was not going to tow him, and we found ourselves being pulled backward in spite of our motor, boxing the compass.

As we towed our prize in, we had to go very slowly in order not to force so much water through the shark's mouth that he would "drown." On some trips we would try to inject a shark then and there. The skin on the back is so tough that the sharpest needle or the sharpest knife will bounce, bend, or break. Becton, Dickinson and Company provided us with a special steel syringe and special steel needle, but even with this equipment one had to inject the shark on the somewhat less impenetrable underbelly. In order to do this, it is frequently necessary to get in the water with the shark. This is not recommended procedure for anyone who does not have to do it. Although the shark may be secured by a hook in his mouth and a loop of line around his tail, he still has a tremendous amount of mobility. The hook can tear loose and so can the line on the tail. Understandably, they don't like needles stuck in their abdomens. They can contort and writhe with their jaws snapping in such a way as to make one wish he were virtually any other place but there. If the tail gets loose, a blow from it can knock one unconscious. Furthermore, in shark-infested waters there are likely to be many other sharks about that may be attracted by the commotion or the blood which may be leaking from the hook wound in the captive's jaw. During all this, it must be remembered that one has the syringe in hand, full of radioactive carbon. It is imperative that this not be squirted into the ocean, not only for the sake of the scientist, but for general safety. It is also imperative that the extremely sharp point of the needle not graze or inject the scientist during the process, as this would be a fairly good way of signing one's death warrant, irrespective of the shark. Finally, one must be sure in making the injection that the tip of the needle is in the muscle of the shark's abdomen and has not gone clear through into the abdominal cavity. There are a couple of holes in the aft end of the shark's abdominal cavity that connect directly with the ocean. It was these holes, called abdominal pores, which interested Dr. Clark. One of the things we found out about sharks was that they could use these holes to squirt out any fluid which might be in the abdominal cavity. If the tip of the needle went too far in and the radioactive carbon reached the cavity, the shark could squirt the same radioactive carbon right back out at you through those abdominal, or, as we finally wound up calling them, "abominable" pores.

In order to keep the sharks alive after capture, we used a pen which had been built out into the ocean. Large wooden pilings were driven into the ocean bottom, making a rectangular cage with spaces large enough between each piling so that water and small fish could come in but no large marine animals could escape. One end of the rectangle led up through shallow water onto the beach, so that one could walk into it. We had about a four-mile trip between the spot where the sharks were caught and the pen. For some reason, still not understood, a shark could be lively and in apparent good health at the beginning of this trip and yet no matter how carefully we towed him, he might decide to drop dead at the trapdoor entrance to the pen. Tranquilizers have been found to be useful in quieting wild fowl, cattle, and even horses during shipping. We tried tranquilizers on sharks. Of course, we had no idea of what dosage to give, but insofar as we could judge, the net effect of the tranquilizers was to make the shark livelier. In half the cases it helped to get the sharks into the pen successfully. The other half died. With a fifty-fifty score, it is difficult to evaluate effectiveness.

If the shark was brought in successfully and slid through the trap door, the next problem was to get the hook out of its mouth. This is a procedure where one stands a very good chance of coming up armless. Occasionally the shark seems so tired at this point that he appears willing to let you do almost anything to him; but because this animal is capricious, one never knows from one minute to the next when an apparently lifeless shark will suddenly rear up and take a chunk out of you. Sometimes, if the animal is almost comatose after the tow in and removal of the hook, one has to "walk" the shark around the pen until he revives. One grasps the dorsal fin in one hand and one of the pectoral fins in the other and begins to walk back and forth. When the shark revives, the idea is to get out of there. This ordinarily is not too difficult a task, but it does tend to become a little worrisome if there are other sharks cruising around the pen at the same time. There is a kind of fascination in watching these sleek behemoths cruise relentlessly back and forth in the pen. Sometimes people stand there for hours almost hypnotized by the sight.

Now comes the critical part of the experiment. In order to keep the sharks alive, they must be persuaded to eat while in captivity. This they are often loath to do. Refusal to eat and a starvation-exhaustion death is one of the reasons that so few of the big marine aquaria are able to keep many different types of sharks on exhibit for very long. We felt we were doing well if one out of every twenty-five sharks caught and brought in lived and ate. Once they start eating, they keep on unless they become ill. At Cape Haze we frequently had available the whole rib cage of a steer for shark food. This was hung over the water on a rope. To see a twelve-foot tiger shark come to the surface and bite this neatly in two always gave us pause about the next trip.

When we first went out after sharks we thought it would be reasonable to mount a guard on the boat armed with a 30-06 rifle using 220-grain bullets. The idea was that the guard could shoot and kill or drive away unwanted sharks that approached a diver in the water. We first tried shooting at sharks without anyone in the water. After three or four days we concluded that a fly swatter would be just about as effective. As one diver who really knew sharks said when asked about the beautifully honed ten-inch knife which he carried underwater; "This knife is terribly important if any sharks go for me. If a shark comes in purposefully toward me, I pull out my knife, grit my teeth, and then I cut my own throat."

For a man in the water, defense against a shark, if the shark has "blood in his eye," is almost impossible. The shark repellent of World War II years was devised on the theory that one thing which sharks don't like could be extracted from shark meat. Thus chunks of dead shark should be the worst possible kind of bait with which to catch other sharks. If this is true, no one has told the tiger sharks about it. Some of the biggest tigers we caught were taken on shark-meat bait. The nastiest of all sharks in the Atlantic and Gulf waters in the United States are the white, the tiger, and the hammerhead. This doesn't mean that I recommend any of the others as pets, but it is recommended that these three be given the widest possible berth.

Work with the sharks continued day after day. It meant early rising, collecting and preparing gear and bait, and then going out to where we had left our line the evening before, to see what fate had brought us.

Hauling up these lines and working with the sharks is often backbreaking work. It can become particularly difficult when a high sea is running and the boat is pitching and yawing. As one tries to pull up the line laden with sharks in order to inject them, put loops of line over their tails, or some of the other things necessary, the whole operation becomes increasingly more dangerous. Occasionally, rather uncomfortable circumstances would arise. At times when we were returning to the dock with several sharks tied on the stern, we would be caught in a tricky channel with a high following sea. It was most disagreeable to see the sharks swimming about six feet above one's head in a swell as the boat wallowed in a trough. As the swell came rapidly toward us and the boat tended to broach to, it looked as though the sharks would crash right into the cockpit on top of us.

In working with an animal such as the shark in conditions such as those described above, it is unquestionable that one has close shaves and near misses. We were no exception. The work which we put into this problem was quite considerable.

However, in spite of the time, the effort, the toil expended, and occasionally the danger, we still have not collected enough radioactive squalene to do the experiments which we wish. The yield from the livers of the sharks we caught had too little squalene, and the numbers of sharks were too few to give us enough material to work with.

Therefore, this research is still incomplete. However, as Dr. Marshall Brucer of Oak Ridge has stated, "The one thing that one can be sure of in research is that one is going to fail." This is true. When one goes into the unknown, months and years can be spent in futile exploration and frustrating experience before he arrives at a successful conclusion.

However, as in the pursuit of all basic knowledge, none of this effort is really wasted. For instance, in working with sharks as much as we have, we learned a great deal about the behavior of sharks and their responses. Dr. Eugenie Clark has since continued the work, and the resulting information may prove to be very useful in the development of more effective shark repellents. As more and more people take to the water, either as skin divers or boating enthusiasts, the problem for them as well as for military personnel downed at sea becomes acute. An effective shark repellent is devoutly to be desired.

Even though we have not as yet been able to achieve success in the squalene experiments, other major dividends in knowledge have come out of this research endeavor, among them a piece of very useful information that has been developed from our studies on the function of the strange structures in sharks, previously mentioned, called abdominal pores. No one has ever known the function of these anatomical structures. As we have begun to develop insight as to what and how they are used by the shark, we have gained information which may have considerable importance. It is obviously important to the shark but may also be important to us in our understanding of methods to help us control man's responses to sudden changes in pressure under water.

Finally, a practical aspect of the work is in the knowledge we have gained of the behavioral characteristics of sharks, which become helpful in trying to catch them. The shark, like most other marine animals, is very rich in protein. There are many areas of the world, particularly island countries, where sharks abound in surrounding waters. In these areas the population is frequently starved for protein and actually has a protein-deficient diet. The shark could be a very valuable adjunct in the diet of these people. To be able to catch sharks in adequate numbers and to process them in such a way so that their meat is edible and nutritious becomes a very real problem for areas as close as Puerto Rico. Thus, even though we have not yet achieved our initial objective, during the course of the work we have acquired a body of knowledge which is basic information on a biological problem and can in turn be taken by other disciplines and specialties and used for the development of practical problems.

This is a good example of the lack of waste in basic research, for here even negative answers are valuable in that they prevent others from making the same mistakes. Furthermore, any knowledge gleaned will sometime and in some way be of use to others as they go in pursuit of their own problems. Meanwhile, the squalene experiments are still under way and no final report can be made at this time.

This chapter on sharks indicates the breadth and latitude of scientific exploration. The entire project started as an investigation in basic research in the problem of cholesterol, a problem which is important to heart specialists or cardiologists. The typical picture of the cardiologist as a man at the bedside with a stethoscope and electrocardiogram must obviously be painted on a broader scale. This doesn't mean that a cardiologist has to wear flippers and a face mask, but it does suggest that the strict borders between specialties have begun to crumble and disappear.

The ocean is an enormously rich storehouse of biology, with innumerable treasures that are still untapped. It is not only the shark which has provided a tool for research in human disease. This is only the beginning of the story of the sea and its riches and how they can be used to help man.

CHAPTER 6

MOOD AND MADNESS

Psychiatry is enough to drive a scientist crazy. The scientist wants to measure things quantitatively. The difficulties in trying to quantify people's personalities or behavior characteristics can be made very obvious by trying it yourself. List twenty friends and acquaintances. Then try to put some kind of numerical value on all the different aspects of their personalities and behavior. It is obviously hopeless, for "how" happy is a cheerful individual? Can someone else be graded as three-fifths as happy? Is someone peculiar? How peculiar must he be to be different, odd, weird, or insane? You may think Mr. X is peculiar because he does certain things. He may think you are peculiar because you don't. Who is to judge how much of what makes someone else odd? This is one of the prime difficulties of the scientist who wishes to study mood and madness. Of course, some individuals, such as a homicidal maniac or a catatonic schizophrenic, are obviously insane. As soon as such a statement is made, one can legitimately ask, "How does one define 'insane'?" Clear-cut answers with which all will agree are frequently not to be had.

Let us assume that "Factor Z" causes insanity. Will a cheerful, generally happy, extroverted individual manifest the same behavioral symptoms when hit with "Factor Z" as will the moody introvert?

All of these unanswered questions make the attempts of the scientist to quantify in psychiatry extremely difficult. Until he can quantify, he can but poorly understand how much of what does which.

In an earlier chapter, it was mentioned that the early biochemists invaded the field of psychiatry but, within their ability to measure, could find no difference between the sane and insane. The field was left to the psychiatrists. The two principal weapons which the psychiatrists had were psychoanalysis and psychotherapy. They attempted verbally to develop insight, understanding, and reassurance for the patient. These techniques can work if the psychological problems are due to lack of insight, lack of understanding, frustration, fear, or anger. In general, people with such problems are described as neurotic, while the really insane group is described as psychotic. What could the psychiatrist do for the psychotic patients? Very little. He could try a few things such as various types of shock, insulin or electric. A series of terrific jolts of electricity can in some cases bring improvement—but how, or why, no one knows.

It is clear that great psychological pressures can produce neurosis and perhaps psychosis. But is it possible that something other than such pressures can affect mood and madness? Might such changes be caused by some fault in body chemistry? Or might changes in body chemistry be produced as a result of psychological pressure itself? Is there any evidence to indicate that chemicals can affect the mind? Indeed there is. Women can show personality changes at the menstrual period and during menopause. There is also a type of insanity called post-partum psychosis that occasionally affects women after childbirth. Hormones, which, of course, are chemicals, are a pretty good bet to be involved in these situations. Too much adrenalin in the blood can make a normal individual feel fearful and anxious. (Of course, fearful and anxious people frequently pump their own adrenalin into their blood, but I refer here to injected adrenalin.)

Certain drugs in the cortisone family can produce temporary elation and happiness.

Many narcotics can also act on people's brains. Narcotics not only dim the feeling of pain but in many individuals produce a feeling of sublime happiness and the ability to disregard all the problems which beset them. It is this chemical reaction with the individual's brain which makes narcotics so dangerous. Obviously if there were no feeling of pleasure from narcotics virtually no one would become addicted. Actually there are some people who do not react with this feeling of intense pleasure from narcotics. Here again is an example of how two people can vary considerably in their response to a single drug. Once an individual is addicted to narcotics, there is apparently a series of major changes produced in body chemistry, so that the withdrawal of narcotics from an addict becomes an extremely painful process. This is still another link in the evidence, available to us as long as opium has been used, that pointed the way to the importance of chemistry and man's mental state.

In spite of many such bits of evidence linking chemical and mental changes, so-called psychochemistry did not really get off the ground until after World War II. Two events resulted in creating intense interest in this new area. The first occurred as a Swiss chemist was working with a chemical derivative of ergot. Ergot is a fungus which affects rye and other cereals. Yesteryear, so-called epidemics of insanity would affect whole communities the inhabitants of which had eaten bread made from grain contaminated with ergot. In this instance, the chemist had a rugged and unforgettable experience. During the course of working with a derivative called lysergic acid, he rapidly developed symptoms similar in many respects to schizophrenia. By the next day the symptoms were gone, and he correctly assumed that they were due to the lysergic acid. Further investigation showed that a few millionths of an ounce of this substance could produce these symptoms in man. What does this single piece of information tell? First, "chemical insanity" is possible. Second, extremely minute amounts of a chemical are enough to produce this change. The amounts are far smaller than investigators are used to looking for and working with in terms of causative chemicals in disease.

Psychiatric investigators then began to consider other agents which had been known for a long time to produce hallucinations and mental symptoms. Most of these were discovered long ago by primitive peoples, such as the peyote cactus used by American Indians of the Southwest. Many such substances had similar chemical structures. The quest was becoming exciting.

The second major impetus in the field of psychochemistry was the inadvertent discovery of the tranquilizers. These substances also have a chemical affect, direct or indirect, on the brain.

These studies will eventually change the entire approach to mental disease. As exciting as the leads may be, there are roadblocks. One of the logical groups to pioneer in this new field are the psychiatrists. But all the training in the world in the doctrines of Freud, Jung, or Adler does not equip a man for a complex chemical field. The amounts of the chemicals which are needed to produce mental changes are frequently smaller than the amount that can be measured or even identified by conventional chemical methods.

Thus one is confronted by the following dilemma. We know there are molecules of certain chemical substances present which can produce severe mental changes. There are no known chemical methods which can identify or measure these molecules in the amount in which they occur. If chemical procedures cannot hope to work in this situation we must fall back on other techniques. Actually we have had to enter the realm of physics. One of the classical chemical methods is to cause a reaction of the unknown substance with other chemicals so as to produce a certain color. Thus, in the measurement of blood sugar or other blood or urinary constituents, one merely has to carry out the right series of chemical reactions to develop a color, blue, green, yellow, red, and so on. The amount of color is proportional to the amount of chemical present. Of course, one cannot measure the amount of color with the naked eye; hence, a physical device known as a colorimeter was developed for routine use in biochemical laboratories. However, even the most complex and delicate instrument has a limit below which it cannot successfully measure color. This means that if the color is too dilute, the machine cannot hope to perceive it.

The chemicals which are active upon the brain are present in such small amounts that they are below this color threshold. Unfortunately, in science there is no way known to intensify or to amplify a color. Thus, we had to turn to certain techniques in physics in our attempt to measure the tiny numbers of molecules.

Specifically we sought to use a physical phenomenon known as fluorescence. This technique takes us into the field of physical chemistry, chemical physics, and optics.

What one must do in order to use the technique is to find a certain type of light which that molecule one wishes to measure will absorb. Very often the only useful wave length which one can utilize for this phenomenon is down in the ultraviolet range.

After a molecule has absorbed this light, it becomes excited to a more energetic state. The molecule wishes to return to its former more placid situation and, consequently, wants to give up the excess energy it has absorbed. It can do this by several methods, one of which is to emit light of its own. In other words, a unit of light has been absorbed which excited the molecule, and the molecule can return to its previous state by emitting another unit of light. It is characteristic of this phenomenon that the molecule will absorb a certain wave length of light and will emit another wave length. Thus one has a method whereby the "fingerprint" of a molecule may be obtained.

Admittedly, the light which a single molecule can emit is incredibly tiny. However, although we cannot intensify color, we can intensify light. This is done by converting the light into electricity and amplifying or multiplying the electricity until it can be read on a meter.

Everything about this technique is delicate and difficult. First of all, since most substances in which we are interested absorb light in the ultraviolet range, it means that we must have a very special optical system. Ultraviolet light will not go through glass, but it will go through quartz. If one has to make a special lamp with a quartz sleeve instead of a glass one and if all the prisms and other optics, including test tubes, have to be made of quartz, the price and complexity of building such an apparatus increases almost astronomically. But even after one has worked out the system, there are many other complexities in physical optics, spectroscopy, and electronics that must be solved before one can hope to make accurate measurements.

If we return now to our psychiatrist who has been trained primarily in medicine, psychoanalysis, and psychotherapy, we find that he cannot enter this new field of psychochemistry unless he has mastered the complex science of chemistry. In addition, he must also become conversant with all of the germane aspects of the physical sciences just mentioned, which are absolutely vital in creating and understanding machines and devices that will measure the critical chemicals in question.

When I first began research in this field, I had to build my own device for measuring fluorescence. Some years later, instrument companies became sufficiently convinced of the utility of this type of device to produce it commercially. Unfortunately, there is not now available anywhere in the United States a fluorescence-measuring device that is sufficiently advanced or effective to give us many of the vital answers which we need in this area of psychochemistry. Ironically enough, many of the men in psychiatry who have mastered some chemistry are now using commercially made devices, but they do not have adequate understanding of the limitations of the instruments they are using. Hence, many of them are working with suboptimal tools; but not being able to evaluate their adequacy, they are coming to a series of erroneous conclusions which cannot be corrected until better instrumentation is available.

As these words are being written, we have just noted in the scientific literature of the Russians evidence that they are working on various aspects of the same problem of fluorescence. Looking at their data shows us they have available instrumentation that is giving them the kinds of information we would very much like to have. In short, they have an excellence in this field of instrumentation that surpasses ours. Hence, they are able to make fundamental studies in this and vital allied fields which we cannot make as yet.

As the average psychiatrist knows little of chemistry, the average chemist has no background in psychiatry. Thus a psychochemist must be a new breed versed in psychiatry, neurology, chemistry, and perforce, some physics. Again we see the need for broad training beyond the confines of strict specialization. Today Freud without molecules is passé.

However, there is a further problem. Most research aimed at eventual human consumption begins with laboratory animals. But where and how do you get crazy mice? How could you tell whether a certain drug made a mouse happy? Will a drug that can induce hallucinations in a man have the same effect on a mouse? Doses of lysergic acid that would really rock a human being have no observable effect on a mouse.

A huge search is now under way, ranging from Siamese fighting fish to horses, for some visible characteristic produced by a drug in an animal that can be correlated with a mental effect of the same drug in man. In the meantime, much research is actually being done on human beings. Investigators try drugs on themselves—a dangerous but necessary business—in order to be their own guinea pigs. Such work indicates that the same drug in the same dose may produce different effects in different individuals. Still we only have descriptive rather than quantitative methods to describe these changes.

One of the approaches which is being studied at the New England Institute for Medical Research is a theoretical one.

We look at some of the chemicals known or thought to be involved in normal brain-cell function and postulate, in terms of known or suspected mechanisms, what the chemical fate of the substances might be. The thinking behind this attack on the problem is that in abnormal mental states an imbalance either of normal chemicals or abnormal chemicals may be produced. In the enormous mixture of chemicals in the body, it is unlikely that you will find something you are not looking for. Thus we work out theoretical substances in the context of what is known, and then we search to see if they are there. The first phase of this work has taken two years.

We believe we have found an abnormal substance in schizophrenic patients as contrasted with "normal" individuals. We are forced to say that we "believe" rather than we "know," because technical problems have thus far prevented us from making sure. The substance in question differs by only a few atoms from many other similar substances that are present. It is something like trying to find three or four specks of paprika in a bushelful of ground red pepper. If we can establish our "belief" as fact, it might point the way to the chemical basis of schizophrenia. If the theoretical approach be correct (a very big "if"), there is very little doubt that we can design appropriate molecules to correct the disorder.

Lack of adequate funds slows this research. If only a tiny fraction of the hundreds of millions spent for the maintenance of state and private mental hospitals were spent on basic research, we might empty the hospitals. Last year more was spent on research in poultry nutrition than the entire United States budget for basic research in mental disease. One begins to wonder about a mentality which places greater emphasis on fat chickens than on tens of thousands of mentally disturbed children and adults.

Thus far we have spoken primarily of insanity. How about mood? For simplicity's sake, let us assume that there are two kinds of mood. The first applies to people with a relatively constant cheerful and happy disposition as opposed to the chronically surly or moody type. The second is that of the individual who is at times in a good mood and at other times in a poor mood. Is it possible that both or either of these types of people have their moods dictated by their brain or body chemistry? We think that this is certainly a possibility. Of course, circumstance, such as making or losing a million dollars, can have a lot to do with mood. But even in such a case, there are some people who can lose a lot of money philosophically, while others can go into a funk so deep that it ends in suicide. The individual's "personality," his upbringing and environment all play a role. But in spite of the personality and environment and background, it seems probable that we may eventually be able to make almost anyone "happier" than he is. Many psychiatrists are concerned about "happiness" pills.

Some feel that creative people create because they are either neurotic or in some way dissatisfied. The argument here is that if someone is completely happy about everything, he can hardly be motivated to try to change or improve things. Thus, if a businessman is "happy" with his income, why should he try to get new customers? Our impression from the tranquilizer type of "happiness" pill is that initiative, ideals, and dedication do not weaken. The individual is just less tense and less miserable.

It is possible, however, to rob an individual of any initiative with drugs like lysergic acid. Basic research in Russia is concerned with the development of such substances. Imagine what would happen to any government if such chemicals were distributed in the air over a capital city just before an all-out attack. The amounts of such chemicals necessary to have such an effect are very small. Several "innocent" private planes flying over a city spewing this substance out as an aerosol might rob a major part of the key personnel of their ability to make decisions or act upon them. This is a rather horrible thought, and people of the Free West do not ordinarily think along such diabolical lines. There are others, however, who specialize in diabolatry. That we don't think a certain thing is "cricket" is almost a sure guarantee the other fellow who does not believe in fair play will try to exploit it. The Soviets are also interested in many of these drugs because of the effect that they have on individuals during an interrogation. A captive under the influence of such drugs would probably be willing to tell anything he knows.

But let us forget this rather hideous thought and go back to happiness. A recent series of discoveries has added a possible new dimension to the problem. Most of us have had the experience of waking up some mornings feeling on top of the world and on other days "getting out on the wrong side of the bed." Some people with certain chronic diseases seem to be able to predict when bad weather is coming because the "old shoulder aches." Is this just happenstance? How can weather make one feel better or worse? Low and high pressures and low and high humidity have been artificially created in special chambers, but these changes have not had much effect. However, recently some investigators have been wondering about electric charges in the air. Even so-called pure air is filled with tiny particles of dust and other matter. Anyone who has ever seen sun slanting in a window has noticed dust motes floating in the air. These particles usually have an electric charge on their surfaces much like the static electricity that one can build up in one's body by shuffling his feet on a wool carpet in crisp winter weather. The charge on these particles, and hence in the air we breathe, can be either a positive electrical charge or a negative one, depending on which charge is predominant on the particles. Recent experiments seem to indicate that in air with a predominant negative charge, individuals generally have a feeling of well-being. If the charge is switched so that it is positive, depression and gloominess seem to take over. Reports claim that someone with asthma or allied diseases can go into a violent asthmatic attack in a room filled with a positive charge and recover rapidly and feel fine as soon as the charge is changed to negative. At least one air-conditioning firm is including in its new air conditioners a device to make the charge in a room a negative one. We have no idea as to why or how this works. Indeed, since "feeling well" is so subjective, we are not even sure that it does work.

It is, therefore, extraordinarily difficult to find out what the optimum amount of negativity may be, since we cannot quantify a subjective feeling of well-being. However, if these experiments are confirmed, they might explain the responses of people to weather changes, for different weather conditions are accompanied by varying types of charges. They may also explain why some individuals always feel better in certain geographic locations, for the charge in the air at the sea shore can be very different from the mountains, and so on.

Studying the effect of electrical charges on human emotions is a bit frustrating because there is still relatively little one can put one's teeth into experimentally to find out what possible reactions the charged particles in the atmosphere can cause in the brain.

Any work involving mood and madness has fascinating possibilities. If we can hope to change man's mood for the better, might this not apply on a large scale to nations? The sociological implications are staggering. Tyranny does not stand much of a chance of taking over in a happy nation. Tyrants need the malcontents, the angry, the vicious, the greedy, the power-hungry, and the haters to back them so they can achieve power. Might a single chemical help reduce man's inhumanity to man? I do not suggest a chemical conscience for man, but perhaps many of those who hate so much have a chemical imbalance which drives them. Perhaps stabilization of the imbalance would allow normal conscience to function.

Though to some this might sound like science fiction, it is not beyond the realm of possibility with the knowledge now at hand. With such possibilities ahead, one can hardly blame the basic research man for feeling frustrated that poultry nutrition is deemed more important and that basic research is starved for funds. Not even "happiness" pills can make him feel better about this. Research on deodorants, depilatories, lipstick, nail polish, and home permanents have budgets of tens of millions of dollars. Basic research on the way the mind works, how it becomes sick or warped, has a tiny, inadequate budget. This is certainly another area in which, once we know the truth, we can hope to liberate men—in this case, tens of thousands from the tyranny of insanity.

CHAPTER 7

R. F.

R.f. stands for radio frequency. Most of the world's population is familiar with radio frequency. Indeed, in a great part of the world where the mass of the population is illiterate, radio is the sole source of news, information, or propaganda.

The same type of radio waves are responsible for radio, television, and radar. All of these waves travel with the speed of light, and they differ from one another only in the length of the wave. The length is determined by the number of inches, yards, or meters between the crest of one wave and the crest of the next. Thus, as you tune your radio from one station to another you are tuning to a different wave length; the same is true with television. However, it is not common in scientific parlance to speak of "wave length" in the radio and television ranges. The word "frequency" is used instead.

When you consider the number of radio and television stations and the number of radar systems for commercial and military purposes, it must be apparent that the area around you is constantly filled with these waves traveling in all directions. This has been true since the earliest days of wireless telegraphy.

Radio frequency is so commonplace that most of us seldom think that we are constantly surrounded by these waves and that they are going through our houses and through our bodies day and night, the clock around. Since World War II, with the big increase in electronics, more and more diversified use has been made of radio frequency. It has been found that you can send out a very intense beam which will create enough heat to cook food. Devices using such a beam are currently on the market under the name microwave ovens. It is the same principle of producing heat that is involved in diathermy, which also uses radio frequency. Astronomers now find they can pick up tiny radio signals sent out from atoms that are millions, billions, and trillions of miles away in space. This has given rise to a new field called radio astronomy.

One would think that, since radio frequency is so commonplace and has been with us so long, it would be unlikely that any dramatic new discoveries might be forthcoming in terms of its effect on living matter. Louis Pasteur once stated that "chance favors a prepared mind." This is certainly true in basic research when one never knows what one may encounter. One can never predict how a very tiny clue might open up an enormous and exciting field. One such clue was just about buried in the enormous technical literature on electronics and r.f. It was the observation that occasionally individuals who had been inadvertently caught in a high-intensity radar beam developed cataracts in their eyes and damage to their testicles. This was initially a source of some concern because the military uses enormous amounts of radar, as do many private corporations. The question was raised as to whether or not there might be a subtle damaging effect of radio frequency that had not heretofore been noted. The armed forces in the United States put a considerable amount of money into the hands of research teams, primarily in universities, to try to determine what, if any, damage there might be. As these investigators pursued their studies, they found—not unexpectedly—that an intense beam of radio frequency could produce heat, just as it does in diathermy. They concluded that the damage to the eyes and testicles of individuals who had been exposed to an intense radar field was due simply to a heating effect.

My colleagues and I had come across several of these reports in the scientific literature and found that they were quite unsatisfactory, for we could recall many patients with diseases that produced extremely high fevers, such as malaria or pneumonia, but never resulted in any damage similar to that created by radio frequency. Indeed when one calculated the amount of body temperature rise that individuals who suffered ill effects from radio frequency had sustained, it turned out to be rather modest in comparison to that of a patient with severe recurrent malaria. This discrepancy was baffling. We suspected that there might be a dangerous component in radio frequency. To suspect is one thing. To try to find something when one has not the foggiest notion of what to look for or how to find it is far more difficult. I was, however, sufficiently perturbed to write one of the major corporations who made microwave ovens for the domestic kitchen, suggesting that these might not be completely safe devices for housewives to play with. This suggestion was brushed aside.

As a result of a series of scientific findings, the idea finally occurred to us that it might be possible to investigate certain effects of radio frequency in a new way. Most of the research up to that time had centered around devices which would produce many watts of power. Obviously if one were to put enough heat energy into an animal, one could kill it by broiling it to death. Thus, heat was a limiting factor as to how much energy one could pump into a living organism. There seemed to be a possibility of getting around this heat barrier. Since the heat produced in an organism by r.f. is a result of the average power, we thought we might get around this by sending in very short but powerful pulses. This thought was based on the theory that the effects of radio frequency upon living cells might be a result of peak power rather than average power. Thus we would turn on a radio frequency field for a millionth of a second and then let a few thousandths of a second pass before we let in another blast of a millionth of a second. The average power or energy produced by this pulsing technique was very tiny and not enough to produce any significant amount of heat.

We began our study by exposing rats to such an intermittent-pulsed radio frequency field. We observed changes, but they were so complex that we felt we could not rely upon the data. However, what we did observe was sufficiently exciting to encourage us to pursue this investigation further. We would try to find a biological system far simpler than that of a rat.

We began by using single-celled animals and bacteria. We constructed a piece of electronics apparatus that would give us the ability to pulse our energy and to pick many different wave lengths or frequencies to study.

In early experiments we noted that if we put certain bacteria in our radio frequency field, they would line up nose to tail in long chains. A similar phenomenon had been noted many years ago by some German and Swedish scientists working with inert particles of matter. It was an eerie sight to look through a microscope and see thousands of bacteria in their normal random arrangement, and then turn on a radio frequency field and see them suddenly line up into dozens of chains, each of which comprised many hundreds of bacteria stretching from one end of the microscope field to the other. As soon as the force field was turned off, the bacteria would gradually return to their normal random distribution.

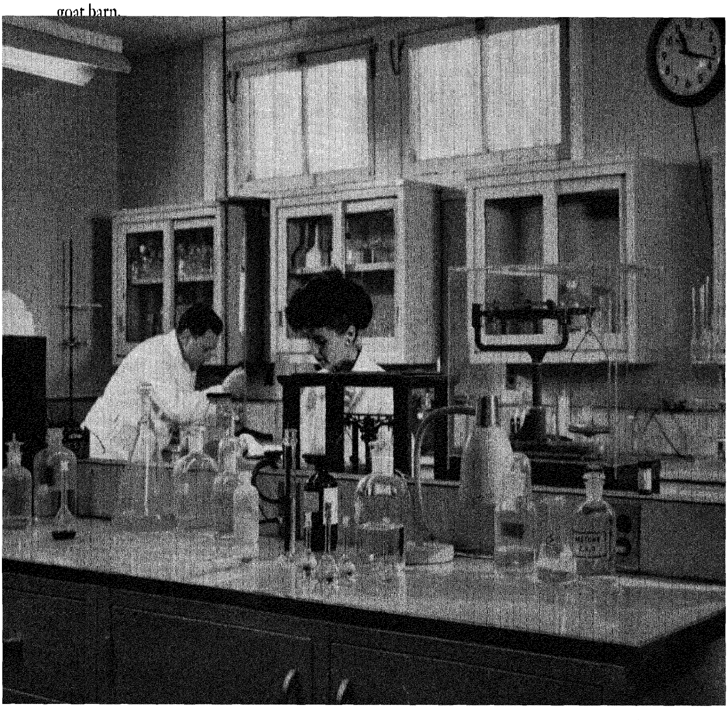
We could hardly wait to repeat the experiment with other single-celled organisms that had the power of motion. These included common one-celled animals such as the paramecium and the amoeba, as well as some of the bacteria which can move by virtue of a tail-like apparatus that whips back and forth. Normally these organisms swim randomly about in all directions. When we turned on the force field, it was as though a minute invisible hand had affected each one of them. Their random swimming ceased immediately, and they began to swim back and forth in straight parallel lines. Furthermore, they were unable to leave this rigid back-and-forth pattern as long as the radio frequency field was on. It gave one the impression of looking out of the window of a tall building down at the traffic on the street below where all the cars are moving up and down and none move crosswise. In these circumstances, of course, there are men at the controls whose minds are directing the course of the vehicles. In the case of our small organisms, we knew that normally they would swim all over the place. The radio frequency field prevented them from doing so. The instant that the field was turned off, however, they immediately returned to their normal swimming pattern, rushing about in all directions.

Here was a unique phenomenon. Why had it never been observed before? However, this was only the very beginning of a most exciting story. The next obvious step was to change the wave length or frequency in order to see whether or not this would affect the swimming of our one-celled organisms. To our complete astonishment, as we increased the frequency the animals suddenly stopped swimming from left to right, made a rightabout-face, and began swimming up and down. We could not believe our eyes. We repeated the experiment again and again, and yet again. Sure enough, at one frequency the animals went back and forth in one direction, and at a higher frequency they wheeled about to pick up a new back-and-forth direction at right angles to the path that they had been traveling before.

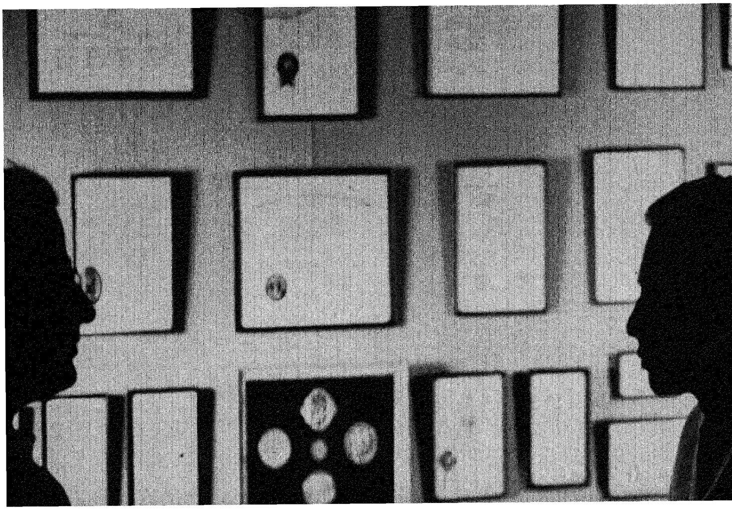
As we made more and more critical measurements the findings became more startling and more exciting. We found that if we put three or four different species of organisms under the microscope we could pick out a frequency which would affect a single species and leave all the rest apparently unaffected. Thus, by selecting a frequency and using the right voltage, we could compel our tiny martial cells to go back and forth, up and down, or behave as though they were completely unaware that there was any r.f. at all. Therefore, a specific radio frequency could cause various animals to go in a direction that we wanted them to.

As we examined this phenomenon ever more closely, I found myself seated one day looking into the microscope at a paramecium that had become trapped in some debris on the microscope slide. He was wedged in so firmly that he could not respond to the radio frequency field when it was turned on. However, I noted a tiny particle inside the cell that was flipping back and forth whenever I turned the field on or off. This meant that we had the possibility of affecting tiny structures on the inside of cells irrespective of what we did to the cells as a whole. The implications here were staggering. Could we control vital cell molecules and

The New England Institute for Medical Research when it was little more than a 130-year-old goat barn.

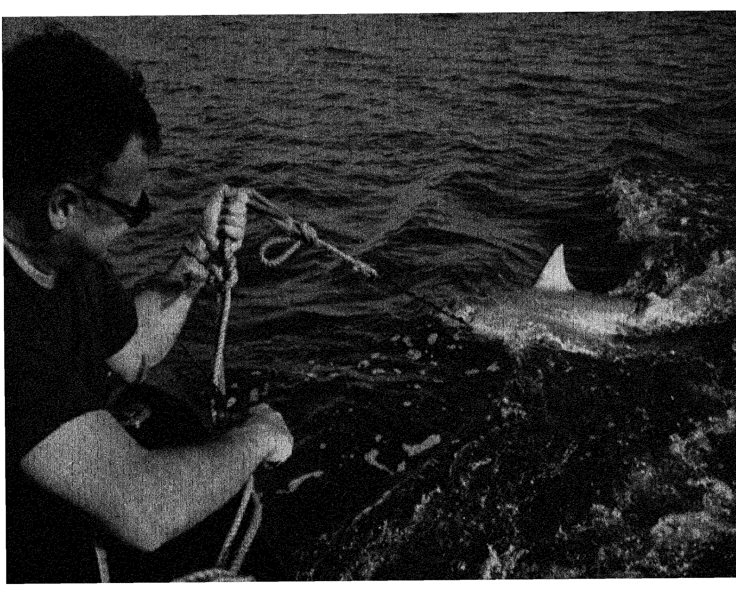


A laboratory of the New England Institute for Medical Research as it looks today. (Photo.



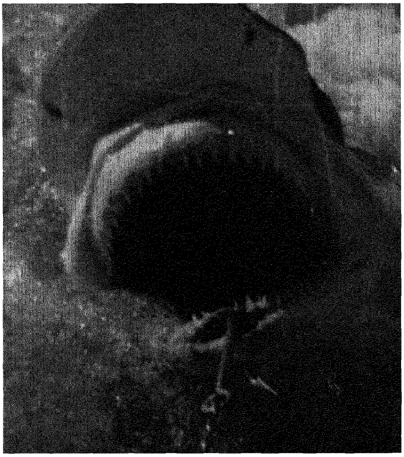
Two scientists of the New England Institute for Medical Research. Behind them on the wall are diplomas, degrees, awards, and certificates of service of one of them. Average age, 33 years. Average number of years of postgraduate study, ten. (Photo. Fred's Studio)

The author urging a shark to come alongside so that he can be injected in the open sea. (Photo. Mottar)

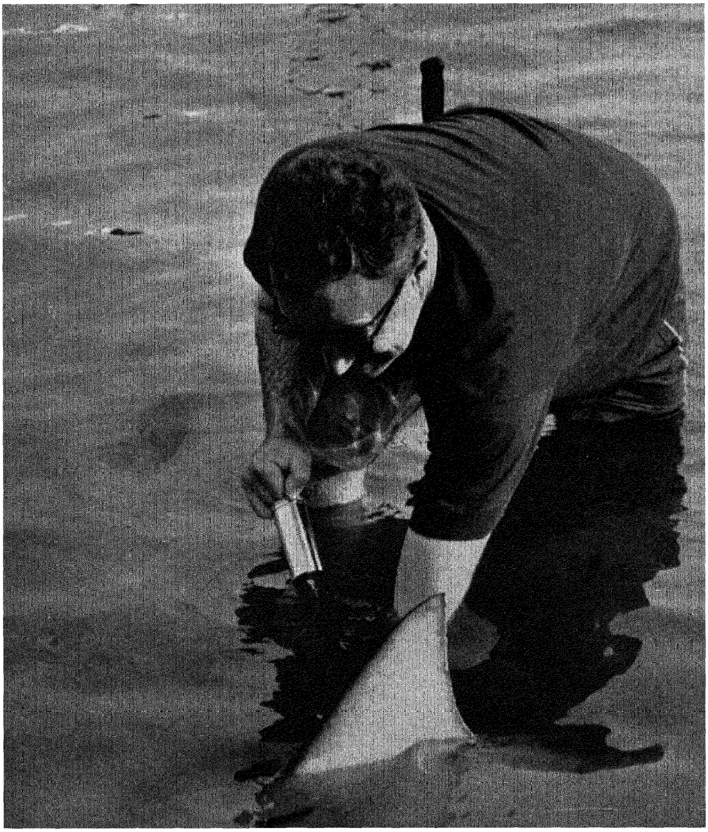


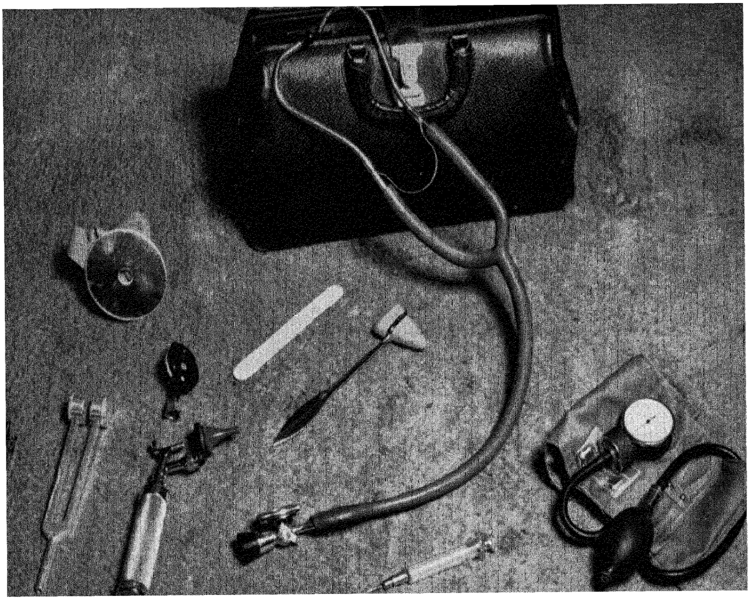
The awesome spectacle of "looking down the throat of the enemy." A typical shark caught for cholesterol experiments.

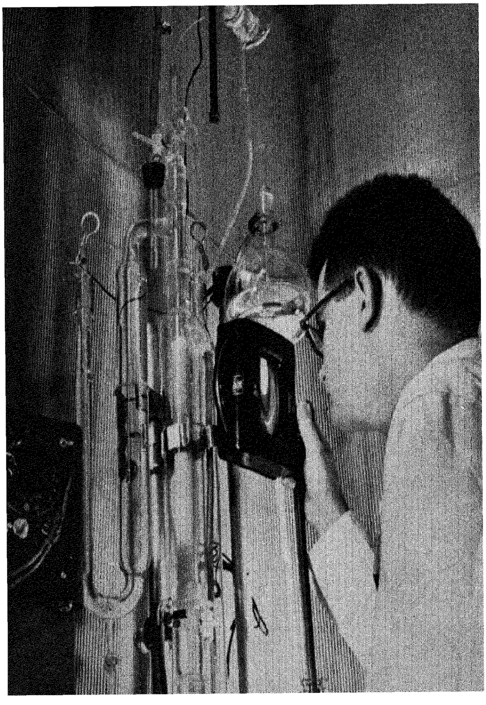
(Photo. M. S. Heller)



Below: The author injecting radioactive carbon into a living shark caught in the open sea and now confined to a pen built out into the ocean. (Photo. Mottar)





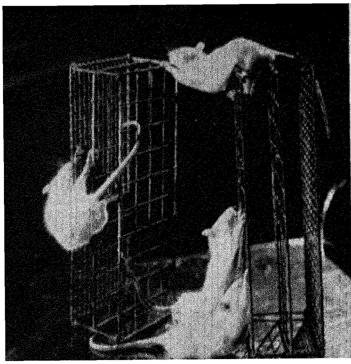


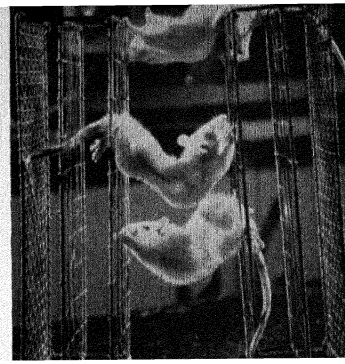
Above: The important tools of the physician's black bag today, essentially unchanged for decades. Flash light, oto- and ophthalmo-scope, tuning fork, tongue depressor, blood pressure cuff, reflex hammer, head mirror, syringe.

(Photo. Fred's Studio)

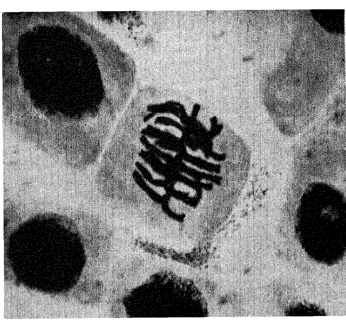
Left: The type of tool for the physician of tomorrow. The scientist here is making a fluorimetric inspection of a column chromotographic electrophoretic separation of a blood fraction.

(Photo. Fred's Studio)

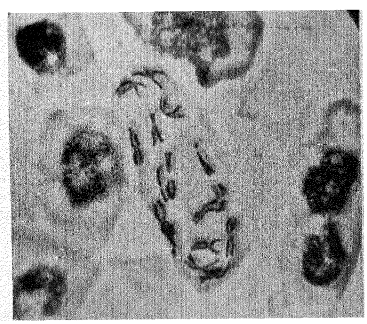




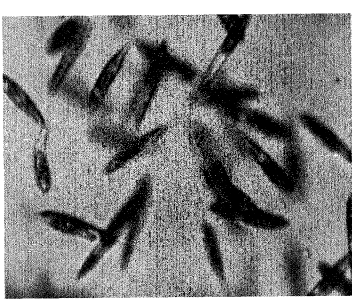
Catatonic rats. These rats will maintain these weird positions for 15 to 30 minutes without moving. This catatonic effect has been induced by a minute amount of a chemical. The effect wears off completely in about an hour.



A normal cell in the process of division.

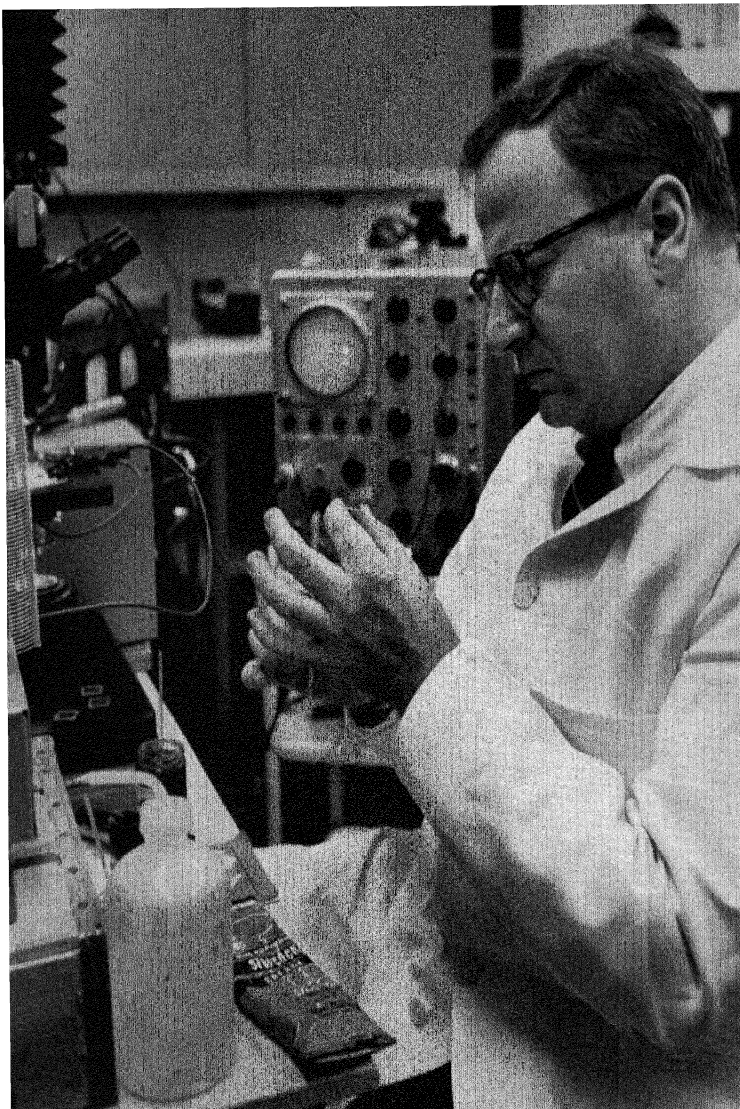


The same type of cell at the same stage of division showing the abnormalities produced by radio frequency.

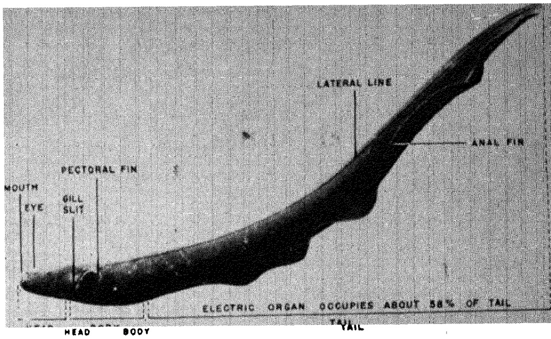


Unicellular animals moving normally in a random fashion.

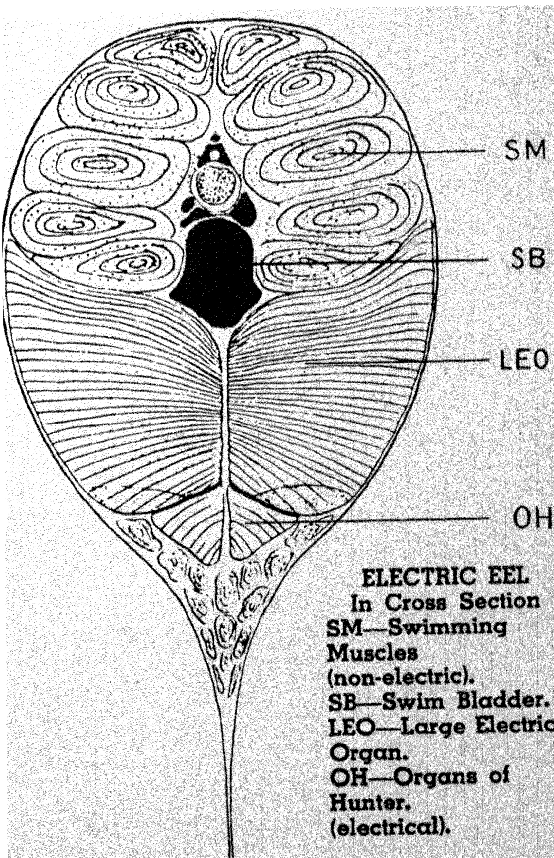
The same animals a few seconds later under the influence of a radio frequency field. Their movement is no longer random, but rigidly controlled.



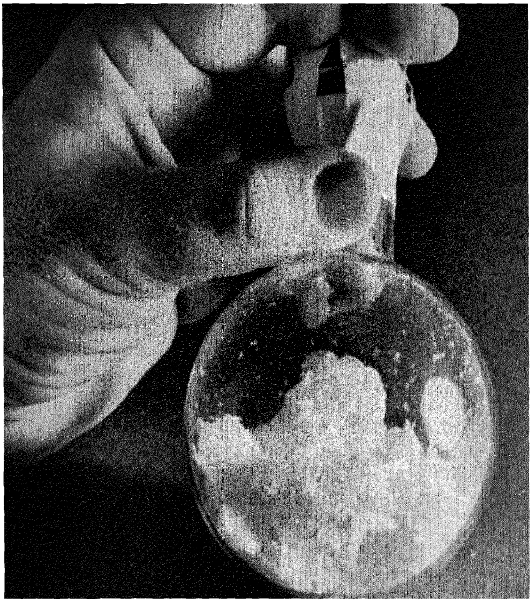
The author preparing cells for testing in radio frequency apparatus.
(Photo. Arthur Leipzig, East Meadow, Long Island)



While this photograph shows quite a small electric eel -- it is only about 7 inches long -- the proportion of head and body to tail is the same as in the very much larger eels ten times longer.



ELECTRIC EEL
In Cross Section
SM—Swimming Muscles (non-electric).
SB—Swim Bladder.
LEO—Large Electric Organ.
OH—Organs of Hunter. (electrical).



Left: The lethal molecule. The amount of purified botulinum toxin in this flask is enough to kill about one half the population of the earth. (Photo. Fred's Studio)

Below: In the flask are 8 grams of a drug which produces hallucinations as a type of "chemical insanity." This dose is enough to affect the total population of Washington, D. C. Released from a small airplane as an aerosol prior to an attack, it could well prove utterly disastrous.

their processes in this manner? Could we intrude our force field into a cell and selectively affect vital processes or life itself? The most logical method to explore this most exciting of all possibilities was via r.f. effects on heredity. One must remember that a living cell is a wondrous thing with a fantastic amount of information coded into its central part, which is called the nucleus. This information tells the cell what it must do, how it must perform its work, when to divide to form two new cells, and even when to die. When a cell divides to become two cells it must make sure that all of this vital information which is coded into tiny molecules must be duplicated so that the new cell has all the information that the parent cell had. Virtually all life proceeds by this system of cell division. After a sperm hits an ovum in human conception, cell division begins and from thereon there are hundreds of thousands of cell divisions which finally produce the child, and the man to be afterwards.

The processes of cell division have fascinated scientists for generations. They have been able to watch how, when a cell begins to divide, the material inside the nucleus becomes organized in an intricate manner. This critical nuclear material gradually divides in two, following a set pattern. This pattern is like a ballet, with all the genes and chromosomes, which contain the coded information, going through a classical series of maneuvers until division is complete. This "heredity ballet" can be observed under the microscope. All of the heredity of man is incorporated in these processes. When an abnormality occurs in this process, there is as a result a mutation or a freak. Sometimes these freaks can be tremendously useful, such as a new type of corn which has more and sweeter kernels, or a new type of elm tree which is resistant to certain diseases. Other times, however, the result of faulty or abnormal cell divisions can be disastrous. For instance, a cancer cell is one that has lost the critical information which controls its rate of growth and its further division. Hence it grows wildly and uncontrollably, crowding out normal cells and eventually killing.

This and many other possibilities flashed through my mind when I first noted the response of that tiny particle in the paramecium to a radio frequency field. A study was immediately undertaken to test the effect of r.f. on heredity. The first material that we studied was the root tip of the garlic plant. This was chosen because its chromosomes are so large that they can be easily seen under a microscope, and abnormalities could be readily spotted. We placed normal living garlic plants in water, and through the root tips we pulsed our radio frequency field. We then waited twenty-four hours to see what would happen. When one of my colleagues, Dr. Teixeira-Pinto, brought in the results, he could scarcely believe what he saw. We had indeed created a host of abnormalities. Some were similar to those that are produced as a result of the damaging effect of radiation or of poisons. Other changes and abnormalities occurred which, to the best of our knowledge, had never been seen before. This was enormously exciting. Up to this time the only forces that could produce hereditary abnormalities were random or damaging, such as radiation. Thus, if one hopes to get a beneficial mutation in corn from the use of radiation, one has to expose many thousands of seeds in the hope that by happy chance one may be injured in just the right way so as to produce a useful abnormality. When radiation hits living matter, it has all the subtlety of an exploding bomb. However, in our radio frequency field, we were no longer cursed by the problem of randomness. We could control the frequency, the voltage, the pulse, and all the other critical physical constants in any manner we wished, and the possibilities loomed up before us that we might be able to produce beneficial abnormalities at will and tailor-made.

It also occurred to us that one might conceivably use this same force in order to curb malignant and uncontrolled cells such as occur in cancer. After the first great excitement of the early experimental results, work settled down in earnest. Then, as is common, came the problems. The first problem was to improve the electronics. Unfortunately, ours is not a simple system to design. We hoped that radio engineers from various universities and industry could help us with our problems; but to our dismay, most of them were as baffled as we were with the peculiarities that this particular device demanded. The difficulty lay in the fact that most radio engineers are used to thinking in terms of fixed physical systems with definite electrical values, such as an antenna. However, in our system of electronics the biological material which was being examined was an intrinsic part of the electrical circuit. None of the engineers had ever tried to design electronic circuits which had as an integral part of the circuit bacteria, animal cells, or tumors. Furthermore, all of these biologic substances varied from one experiment to the next. Thus, we had to design and build new apparatus from scratch.

As usual, in a new field, difficulties mounted almost daily. One of our most important techniques for determining the effect of a certain frequency of r.f. on cells was watching their response under the microscope. Unfortunately, the microscope is metal and in many cases acted like an antenna. Our energy, instead of going into the cells, would go into the microscope and down an electric cable which connected to the arc lamp used to illuminate the microscopic image.

Unfortunately, there is no such thing as a plastic microscope. Thus we had to build around a whole series of complexities and, from the electronic point of view, improbable situations.

As soon as the first of our scientific papers on the subject was published, we became deluged with inquiries, for all manner of scientists wanted to put all kinds of things into a radio frequency field to find out whether or not similar phenomena would occur. As soon as we knew that we could make very tiny particles behave in a r.f. field, we became curious as to whether or not we could make molecules line up in much the same way as bacteria. This would have major implications in such fields as the making of plastics, rubber, and many other synthetic substances. Our preliminary experiments indicated that we could produce this effect in molecules with the right physical conditions. Because of potential industrial implications we were approached by several major corporations for help in learning this new technique. It was ironic, we felt, that several of these companies had turned down our requests for basic research funds because they thought this type of research was "not practical or fruitful." Now this very same "impractical" research had produced something that they were extremely anxious to capitalize upon.

Further interesting applications of this technique turned up when we found that we could separate different kinds of penicillin which heretofore had defied all attempts at separation. These tiny penicillin spores appeared to be identical by every other method of measurement. However, some would produce a very useful and powerful penicillin while others would not. It is naturally of interest to pharmaceutical companies to have a method whereby they can separate this "penicillin wheat" from the "penicillin chaff." The radio frequency field apparently interacted with the very minute components of the spores that were responsible for their being different from one another and, hence, could effectively glean the useful from the useless.

Unusual interest in the use of r.f. also developed in other fields. In some of our early experiments we used mixtures of oil-sand and water, for we felt that such mixtures might help us better to understand the physical theory which underlay the unusual effects obtained from the r.f. field. Suddenly we found that we had the attention of several companies that owned large holdings of so-called oil-sand. This is a type of geologic formation in which there are millions of gallons of oil mixed with sand. The companies have a vital interest in developing a method which is relatively simple and, above all, cheap, to separate the valuable oil from the useless sand.

However, at this point the narrative of our work must stop, for the progress of the research is no farther along than has been reported here. What the ultimate potential of this research will be, we cannot tell. Whether it will be useful in cancer or in many other fields, only time and a great deal more work can tell. It is, however, an excellent example of the value of basic research and the large number of applications into which it can lead and be productive. It is also an example of the tremendous value and, indeed, necessity of having transdisciplinary scientists who can cope with such diverse problems as electronics, radio frequency, physics, genetics, cell biology, and so on.

It is unquestionably true that this discovery could have been made decades ago, if trained research minds had been available who had at their disposal a knowledge of other disciplines. It was mentioned earlier in the chapter that some work had been done back in the 1920's by European workers using inert particles. Had they had any biological training or had biologists trained in physics been conversant with these developments, all of the discoveries noted in this chapter could certainly have been available twenty-five years ago.

The failure of numerous electronics engineers to cope with our particular problem in designing the right circuits, because part of the electronic system was biological, is an indication of the limitations which training in a single discipline produce. The scientist of the future, particularly in medicine, must become ever more versatile in his ability to utilize the discoveries of the physical universe to investigate more deeply the phenomenon of life. Thus, the data which we have thus far is just the beginning of what promises to be an important and exciting chapter in science.

Recently, work performed by other scientists in Washington has added another dimension to the basic phenomenon we have described. Again the scientists involved were multiple-trained in physics, nucleonics, electronics, and medicine. They performed experiments in which r.f. was directed at the head of a monkey. At one critical frequency, with the transmitter in the right position, they could kill the monkey. As they departed from this critical frequency, the lethal properties of the r.f. vanished. Here is still another aspect of radio frequency which must give us pause, for to be able to kill at a distance with r.f. is without question to have the proverbial death ray. From the preliminary observations, the scientists working with these monkeys have concluded that there is a specific effect on certain of the critical brain centers and it is this effect which causes death. Thus, out of basic research comes a potential weapon. However, far more important to scientists is the possibility of using r.f. as a delicate probe to explore the brain and the nervous system. Perhaps in time this probe may become a tool of healing for certain nervous diseases, or even mental abnormalities.

All these are intriguing possibilities, stemming from the exploration of the unknown frontier. This is the type of work that is exciting, challenging, and tremendously rewarding. The horizons are limitless, but we need more basic-research men—broadly trained—to exploit this enormous frontier.

CHAPTER 8

ELECTRIC EELS

In the headwaters of the Amazon and Orinoco rivers, there are several members of the animal kingdom that can make life unpleasant or terminate it abruptly.

One of the most intriguing and physically unattractive is the electric eel. These fish can grow to over ten feet in length. As they slip slowly and silently through the water, they present an ominous sight indeed. Periodically they come to the surface because they breathe air and cannot obtain oxygen from the water as other fish do.

There are many interesting animals on our planet, but the electric eel holds a unique place. One of my colleagues, Dr. J. M. O'Brien, and I became interested in a certain peculiarity of the electric eel because it seemed germane to a research problem in which we were interested. This problem was related to the formation of cataracts, which first dim vision and finally, if not removed by operation, will result in total loss of vision.

As it turned out, the electric eels were not helpful in this research; but by the time we learned this fact, we had accumulated quite a bit of information about these fish.

They are such improbable animals that one is reminded of the statement of the old farmer: "I may have seen it, but by golly there just ain't no such animal."

The man who guided my colleague and me through a primer course in these fish was Christopher Coates, Director of the New York Aquarium. Electric eels have been of special interest to him for some years. The story of Coates's interest and the vital role that these animals played in World War II is a fascinating one. It demonstrates the need for interdisciplinary basic research, the great obstacles in the way of the basic research man, and the tremendous potential that fundamental knowledge has for utility by man.

Everything about the electric eel is bizarre, including his looks. In a ten-foot eel, about the first eight to ten inches contain all the vital parts of the animal—heart, lungs, intestinal tract, and so on. All the rest is a series of electric batteries. Electric eels are blind. They are not born blind; it is merely that their eyelids keep growing together until they are permanently shut—why, no one knows. Their main bank of batteries are used for offense and defense and to obtain food. A fully grown eel can send out about 400 to 600 shocks of electricity per second at 600 volts and up to one ampere. This can easily kill a man or even a horse.

One of the animal men working for Coates was filling an eel tank with water from a hose with a brass nozzle. His fingers touched the brass, and the current from the eel, flowing back through the column of hose water and into the nozzle, knocked him right across the room. This is an enormous amount of electricity. Since electricity is energy, it is quite possible to calculate how efficiently these eels produce it. One can calculate the total amount of energy which the eels can possibly derive from the food that they eat and compare this to the energy released in the form of electricity.

This is comparable to determining the efficiency of an electric generator by computing the amount of coal necessary to produce the steam to run the generator. On this basis, the eel is far more efficient than any light-and-power company in the world. He is even more efficient than atomic-reactor-produced electricity.

As was pointed out, eels are blind. How then do they navigate, let alone find fish underwater, and after stunning them with electricity, go unerringly to their victims and swallow them? This was a puzzle until it was found that in addition to their big electric guns they have another, far smaller, electric generator. This sends out a current through the water. That much we know and can measure with an oscilloscope. But in some completely mysterious way, this electric current functions like radar, which it definitely is not. Sonar and radar work because the sound or microwaves bounce off a surface and return to be picked up. Electricity does *not* bounce.

It seems that no one has explained this to the eels, however, and somehow they get a signal back telling them just where an obstacle or a fish may be. To make matters more confusing, it now appears that the return signal carries information on how electrically conductive the obstacle may be so that the eel can distinguish between a fish and a stick. This would seem obviously impossible, but, again, no one has told this to the eels. On either side of the eel's head is a row of tiny pits which apparently receive this mysterious return signal. We know this because if one fills the pits on one side of an eel's head with vaseline, he will keep swimming in a circle like a boat with a jammed rudder. If the pits on both sides are filled, the eel stops dead in the water and won't move. Obviously, there must be nerves of some sort connecting these pits to the eel's brain in order to convey the information picked up by the pits. However, search as we may, no one has ever found any nerves where they ought to be.

Any navy in the world would probably give a small fortune to figure out an electrical underwater-detection system which not only can work at a considerable distance but can identify the underwater object by its conductivity.

This is only a small segment of the amazing electric-eel story. The eels have already made a major contribution to the United States. They were responsible for saving possibly tens of thousands of American lives in World War II. Just how this was done is a classic story of basic research performed against great odds, and the kind of contribution it can make. Virtually all higher animals produce electricity, but on an infinitely smaller scale than does the electric eel. Every time a man moves a muscle, it is an electric current running down a nerve that carries the message and the command. The nerve fiber, however, does not end *in* a muscle fiber. There is a so-called "junction" between nerve fiber and muscle fiber. It is at this junction that a complex series of molecular events occur.

To simplify them, let us say that the electric current coming down the nerve causes the formation of substance A, which passes across the "junction" to cause the muscle to contract. Let us assume that all around this "junction" is another chemical substance, B, which will neutralize substance A. If A is not neutralized by B, the muscle will stay contracted. Though this is quite an oversimplification, it is adequate to explain the so-called "nerve gas" developed by Germany in World War II. The "nerve gas" knocked out substance B. Thus, if one absorbed nerve gas into one's system and took a breath, the breathing muscles would be paralyzed in contraction and one would suffocate. Neither side used poison gas in World War II, owing to a tacit understanding. Implicit in this understanding was the fact that if one side developed a gas which the other side could not duplicate, it would be used. The Germans, because of their support of basic research on these substances, had been able to develop "nerve gas." When our intelligence service revealed the German "nerve gas," it became a triple A priority for us to do the same. The problem was solved, but without electric eels it could not have been done. Part of the electrochemical system of the eel involves substances A and B, and thus they are the crux of the matter. Much of the actual detail of nerve gases and how they operate is still classified material.

Let us, however, go back to the time in 1933 when Chris Coates first began his work on the electric eels, without which the nerve-gas problem could not have been solved about a decade later.

When Coates first began to work with the eels and for years thereafter, there was, as usual, no money available for basic research. Finally he began to receive amounts of about four or five hundred dollars a year to support his work. The questions with which he was confronted are the classic ones. "Why do you want to investigate electric eels? What do you plan to discover? What 'practical' purpose will it serve?"

Electric eels were imported to the United States from the headwaters of the Amazon for sale to zoos and aquaria. While the dealer still had the eels and was looking for customers, Coates was permitted to keep the eels "on deposit" and work with them. He had to be careful because if he damaged or killed one, he would have had to pay the dealer the sale price—$100 per foot of eel. And in the early years Coates could not afford even six inches. With no money and virtually no equipment, he kept doggedly to the task. His first problem was to try to measure their electric output. Everyone said that the eels emitted electricity, but no one had proved it to his satisfaction. Coates rigged up all kinds of ammeters, voltmeters, and other devices to measure electricity, but the meters always read zero. While the meter was still reading zero, he could touch the eel and be knocked flat on his back.

If the eel was producing electricity, why didn't the meter show anything? And if the eel was not producing electricity, what was knocking him all over the room every time he touched the animal? For several years, Coates had the most shocking (literally and figuratively) series of experiences of anyone in the United States. I have been shocked on three occasions while working with these eels and have the greatest admiration for someone who willingly accepted this kind of punishment as a routine price of his investigation. Now, in the light of current knowledge, an investigator can handle the eels with relative impunity. In the early days of this work, however, Coates was constantly flirting with exposure to a fatal shock.

Finally, still without funds and paying some of his expenses out of his own pocket, Coates found a collaborator who could help with the physics of the problem. It was pointed out that conventional electrical measuring devices might not work if the eels were pumping out intermittent current. If this were the case, a neon test lamp should show if the shock were electrical. Coates rigged such a test lamp to an eel and saw the lamp glow brightly. The first step toward quantitative measurement had been made. Another high point about this time was Coates's acquisition of his own electric eel. An animal dealer presented it to him in return for some publicity. Then, in 1938, Coates met with Dr.

David Nachmansohn—a man later to play a cardinal role in cracking the chemistry of the war gas.

These two continued their work—still with no funds, Coates spending his own money in order to keep the research going forward. Finally, in 1941, they received a grant of $1,500 to buy eels. Then, when the nerve gas came into the picture and it became a matter of national policy and urgency, money became no object.

This is a classic story for many reasons. There is the typical unwillingness to support basic research because it has no apparent "practical" purpose. Then there is a sudden burst of "cost be damned" attitude when—and only when—an enemy is shoving a comparable discovery down our throats. But money, even on a "cost be damned" basis, cannot buy trained brains overnight. Nor can it buy in a week or a month that body of basic knowledge which comes from years of patient and persistent investigation. Americans delude themselves that if one puts enough money into a project and strains mightily, anything can be done. Ships and tanks and planes can be handled this way, but the creation of scientists and scientific knowledge cannot. Trained brains and trained knowledge are human products, not machines. As was recently pointed out, one cannot reduce the nine months required for pregnancy to one month simply by making nine women pregnant.

In an earlier chapter it was indicated that the situation is improving—but so very, very slowly. Obviously, only the first part of the electric eel story has been told. There are, without question, many more vital horizons still ahead just in the study of this one strange animal. Today, Chris Coates has plenty of "project money." But it does him little good; he has no laboratory in which he can do basic research, because there is no money available for such a purpose. Furthermore, he cannot obtain the highly trained and qualified scientists who are needed to solve the many complex problems still outstanding in the study of electric eels. Such scientists exist, but none of them is willing to take the job. Not only is there no laboratory available for basic research, but there are no funds for a secure salary for the scientists. Very few scientists are willing to take a position for, let us say, only two years, with no tenure or security and with an extension of another two years dependent upon whether another "project grant" can be obtained.

It is little wonder that the highly trained scientist will not want to accept such a position, in spite of its provocative and intriguing nature, and will take instead a job in industry doing something "practical." In industry he can have the facilities, the salary, and the tenure. He can have a family, a house, and send his children to college. Because of this, we probably have the world's best and most versatile deodorants, lipsticks, dishwashers, and television sets. But the Germans found the nerve gas first. And the Russians launched the first Sputnik. When will we learn? If we don't learn soon, it will be too late.

Many of the problems presented by the electric eels are still left unanswered. They must be attacked by a transdisciplinary approach, and there is little doubt that much valuable information will become available as a result of this study. Funds to support the scientists and their exploration are badly needed not only for this but for countless similar areas.

It was indicated earlier that if we understood how the electric eels worked, we might be able to develop a similar detection system for submarines, which is of vital concern today. The methods used by the eel to produce electricity might easily be adopted, if the mechanism were known, by light-and-power companies. It would be equally intriguing to understood how the eel can be "immune" to tens of thousands of volts of electricity if one attempts to shock him. From a chemical point of view, the eel should be as susceptible to electric shock as any other animal. He most certainly is not, and we don't know why.

It should be mentioned finally that the electric eel is not the only fish which produces electricity for the purposes of defense and food gathering. However, he is certainly the most efficient and dramatic in the animal world. There is another fish called the "stargazer," which rests at the bottom of the water and waits until another fish crosses above him. His eyes are focused upward, and when an unsuspecting prey cross his line of vision, a shock is sent out which conveniently drops the fish into the stargazer's opened mouth.

The waters of the world contain a richness of life which equals, if not exceeds, that of land. We have not even begun to tap the tremendous resources hidden here.

If the basic research men are given the facilities, the funds, and the time, the benefits which can accrue to man are incalculable.

CHAPTER 9

THE LETHAL MOLECULE

Most of us have difficulty in conceiving the significance of enormously large numbers or enormously minute numbers. The concept of eight million light years is such a huge distance that only astronomers and physicists have a real appreciation of the amount of space it represents. It is even difficult to develop a sense of reality in human terms when numbers get too large. For instance, a newspaper headline stating that a million people are starving to death in India may be read with cursory interest by many people. On the other hand, a story about a small boy trapped at the bottom of a well shaft can cause national interest and concern.

When Pasteur first proposed the germ theory of disease, a large number of skeptics refused to believe that anything as tiny as bacteria could possibly render something as large as a man ill, much less dead. Today we no longer have much of a problem in believing that bacteria cause disease, although the numbers involved are very small. Let us assume that a million bacteria are enough to render an individual ill. The total weight of a million bacteria is a thirty-millionth of an ounce, and yet this thirty-millionth of an ounce is sufficient to make a two-hundred-pound man (who is 10,600,000,000 times the mass of these bacteria) quite sick. Hence, the weight of bacteria which can incapacitate a two-hundred-pound man is astonishingly small. If we make an analogy in terms of weight, it is as though a one-ounce bullet could sink or immobilize ten thirty-thousand-ton battleships.

However, this is just the introduction to the story. Certain bacteria produce poisons. Some poisons, of course, are much more potent than others. The most potent of all has been investigated rather extensively at the New England Institute for Medical Research and everything we have discovered about this poison strains the imagination. If we return to our two-hundred-pound man, the amount of this poison necessary to kill him is such an incredibly small amount that it seems to be impossible. I have mentioned that somewhere in the neighborhood of 1/10,600,000,000 of this man's weight in bacteria was enough to make him sick. However, in terms of this poison, it takes only about 1/570,000,000,000,000,000 of his weight to kill him. That is the equivalent of sinking not ten thirty-thousand-ton battleships with a one-ounce shot, but six hundred million of them. If these figures seem to stagger the imagination of the average individual, which I presume they must, it may be of some consolation to know that the lethality of this poison is amazing even to the scientist.

This particular deadly poison is called botulinum toxin. Actually, "botulinus" means "sausage," for this is where the first of these bacteria were found. If the numbers already given to suggest its potency are too unreal to grasp, perhaps it will suffice to say that it is approximately one million times more poisonous than cyanide.

If an individual gets some of this toxin in his body it affects the nervous system, knocking it out of action. When vital nerves are affected, such as those which control the diaphragm and hence breathing, death due to asphyxiation occurs. The rapidity of death depends on the dose of the toxin. Fortunately, botulinum poisoning is usually not of great concern to most of us, although it does occasionally show up as a cause of death from foods which have been improperly canned. The last outbreak of botulinum toxin in commercially processed canned foods in the United States was quite some years ago, and today cases of botulinum poisoning usually result from improper home-canning methods. In 1957, however, there was a serious outbreak of botulinum poisoning in Argentina, with over four hundred people affected. In this case the culprit was canned pimentos.

Via the scientific grapevine we have also heard of a relatively recent Russian epidemic in which a reported thirteen thousand persons died owing to botulism from improperly canned squash. This seems strange, for in the normal course of events, as soon as signs of botulism are detected by a physician, a search is rapidly made to determine the source of the contaminated food, which is then destroyed. Thus it seems as though all these people must have eaten this batch of canned squash at virtually the same time. It might be that all the inhabitants of a large labor or prison camp were fed the contaminated squash at one time. Since the reported outbreak occurred in Siberia, this might well be what happened. The information was obtained from a Russian refugee who claimed to have been one of the physicians called in to help cope with the epidemic.

While the role of botulism in human poisoning is not of major concern to most people in the United States, the toxin does affect an astonishing amount of wildlife. It is estimated that tens of thousands of pheasants and wild ducks, not to mention geese and other animals, die from botulism annually. This has been the despair of conservationists and is a particularly sticky problem for wildlife departments that try to raise pheasants and ducks in order to stock game preserves.

The effect that botulism has on wild fowl was brought to our attention by a disastrous epidemic in New York State, where seven thousand pheasants were killed in one season owing to this toxin. We at the New England Institute for Medical Research became involved in the affair in a peripheral sense when we were consulted on the possibility of making a vaccine for young birds in order to protect them from any future exposure to botulism. This type of infection is a major problem in this country not only with wild fowl but with animals such as mink. In South Africa as well as in Australia, it is a major problem in cattle raising. We are not quite sure how botulism is spread in different types of animals, for whereas botulinum toxin is enormously poisonous whether it goes directly into the blood stream through a cut or is inhaled, its most common route of entry is via contaminated food. One of my colleagues, Dr. D. A. Boroff, solved the problem of making a successful vaccine to protect the birds, and this vaccine is now in routine use.

The botulinum toxin has a far greater importance in another area. In terms of national security, one immediately thinks of the most poisonous substance in the world as a potential weapon in biological warfare. Indeed, every chemical and biological warfare agency of every nation in the world is probably working on this problem. Certainly the Russians are, as we know from the papers they have published on the subject.

An ideal agent for chemical warfare is one which can destroy the enemy's will to fight without seriously damaging his factories, cities, productive facilities, farms, and so on. Needless to say, hydrogen and atomic bombs are not designed to leave anything intact. Many feel that since we have relative parity in hydrogen bombs and missiles with Russia, probably nothing other than a madman or an unfortunate mistake would trigger a nuclear war. But there are other ways to win wars. If such means would result in delivering the entire economic, industrial, and agricultural complex intact to an enemy, he would find it preferable to an attack which could destroy major cities and render huge areas of land so radioactive that they would be uninhabitable for years. Therefore chemical warfare receives very serious consideration by powers that are aggressive in their attitudes, as well as by powers that may have to defend themselves against such an attack. It is little wonder that so many countries are interested in botulinum toxin as the most poisonous substance on earth and that there is so much work being carried on in Russia in this area.

At this point let us pause to consider the chemical nature of this poison, for this is vital. For instance, the major failing of botulinum toxin as a weapon of war is that it is a protein. Protein is one of the chief building blocks of all living matter. However, skin protein is different from muscle protein and this in turn is different from blood protein, even though all proteins are made up of virtually identical, smaller building blocks called amino acids. There are about twenty different amino acids. We know the structure of these amino acids quite accurately and have known them for some time. They are composed of atoms of carbon, hydrogen, oxygen, and nitrogen; and two of them contain sulfur.

Proteins are merely amino acids joined together in a repetitive, orderly chain. In order to get some idea of the size of a protein molecule, we assume the weight of a hydrogen atom to be 1, that of carbon to be 12, nitrogen 14, oxygen 16, and sulfur 32. On the basis of such numbers, a molecule of water has a weight of 18 and a molecule of the amino acid called glycine would have a weight of about 75. This we call a molecular weight. A protein may have a molecular weight as high as several million. Thus, in terms of weight, a protein molecule is one of the largest molecules to be found in nature. However, it is not enough merely to know the number of carbon, hydrogen, nitrogen, oxygen, and sulfur atoms in a molecule; indeed, it is only a fraction of the story to know all the amino acids in a protein.

It is obvious that there are many hundreds of amino acids in a protein molecule with a molecular weight of one million. Only recently have scientists been able to figure out the precise amino acid alignment of one or two proteins. This information was obtained by determining just how and in what sequence these amino acids are joined together.

A vital factor which determines the character of the protein—that is to say, what makes a certain arrangement of amino acids become muscle and another arrangement become skin, depends not only on the order in which these amino acids are joined together, but on the kind of three-dimensional structure the amino acids make. One of the most common forms of protein is that of a helix, or a coiled-spring-shaped configuration. The molecule of protein must maintain this particular springlike configuration in order to remain an effective biologically active molecule. Thus, if one stretches a spring beyond its elastic limit, one still has the same amount of metal as one had in the beginning, but it no longer serves as a functional spring. In the same way, if you stretch the structure of a protein beyond its limit of elasticity, you will no longer have a functional protein.

When one interferes with the structure of a protein in such a way that it cannot return to its original shape, the protein is considered to be "denatured." Unhappily, most proteins are rather delicate in their ability to resist chemical and physical forces that tend to denature them. Heat, acid, alkali, and oxygen are all factors capable of denaturing proteins. Different proteins will vary in the ease with which they can be denatured. Botulinum toxin presents a contradictory picture, being both easy to denature under certain circumstances and very difficult to denature under others.

One of the strange aspects of the botulinum story is that the toxin is resistant to acid, which is one of the most powerful denaturing agents for most other proteins. Most proteins which are eaten by man are partially denatured by the hydrochloric acid of the stomach; then other complex substances in the digestive process are brought to bear, which further break down proteins into the amino acids from which they are made. As a matter of fact, it is generally assumed that a protein molecule cannot withstand the chemical onslaught in the digestive tract and remain intact. Furthermore, it is also assumed that a protein molecule is just too big to get through the wall of the stomach and the intestinal tract and into the system. It has to be broken down into its smaller components in order to be absorbed. This holds true for practically every protein we know, except botulinum. Botulinum not only seems to be able completely to resist high concentrations of acid and other digestive substances, but it seems to pass unscathed out of the digestive tract through holes supposedly too small for it.

Furthermore, the amount necessary to kill a man is ridiculously, if not inconceivably, small. However, in spite of the botulinum toxin's ability to withstand the rigors of acid, it falls to pieces in alkali; and, indeed, even if it is stored on a shelf, it will gradually change in some still unknown way so that its toxicity is lost. The more one dilutes this toxin, either in air or in a solution, the more rapidly the toxic effect disappears. Thus, although seven ounces of pure toxin would be enough to kill every man, woman, and child on the face of the earth, the problem which confronts the chemical warfare people is how to treat this substance to keep its toxicity even though it is highly diluted. Obviously, if this could be done, a relatively small amount dropped into the reservoirs of a city such as New York could kill between three and seven million people in the course of a few days.

The antitoxins which have been developed to be administered after the poison has begun to work are relatively ineffective. Thus this is, indeed, a rather hideous weapon to contemplate. If an aggressor nation could find a way to protect this purified toxin from being denatured, it could spread it freely in reservoirs or in the air as a dust in a concentration so minute no one could detect its presence. The affected individuals would not know anything was amiss until symptoms began to appear, at which time it would probably be too late.

The question might well be raised as to why a basic research laboratory such as the New England Institute for Medical Research is interested in working with a substance which is so demoniacal. The answer is twofold. First, we are curious as to how so few molecules can interfere with enough vital processes to be lethal; and, second, it is our feeling that because so few molecules can have such a major effect (primarily on the nervous system), this toxin can be used as a powerful chemical probe for us to investigate the mechanism of the action of certain parts of the nervous system. As with all basic research, we cannot envision what might come of this work. It might hold the key to a host of nervous diseases and other maladies, not to mention a more vital insight in correlating the structure of proteins with their action.

The planning and reasoning behind our attack on the botulinum molecule is much like a detective story in the truest sense of the word. If an extraordinarily small number of molecules can paralyze enough nerve-fiber endings to cause death, we can make the mathematical assumption that a single molecule of toxin is capable of knocking out the function of a whole nerve fiber. In terms of size, this would seem to be pretty preposterous. It would be almost as though someone were standing on top of Mount Everest and by swinging a small sledge hammer managed to split the mountain. Considering the size of the molecule of toxin and the nerve, the analogy is not too strained. One might feel that it would be absurd to expect a sledge hammer to have much affect on a hill, much less split Mount Everest, and we feel the same way about the possibility of a single molecule of botulinum toxin knocking out a nerve.

Unfortunately, there is a major difference between what we would expect and what we see. Everest *is* split and the patient or the animal *is* dead. Now it is up to us to find out *how* the hammer split the mountain. Obviously, there must be a very critical site where this action takes place. We might make a further analogy, this time to the diamond cutter. After a diamond cutter has studied the structure of the diamond, he knows where to place a specially shaped wedge so that by tapping the wedge very lightly he can split the diamond the way he wishes. If we assume that the botulinum molecule is the wedge and the nerve is the diamond, perhaps we can learn about the structure of the nerve by studying the shape and configuration of our molecular wedge. So, as with other detectives, we work with the clues we have.

Thus, if we have a pretty good idea of the shape of a key, we can gain considerable data on what the lock will look like into which this key fits. The big problem lay in how to find out more about the shape of the key. I indicated previously that the structure of one or two proteins had been determined. The first one whose structure was analyzed was insulin, with a low molecular weight of just a few thousand. This monumental piece of work took a whole team of scientists over eight years to accomplish.

The technique is tremendously complicated and uses many hundreds of chemical procedures as one amino acid after another is chipped off the end of a protein molecule and analyzed in such a way so that when the entire structure is taken apart one has a pretty good idea of how it was originally put together. However, insulin is a small molecule compared to a molecule of botulinum toxin, which has a molecular weight of about one million, and the idea of devoting possibly a decade or two to taking botulinum apart piece by piece is not a very attractive one. At the outset of this work, all we knew was that botulinum was a protein made up of the usual amino acids, and all we could specifically test for was its biologic or lethal action. To measure its lethality quantitatively, one injects concentrated toxin into some mice, which will then die rapidly. By diluting the toxin time after time and injecting each new dilution into several mice, one can finally ascertain what is known as the "minimum lethal dose." Less than this dose will not cause death. The accuracy of this technique is so poor that one's determination can be wrong by a factor of 10. This is a time-consuming chore and kills an enormous number of mice, for it must be done for each new batch of botulinum toxin that is produced, because the toxicity varies from one batch to the next. Since chemical analyses indicated that the toxin is made up of the same kind of amino acids as make up innocuous proteins such as muscle, we decided to tackle this problem by using techniques of physics rather than those of biology and chemistry.

This problem was a joint effort, as is true for most of our research. It was decided to use the relatively new technique of fluorescence, involving physical principles which have been available for some time but which have never really been thoroughly exploited for use in biomedical problems. The object of this approach was to attempt to make the botulinum molecules fluoresce. This was the same basic principle I had used ten years before when I was trying to determine how much adrenalin a normal individual has in his blood stream. Because of our longstanding interest in fluorescence as a tool and because we have another major research program under way involving certain chemicals present in mental disease that can only be measured by fluorescent techniques, we discussed the possibility of inducing the botulinum molecule to fluoresce. From everything we knew and from everything which had been written, it was quite clear that we could not expect to get a specific fluorescence from the botulinum molecule. However, there is a major watchword in science that was beautifully coined by Dr. Simon Flexner, the first head of The Rockefeller Institute. He stated: "Unless you let scientists make damned fools of themselves, you will never have any great discoveries."

Consequently, we ignored all previous data and went ahead to see whether or not we could make the botulinum molecule "glow." The chances against the success of the experiment were great. As you may remember from an earlier chapter, the emission of light, or fluorescence, occurs under special conditions. These conditions demand that the correct wave length of light hits the molecule and that the energy of the light is absorbed by this molecule. When this happens, the molecule can be considered to be in an excited state. It is anxious to get back to its original, more placid, condition and in order to do so must give up energy.

This it can do by several means, one of which is the emission of a minute amount of light of its own. Almost inevitably the wave length of light which it gives off is different from that which it absorbed. It was this phenomenon that we were hoping for. We hoped to be able to find the right wave length to excite the molecule and, further, we trusted that the molecule would respond by emitting light of its own at a different wave length. We felt that if the botulinum molecule responded in this way we could probably gain considerable information by studying the light that was absorbed and then emitted, and get vital data on the possible critical structure of the molecule. This hope was based on the fact that proteins have a definite shape and structure and if a molecule will fluoresce, the type of fluorescence can reflect, if one is lucky, a crucial part of the structure. If that part of the protein which is responsible for fluorescence is also responsible for its biologic activity, one has a powerful tool.

Thus, fluorescence might serve as a physical means of measuring quantitatively the number of active toxin molecules. If we could do this, there would be no need to sacrifice many mice in testing each new batch of toxin to ascertain the rather fuzzy quantity of a "minimum lethal dose."

Instead, we could place some of the toxin in a test tube and accurately measure how many lethal molecules we had.

Almost four years have gone into this work. The right wave length has been found to excite the botulinum molecules. Under the appropriate conditions they will fluoresce, and we have been able to measure this fluorescence.

This splendid piece of work by Drs. D. A. Boroff and J. E. Fitzgerald has provided a physical means of measuring the biological activity of a molecule. In addition, because that part of the molecule which glows appears as though it may be specifically responsible for its lethality, the fluorescence can be used to gain knowledge of the specific chemical structure of that part of the molecule.

Let us here use the analogy of the little Dutch boy with his finger in the hole in the dike. Insofar as stopping the flood goes, the only part of the little boy that is important is his finger. However, in order to get the finger in the hole the rest of the little boy is needed. In the same way, only a very small part, or finger, of the botulinum molecule is needed to knock out the nerve fiber, and it appears that the rest of the molecule is serving the function of the rest of the little boy. Thus it is the "finger" of the molecule which seems to be doing the fluorescing.

By taking the physical information from the study of the fluorescence and correlating it with chemical knowledge, we could make a rather shrewd guess as to the specific structure of the molecular "finger." In order to determine whether or not our guess was accurate, we decided to take some chemicals that looked, in terms of their structure, very similar to what we supposed the "finger" to look like. We assumed that if there were a biological "hole" in the nerve endings where the finger of our molecule had to fit perfectly in order to do the job, we might be able to flood the body with chemicals that would closely resemble only the finger. If we had enough of these fingers, we could assume that many of the "holes" in our nerve-fiber "dike" were filled. Obviously, if the holes were filled with a small molecule of the right shape and which in itself had almost no biological activity, it would prevent the finger of the botulinum molecule from getting a vital foothold at a critical site. In short, we should be able markedly to reduce or prevent the lethal effect by "plugging" our biological dike.

This is precisely what we have been able to do. Interestingly enough, the chemical structure we used to plug the holes is a substance that has for some time been suspected of being involved in nerve activity, but to date there has been no definitive evidence that it plays a role. These experiments suggest that the "fit" in the hole is too good to be happenstance. This is about as far as this research has gone to this point. It is obviously only the first chapter, and many more chapters remain to be written. It demonstrates, however, the techniques that we have described as molecular engineering designed to prevent or cure diseases.

This is one of the exciting areas of the future. It is a vivid example of how one can proceed to attack disease on a molecular basis once one has fundamental information on the molecular nature of normal and disease processes. The chemical which we used for plugging is not a cure for botulinum poisoning, because it is destroyed or used up in some way by the body after a relatively brief period; and while it prevents the botulinum molecule from entering the vital site, as soon as the plugging finger disappears the site is again vulnerable to the lethal molecule.

As with all research in the fundamental stages, one makes various hypotheses which seem to fit the facts and then tests them. If they work out, as appears to be the case with botulinum toxin, one assumes that the hypothesis has much greater validity. In anything as complex as a living creature, however, there is always the possibility that another set of facts is responsible for the successful series of experiments.

Further work may bring to light new data that may revise the entire original concept. So, in basic research, whenever the scientist gains data which appear to give a neatly wrapped package, he must always put himself in the position of the devil's advocate and try to attack the structure of his own hypothesis in order to test its validity. This is true of our work on the lethal molecule of botulinum.

CHAPTER 10

HELP!

Which is more important: dog food, or research on diseases such as cancer, leukemia, heart disease, and mental disease?

This is a legitimate question, because the total amount appropriated by the United States Congress last year for research on all diseases was equal to the amount spent by Americans on dog food. Intriguing as such a statistic may be, it is even more interesting to take a good look at the maze of things listed under the heading of research.

Research is a term very much like an umbrella, which is used to cover many things. Most people do not look too carefully into where their dollars go when they give them for a "medical" cause. They seem to assume that these dollars go toward the type of fundamental research aimed at curing or preventing the disease. For instance, the most successful foundation in the United States is the National Foundation for Infantile Paralysis. It is successful because today there is one effective vaccine in current use and another probably even more effective one coming along. Since its inception, this foundation has taken in over $500,000,000. About 90 per cent of this has been used for patient care, physical therapy, iron lungs, hospital bills, printed material, and so on. Consequently, less than 10 per cent was used for research. However, of this 10 per cent less than 1/1000 of these funds went into the basic research of Dr. John Enders and his colleagues which made the Salk vaccine possible.

Naturally, one cannot disparage the use of funds for the care of people who are stricken with a malady. The real problem is the disproportionately small amount of funds that are allocated for fundamental research. The heart of the matter, therefore, is the difference between applied or clinical research and basic research. Basic research seeks fundamental discoveries. Subsequent efforts to exploit a fundamental breakthrough and turn it into utilizable products is called applied research. Thus the fundamental discovery that the mold penicillin excreted a substance which could kill bacteria was basic research. The effort, costing hundreds of millions of dollars, to develop better methods of growing and culturing penicillin mold, and the examination of thousands of other molds to see if they have antibiotic properties, is applied research. It should be obvious that without a fundamental discovery no applied research is possible. Yet most people tend to prefer to support applied research rather than basic research.

Let us go back in time and assume that we are in a period before the discovery of penicillin. Suppose a scientist interested in molds had requested that you give him some money to support basic research. In all probability you would ask him why he wanted to do this research. The answer would be, "I am interested in molds. There is much about them that we don't know, and hence I would like to investigate them further."

The next, almost inevitable, question would be something like this: "Well, after you find out more about molds, what good will it do; what use can be made of this information; and what product can come from such an expenditure of time, money, and effort?"

To this, a scientist could only say: "I don't know. If I knew those answers, I should not have to do the experiments."

This is usually the time that the listener will decide he is not interested.

If the same situation were to be repeated after a discovery like that of penicillin, an applied research scientist requesting funds could state: "I would like to find a better antibiotic than those which we have now in order to be able to treat more diseases. I think this can be done by examining several thousand molds of different types in order to ascertain if some are more useful than those which we now have."

Most individuals would be willing to support something of this nature. This is something that they can grasp with both hands. They can see potential utility, products, profits, or psychological dividends. The applied research scientist can usually give a fairly good idea of the amount of time and money that it will take to achieve his objective, and he can stipulate what his objective is. The basic research man can merely say: "This is unknown and because this is unknown, I wish to explore."

He can further state that almost anything that we find out—about the world of biology in general, or man in particular—can be used somehow, some way, sometime. This is something which is not easy for people to grasp. It is too indefinite, and yet in this region of the unknown lies all the fundamental knowledge that we must have before we can cope with the many diseases of mind and body about which we can now do relatively little.

Many individuals seem to think that if enormous amounts of money are thrown into applied or clinical research programs the diseases involved may be cured. They erroneously cite the case of the Manhattan District Project, which developed the atomic bomb. They point out: "Look, we spent approximately two billion dollars, put in an enormous amount of effort, and in a few years we had a nuclear reactor and a bomb."

What they do not realize is that the fundamental discoveries which made this whole applied research project possible had already been made. The fundamental discoveries of Max Planck in the nineteenth century, Albert Einstein in the early twentieth century, and other basic research investigators such as Fermi, Bohr, Hahn, Meitner, and many others made possible the Manhattan District Project. Without such basic discoveries, the applied research program could not have been undertaken.

The statement is often made that we do not need any more money for fundamental research because we do not have enough scientists to use the money. This is both true and false. It is true that many scientists are not in basic research because we do not have enough laboratory space or adequate salaries or budgets to support them. Consequently, they either go into industry, government work, administration, or medical practice. If the funds were provided so that these men had the space, equipment, salaries, and budgets to do fundamental research, we would have far more scientists in fundamental research than we have now. Virtually everyone in basic research knows of dozens of investigators who leave the field each year because they can find neither positions nor adequate funds.

At the New England Institute for Medical Research, salaries for doctorate scientific personnel begin as low as $3,600 per year. This alone is a bleak commentary on the nation's awareness of the need for these crucial basic research investigators. But even with such salaries, there are several hundred doctorate scientists each year who express a wish to work at the Institute. Only lack of adequate funds prevents us from increasing our staff and productivity.

In the recent symposium on basic research previously referred to, Dr. Warren Weaver of The Rockefeller Institute stated:

> Strong evidence has been accumulating that we are in fact capable of creating new knowledge. But in spite of our verbal dedication to the importance of basic research, and in spite of our emerging confidence that we have the national resources of imaginative, competent, and dedicated individuals to carry out basic research, it nevertheless remains true that as a nation, we are not giving adequate and suitable support to basic research.

At the same symposium, Dr. Merle A. Tuve of the Carnegie Institution of Washington stated:

> I can say it very simply. The enormous expansion of funds and activities called research has left the private research institute as only a minuscule item in the whole picture, but the function of a research institute seems thereby to have become even more clearcut and conspicuous. It must function as a stable and continuing prototype.
>
> It is important for us to recognize the relatively small size of the annual budget for this academic kind of basic research. The number of the academic men in basic research is still not too different from the prewar number of similar fully trained scientific investigators.

The problem of raising funds for basic research is incredibly difficult. First, one has to compete with applied research; next, one has to compete with many other worthy and older organizations. Virtually all of these organizations can show the contributor that they are "doing something." For instance, the hospital cares for the sick. The community funds care for all kinds of things in which people can see tangible results. The Red Cross renders a variety of obvious and valuable services in normal times and in times of disaster. Universities can point to the students they are turning out and the need for education. National associations devoted to a single disease recruit many supporters from people suffering from the disease, those with close relatives who have it, and those who fear that someday they themselves will contract it. Most organizations have such a built-up group of supporters as this, or college alumni, church membership, and so on. The New England Institute for Medical Research has none of these. Its only products are knowledge and exploration. There is very little emotional appeal to this. It is primarily an intellectual appeal. Very few people who react to an emotional appeal or who want to see "things done" will contribute to basic research. We cannot predict what we will find. We can only promise to go into the unknown and explore. For the people who want to see "things done" it is useless to explain that without basic research there can be no new major discoveries. They insist on knowing just what it is you are going to discover. Thus, in the constant effort to raise funds for basic research, one is in competition with a host of good causes doing good works, whose appeal is to a far greater number of people than can be reached by the straight intellectual challenge of exploration into new frontiers. Many people tend to deplore exploration in the first place. They want something concrete, practical, and in a definite time period. About five out of every hundred approached will contribute, and we approach only those with whom we feel there is a reasonable chance of understanding and support. Thus sometimes an overwhelming amount of an investigator's time has to be spent in begging funds so that he can do research in the remaining time.

It is appalling to have doctorate and double-doctorate scientists working for a wage scale that begins at $3,600 and rises very slowly. These men have usually devoted almost half their lives to preparation for research which is for the benefit of all men. They are caught in a terrible dilemma. On one side they know the vital and crucial importance of their work and what it can produce. On the other hand, how long can they ask their wives and children to live on such impoverished salaries? Should they stick it out and hope things will change, or should they abandon basic research and go into practice or industry and earn three to five times as much almost overnight? A research man with a brain trained through a decade and a half of study, with keen intelligence, a questing, probing mind, willing to devote his life to research, is our rarest and most precious national resource. These men are not being adequately encouraged, fostered, or nurtured. They are being discouraged in almost every possible way. All too often they cannot find appropriate places to work; when they do they are given punitively low salaries. They have to fight for each piece of equipment, for technicians, for each piece of glassware to do their work. They have little and often no security. As the young men look into the future, they cannot see how they can ever earn enough to have a down payment on a home or to send their children to college.

Great discoveries are predicated on previous knowledge of some kind. These discoveries are built up piece by piece, just like a pyramid. True, one man may place the last stone in place on the pinnacle and, for the layman, he is the discoverer. But the last stone cannot be placed unless all the rest are in position. The world may know the name of the man who finally produced a new drug. But they never hear of the unsung hundreds who made the discovery possible, such as the geneticists who spent their lives breeding special strains of mice without which there would be no discovery. Each new piece of knowledge plucked from the unknown adds to the building of a pyramid. The layman, intent on "practical things," wants to support and applaud the man who places the final stone. He has scant patience with those who lay the foundation.

In basic research, the patient men, the men with vaulting imaginations, are all needed so that mankind will suffer less, be healthier, live longer. They are the handful of men without whom man cannot obliterate the leukemia and cancers, the insanities, the heart attacks. Certainly they deserve better from the mankind they serve than what they now receive.

CHAPTER 11

BASIC RESEARCH AND THE NATIONAL DEFENSE

Perhaps this chapter should be entitled "Basic Research and the Defense of the West." In spite of the fact that there are neutralist countries, the world is obviously primarily in two camps. On one side there is Imperialist Communism, and on the other side there is virtually what remains of the world.

Basic research, or discovery, is never the province of one people or one nationality. It is immaterial to an American patient with pneumonia that penicillin was a British discovery. It is immaterial to an Italian with diabetes that insulin was a Canadian discovery. If we can use the all-encompassing term "Free West" to describe all the countries not under Communism, it is this Free West that we must rely upon for our basic research. If we had to rely on Communism for our basic research information, it would be the beginning of the end. Of all the countries in the Free West, one of those that is in the best position to sponsor basic research, from the economic point of view, is the United States. On the other hand, the heritage of work in basic research and the general respect for the scientists in this field is much higher in many other countries of the Free West than it is in the United States. The message of this chapter is quite simple. World War III—hot or cold—is currently being fought in the laboratories of the Communist states and the Free West today. World War III will be won by whichever side has made and exploited the most profound discoveries in basic research. This is no theory; this is hard fact. This is a fact that will be attested to by every scientist. It is attested to by our top-ranking military men. It is attested to by history. In an earlier chapter it was stated that the Sputniks did not represent the culmination of the Russian scientific challenge, but only the beginning. Unless the people of the Free West, and this includes the United States in particular, can overcome their inertia and real blindness in their attitude toward basic research, the future is bleak, if not black.

Rockets are fashionable today. What the average American does not know is that virtually all of the initial basic research on rockets was done not in Germany, not in Russia, but in the United States, decades ago, by Dr. Robert H. Goddard. In 1945, when the Americans moved into German rocket bases and were querying the German rocket specialists, they were startled to have a German question them about the interrogation. "After all," he said, "you have the man in your country who knows all about rockets and from whom we got all of our ideas, Dr. Robert H. Goddard."

Goddard was ignored in the United States. Goddard was not merely a man with theories, he had the great good fortune of being supported by the Guggenheim Foundation so that he actually built and flew rockets. In 1918, he developed the prototype of the bazooka—in which the Army did not become interested until World War II. In 1926, he developed and fired successfully a liquid-fuel rocket. In 1935, he shot off a rocket that went faster than sound. He developed patents for the multistage rockets and a gyroscopic steering device. He worked out the mathematical theory that is today the bedrock of all rocket propulsion. The story of Goddard is a tragic one for America, for those British who died from V-2's, and for our lag behind Russia in space flight today. For decades it was as though no one had heard of Goddard. His work was brought to the attention of the highest authorities, under the best auspices; but it was ignored. The Guggenheim Foundation arranged for Goddard to meet with the chiefs of Army Ordnance, the Navy's Bureau of Aeronautics, and the Army Air Corps in 1940. The conclusion on the part of the Army was that this was all very interesting, but they felt that rockets would not play any part in the forthcoming war. Naval aviation and the Army Air Corps used a fraction of Dr. Goddard's skill in order to develop jet-assisted take-off devices for airplanes.

Today, the mistakes of the past in regard to Goddard, who died in 1945, are realized. There are two professorships that are now named after him. This is small comfort. If we ignore our Goddards of today, and if the Communist states lavish attention upon similar minds and foster them, the outcome will be fatal for the Free West.

There is a wonderful ironic parody of a real situation that occurs all too often. I have permission from the *Washington Star*, original publisher of the work, to include it here in full.

THE DREISTEIN CASE
by J. LINCOLN PAINE

ADVANCED RESEARCH INSTITUTE
CAMBRIDGE, MASSACHUSETTS

2 August 1961

The President of the United States
The White House
Washington, D.C.

Esteemed Sir:

Some recent work by my colleague, Prof. Hauck of Pretoria, has been communicated to me in manuscript. His findings lead me to believe that scientists may be able to counteract the forces of gravity in the near future. Undoubtedly, if Hauck's new discoveries are further developed and applied, a vast new area of space exploration and missile development will open.

The situation which has arisen seems to call for watchfulness and, if necessary, quick action on the part of the Administration. My colleagues here have urged me to bring this obviously significant development to the attention of the appropriate government authorities. I believe, therefore, that it is my duty to bring to your attention some of the scientific facts which are attached in a separate memorandum.

Of course, my colleagues and I offer our full services towards the further development of this discovery.

Very truly yours,

EGBERT DREISTEIN

THE WHITE HOUSE
Office of the Special Assistant
to the President

16 August 1961

To: The Secretary of Defense

Attached is copy of letter from Prof. Egbert Dreistein. Draft reply for my signature. Be polite. Incidentally, is there anything to this?

GRANT QUINCEY

INTER-OFFICE
MEMORANDUM

Date: 2 September 1961
Ref.: CPT-201/1

To: Col. T. Lee, OPS
From: The Secretary

Prepare reply to attachment. Is the Institute under contract to the DOD? Quote me their budget figures for the last three fiscal years.

Official Use Only
INTER-OFFICE
MEMORANDUM

Date: 29 June 1962
Ref.: CPT-201/179

To: The Secretary
From: Col. T. Lee, OPS

The matter referred to in your memorandum CPT-201/1 of 2 September 1961 has been referred to an Inter-Service Ad Hoc Committee of staff-rank representatives. The committee concurred that there was no consensus on the problem.

Individual views were as follows:

I. The Army feels that ordinary gravity is not fully understood yet and sees little purpose in extending studies into the field of anti-gravity.

II. The Air Force has been conducting small-scale research on anti-gravity at the TOP SECRET level. However, since it is impossible to extend the concept to fit existing weapons systems, a low priority has been assigned.

III. The Navy has recommended a high priority to anti-gravity investigations under the code name of PLOP.

There is no record in DOD files of a facility clearance for the Advanced Research Institute. Prof. Dreistein has never applied for a "Q" clearance. Given the sensitive nature of the anti-gravity question and the extenuating circumstances, the attached draft reply to Prof. Dreistein has been made as clear as classification permits.

The committee reached agreement on a single point: Prof. Dreistein should not be encouraged. A permanent subcommittee has been set up to provide similar assistance in expediting the handling of any future suggestions from members of the scientific community.

DEPARTMENT OF DEFENSE
Office of the Secretary

2 July 1962

To: Special Assistant to the President

In reference to your request of 16 August 1961, attached is draft reply to Prof. Egbert Dreistein.

The receipt of Prof. Dreistein's letter has stimulated re-examination of the status of anti-gravity research in the Department of Defense. Estimated future budgetary allocations for that type of research do not warrant continuation of the projects which have been under way. Accordingly, I have issued an order that they be curtailed.

FRANK WATT

THE WHITE HOUSE
Office of the Special Assistant
to the President

5 July 1962

Prof. Egbert Dreistein
The Advanced Research Institute
Cambridge, Massachusetts

Dear Prof. Dreistein:

The President has directed me to reply to your letter of 2 August 1961. We thank you for your interest and assure you that the matter has been investigated by appropriate government agencies.

Your patriotic interest is very much appreciated and the President is always interested in receiving stimulating ideas of that nature.

Yours very truly,
GRANT QUINCEY

Moscow, Aug. 5 (1964).—A Soviet spokesman announced today that a manned space station has been established as a satellite around Mars and is now observing landing conditions on that planet.

The achievement was credited to the revolutionary discoveries of Prof. Otto Hauck, formerly of South Africa and now in the Soviet Union. He has been awarded three Lenin prizes for his work. . . .

THE WHITE HOUSE

6 August 1964

Prof. Egbert Dreistein
The Advanced Research Institute
Cambridge, Massachusetts

Dear Prof. Dreistein:

My advisers report to me that you have been interested in the subject of anti-gravity research. Because of the grave circumstances in which our Government finds itself as a result of the announcement from Moscow yesterday, I am asking you to lead a new high priority project in that direction.

If you will come to Washington the early part of next week, a briefing will be arranged by representatives of the military services and the Central Intelligence Agency who will be able to give you a little of the historical development of Prof. Hauck's work.

I, as President, personally hope that you and your colleagues will rise to the challenge of this new emergency.

Yours very truly,
HORATIO CALVIN

The national attitude not only among the public but among some members of Congress toward basic research is currently catastrophic. Some of the Senators who are aware of the enormous importance of basic research are Prescott Bush, Hubert Humphrey, and Lister Hill. For several years Senator Bush has been doing everything he possibly can to promote basic research and support people who work in the field. Because of Senator Bush's interest in the national welfare, he has on numerous occasions made major efforts, completely irrespective of political party lines, to bring to the awareness of his colleagues in Congress the critical nature of the problem. On one occasion he personally set up a dinner with twenty key members of the Senate to hear and see directly some of the frightening portents which our lack of effort in basic research holds for the future. Let us look at some of the startling and fearful developments that can come from basic research.

The United States went into a mild state of shock when the Russians flexed their scientific muscles in shooting off the first Sputnik. Scientists everywhere looked upon the public reaction with misgiving. They were afraid that in the public's mind, as soon as we caught up with the Russians' advances in rocketry, all would be serene again. This, of course, is completely false, because the real challenge is still to come in the fields of basic research. The Communist states are actively working on a variety of means derived from basic research to facilitate imperial Communist advances against other countries without open aggression. If the West and the Communist states have a rough equality in terms of nuclear and thermonuclear weapons and the rockets and planes which can deliver them, it is generally assumed that no one other than a madman will trigger off a world-destroying thermonuclear war. But if this race in bombs and missiles results in a standoff, there are many ways that the Communists can still win. They can win a war without fighting or even firing a shot. Let us look at how this might be done.

The meteorologists are sure that when more basic research is done, a definite but as yet undetermined degree of control of the weather will be possible. Weather, of course, is not only vital for the military, but it affects almost every segment of our population and economy. Some of the things affected, just to mention a few, include air and sea transportation, the sale of clothing and soft drinks, radioactive fallout, and agriculture. Tornadoes, hurricanes, ice storms, blizzards and their toll are almost a minor aspect of the total importance of weather.

Who is going to establish weather control first? The Free West or the Communist countries? In the last year for which there are figures available (1955), the number of scientists graduated in the USSR with a doctoral degree in the general field of meteorology was 630. In the same year in the United States, the number of doctoral graduates in meteorology was 2. Who do you think stands a better chance to develop weather control first? If so few students in the United States want to get their Ph.D.'s in this science, obviously the departments of meteorology in many universities are quite small. It is hardly logical to assume that a university board of trustees will assign enough money to a tiny department to support high-altitude research planes, giant wind tunnels, cloud chambers, and all the rest of the expensive apparatus needed for basic meteorological research. Therefore we are limited in the facilities available to train people adequately in this field. But for those who are trained, as was mentioned earlier, how many places are there where they can go to do full-time basic research in meteorology? Pathetically few. For years the United States Weather Bureau and others interested in meteorology have been pleading with Congress to appropriate ten or twenty million dollars to build a national laboratory for basic research in that field. This laboratory would be open not only to all departments in the federal government, but like the Brookhaven National Laboratory on Long Island, it would be open to graduate students of universities to do their doctorate work. Such a laboratory could have those expensive and critical facilities without which adequate training of Ph.D.'s and basic research cannot be done. The existence of this laboratory alone would provide a place where the doctorate scientists in meteorology could go and do basic research.

Now, let us assume that the Russians were to develop weather control before we could. Since we are assuming, let us further assume that they might be able to send us drought, not partial drought, but absolute drought, year after year. With complete crop failure, the entire agricultural portion of our economy could be paralyzed. The reservoirs supplying all the great cities would dry up, and people could not live in a major metropolis deprived of water. They would have to leave. The water table would fall and the wells would go dry. Imperial Communism would not even have to fire a shot. Does this seem like science fiction? So did rockets and space travel long after Dr. Goddard had developed not only the theory and the mathematics but the actual rocketry to do the job.

In the spring of 1958, Congress' answer to this problem was to appropriate an additional forty-five thousand dollars over the previous year's budget. Fortunately, later in the year a bill was passed—still far short of the needs and still not enough for laboratories, but at least beginning to subsidize basic research in weather. Passage of this bill was in no small part due to the efforts of Senator Bush and his work to spread the word among his colleagues. At the previously mentioned Senatorial dinner, the weather problem was placed before the legislators in no uncertain terms.

What other fields of basic research could Communist imperialism use? Let us assume that they wanted to bring a country like Japan to its knees. This might be done by starvation. Japan is a country that is badly overcrowded and has far too little tillable soil to support its people. A great percentage of the edible protein needed by the people of Japan must come from fish taken from the waters around the home islands. Communist basic research is very interested in the poisons which are produced by a variety of marine organisms. They are intrigued by microscopic plant life that can be highly poisonous and, if distributed in the water, afflict fish so as to make them poisonous. Thus it is not only possible, but one of the Free West's very few specialists in marine poisons indicates he has reason to believe that a plan is actually under way by the Soviets to develop a technique to produce enormous amounts of these marine toxins and toxic organisms, fill a fleet of submarines with them, and send the craft around the waters of Japan, slowly discharging their lethal products into the sea. It is estimated that hundreds and thousands of square miles of fishing areas can be effectively poisoned by such a procedure. How long can a starving, overpopulated country maintain political stability? Devilish? Demoniacal? Of course. But then, this is a game which is not being played by the Marquis of Queensberry rules.

Soviet nations are doing basic research on drugs, infinitesimal amounts of which can be dropped in reservoirs and can poison, kill, or render insane tens, hundreds of thousands, and millions of people. This is not a myth. This is something which is possible. Remember the data on botulinum toxin and on the microscopic amounts of drugs which can produce mental abnormalities. Scientists of the Free West are not afraid of the Sputniks *per se*. They are afraid of what the Sputniks represent and the next discovery, not yet imaginable, that the Communist nations may make, which can result in imperialist Communist capture of still another country or people. As a highly placed official of the Pentagon recently stated, "The effort to prove to the public that we are doing what we probably would have been doing anyway prevents us from carrying on in fields which are less subject to public excitement—and which will be important later." When asked: "What are such fields?" he replied, "I don't know. These are the areas of science that no one has dreamed up because we don't have time to sit and dream."

This is why we must have basic research men who are given the facilities and the encouragement and the time to "dream up" great new discoveries and breakthroughs. This must be impressed upon the Congress, for the attitude of many Congressmen, irrespective of party, is so frustrating and so limited as to be simply unbelievable.

For instance, the National Science Foundation was created and charged with the responsibility of supporting basic research in the United States. In no single year since its existence, has it had enough money to discharge even a fraction of what it feels it must—let alone what it could do. Year after year, after the scientists of the agency have indicated what could be done, the Bureau of the Budget has slashed their budget figure by 30, 40, or 50 per cent. Then when this already truncated budget is presented to Congress, the legislators in turn chop it and chop it and chop it.

In testifying before Congress on the need for funds for the National Science Foundation, I pleaded with the Senate to restore a cut of twenty-five million dollars made by the House. After I had described why basic research is vital, one of the Senators turned to me and said, "Well, let's be practical, Doctor. There is an election coming up next year, and if we approve the spending of twenty-five million dollars, what will we have to show our constituents next year as a result of this expenditure?"

I carefully pointed out that if they hoped to get great discoveries one year after each new appropriation, they would be perpetually doomed to disappointment. What would have happened, I asked, if the funds for research on penicillin had been cut off in 1930, one year after the basic discovery was made? I pointed out that between the time of the initial discovery and the time that something "practical" came out of penicillin was about thirteen years. Where, I asked, would your atomic energy be if you had cut off the work of Einstein in 1914 or 1920 or 1925 because nothing "practical" had been obtained at that time from the result of his fundamental equations? Where would you get your atomic and thermonuclear bombs if you had cut off the work of people like Fermi, Hahn, Bohr, and all the others who finally made the bomb possible only after many years of continuous and unremitting work?

Then I turned to the Senators and said: "Do you think for one moment that your constituents would fail to vote for you because you had supported basic research? As a matter of fact," I asked, "don't you think that this might even be a useful plank to have in your platform?"

A senator replied, "Humph, Doctor, it is obvious to see you never ran for elective office."

At the request of Senator Prescott Bush, I made a survey of the basic research budget requirements of most of the federal agencies concerned with either doing basic research themselves or supporting it in universities and institutions. This included such agencies as the Army, Navy, Air Force, Bureau of Standards, Department of Agriculture, Fish and Wildlife Service, United States Weather Bureau, Coast and Geodetic Survey, and so on. In each case, I was appalled by my findings. In terms of worthwhile proposals for research actually in front of these agencies, they had only been allowed, on the average, 50 per cent of the funds necessary to support the work then before them. This, of course, precludes using funds to create new facilities and stimulate new basic research and new investigators. They are not given enough money to support half the investigations or investigators which are currently ready to move on problems.

How does this extraordinary situation come about? In almost every case, it turns out that someone from the comptroller's office inside a department (or from the Bureau of the Budget, in the case of independent agencies) has handed the basic research division a ceiling beyond which they might not request any further funds. Basic research requires knowledge, insight, and a soaring imagination to conceptualize new thoughts. Can you envision anyone less likely to meet these requirements than an accountant in a comptroller's office? Yet these are the men who set ceilings. Once this ceiling is set and a department budget is made, the scientists are compelled to go before Congress and defend their departmental budget. Of course, their part of the budget is indefensible because it is so inadequate; yet should they so state before Congress, they would be guilty of departmental insubordination and would probably lose their jobs before nightfall.

Even after some legislators have begun to grasp the importance of research, they seek to avoid increasing research funds and suggest, "How about putting all basic research under a single agency? Then we wouldn't have any waste or duplication of research effort." To this there is only one reply. "If you want to avoid so-called duplication of research effort, then let us remove every cancer investigator in the United States, except one man. If two are doing cancer research, this is duplication of effort." Naturally, this is idiotic. In the face of the unknown, the more pioneers that attack the frontier, the better chance there is of discovery and breakthrough. Furthermore, if there were a single agency controlling all funds, a single fallible man in charge of a particular division might not think that a certain problem submitted to him for support was worth supporting. Scientists would then have no other recourse. Currently, the way things are set up with multiple programs (although each agency knows what the other is doing), if one agency turns a project down owing to lack of interest or possible shortsightedness, there are others who may pick it up. Many worthwhile projects brought to successful conclusion have been turned down by several agencies before one has finally undertaken support. A bureaucratic control of science would be impossible. Even the Russians know this; and in a land where there is bureaucratic control of virtually everything, the one area which tends to get hands-off treatment is science.

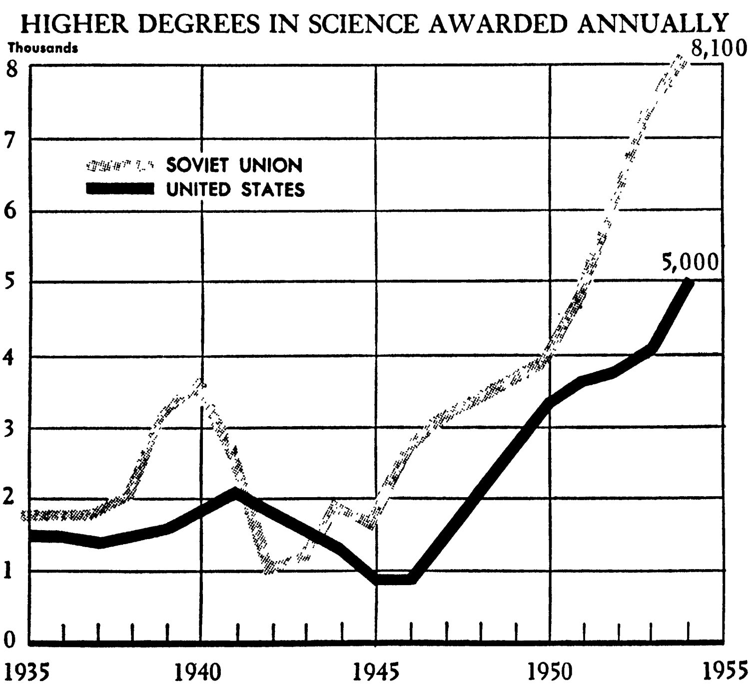
The Sputniks stimulated the United States to make a reassessment of its educational system. Currently, Congress is putting many, many millions into education in order to turn out more scientists. At the same time they are loath to provide the money for facilities where the scientists can go to do their basic research. What is the sense of putting hundreds of millions into the educational process to make scientists if there are not enough places for them to go after they have obtained their education? Why spend these funds to educate basic research scientists if their salaries are so punitively low in the few places which are available that they are forced to leave the fundamental field they have been trained for and go into business? The great discoveries that may come about in the future stagger the imagination today, whether it be antigravity, weather control, drugs which control men's minds, drugs which can prevent aging, and all the other as yet unthinkable wonders that can only come from basic research.

Basic research that tends to be throttled in the United States is fostered and lavishly encouraged in the Soviet countries. Just what do the Russians do?

First of all, all their youth is exposed to science in primary and secondary school. This is something that should be done in the Free World as well. The students of the Free World should be given an insight into science, not because all are expected to be scientists, but because now, and increasingly so in the future, political decisions and scientific decisions will be unalterably intertwined. In order to be good citizens and to vote intelligently, the men and women of the United States of the future will have to have a knowledge of science. American history is compulsory in most public schools. It is compulsory because it is felt that without a knowledge of our heritage and our past, students will not be able to be effective citizens in the future. English is compulsory, and the students must read Shakespeare because the English language and literature are our heritage. If it is important for the citizens of the future to be conversant with Shakespeare or Spenser or Milton, it is equally imperative that they be able to understand the concepts, the risks, and the potentialities of science and the way it will affect their political future.

The Soviets foster science. It is highly competitive but the rewards are so great that virtually everyone who has any scientific potentiality will try for a career in science. This is true throughout the Soviet bloc. Schooling through the Soviet equivalent of college and postgraduate work is virtually free. At the end of this time, jobs with splendid salaries and all kinds of privileges are virtually assured. Soviet research professors can easily obtain salaries that are equivalent to about thirty to forty thousand American dollars per year. In terms of how this salary is related to that of other workers in the Soviet lands, such a scientist gets between fifty and sixty times what the unskilled laborer gets. Compare this to the American figures. Take a look, in the following graph, at the way the Soviets are turning out doctorate scientists compared to our figures.

Scientists are the most powerful tools that any country in the future will have. They are powerful not only because



Comparison of U.S. and Russian higher science degrees awarded.

of their war-making ability. (Indeed, it is regrettable that one has to fight for basic research by hammering at the difference between the Soviet lands and the Free West in war potential, in order that people sit up and take notice. Without using this device, the mere facts do not seem to be persuasive enough.) The world is obviously undergoing an explosive evolution of nationalism. Countries that have been backward and even primitive for years are leaping into the middle of the twentieth century with imperative demands for science in order to bolster and improve their economy and their national strength. If there is a shortage of scientists in the West and a superabundance in the Communist lands, scientists will be exported from Communist areas to these countries. What better way is there to take over an uncommitted or neutral land than to have all the key scientists and technologists act in the double capacity of Communist propagandists? Key jobs in key areas held by Communist exports is a danger which is so obvious that it need not be further belabored.

Finally, the economy of the West and the United States is dependent upon basic research. Think of the role that Goddard's rockets and missiles are playing in the present-day economy of the United States. Economic strength is not only desired by each nation and each individual; it is also a powerful weapon in a cold war. America, rich as it is, will in ten to fifteen years be a have-not country in many respects, as many vital natural resources are used up. Continued economic strength depends upon scientific discovery and technologic exploitation. Countries such as England know that their future is intimately tied up with the discoveries in the use of energy from the atom and from thermonuclear reactions. Think of what the discovery of antigravity would mean to the economy of any nation.

Whether it is the development of new strains of corn or wheat, whether it is medicine or astronomy, basic research is the key to the future. It is a key to which most Americans have kept their eyes closed. It is a key which the Congress continues to refuse to turn. When the Sputniks went up and Congressional figures were rushing about trying to assign the blame, it never occurred to them that their parsimony with basic research funds was in great part responsible. It is a travesty to see the head of the National Science Foundation have to beg Congress for funds to support basic research. Indeed, the members of Congress should be begging the National Science Foundation to use all the money that they possibly can in order to exploit, expand, foster, and support basic research. It is not as though we were talking about billions of dollars (which Congress will joyfully spend for rivers and harbor projects, for agricultural surplus, and for new highways). We are talking about a fraction of this amount. This is all that would be necessary to put us in a basic research posture without which we cannot survive as a free nation and without which the entire West will not be able to withstand Communist imperialism.

We should support basic research not only in the United States but among the other friendly nations of the Free West as well. As was said earlier, the American with pneumonia is not concerned that the discovery of penicillin was made in Britain. The United States has no monopoly on creative thinkers. If you look at the roster of names and countries of origin of the men responsible for the concept of the atomic bomb or many other major discoveries, it is obvious that these men need not have been born or trained in Brooklyn or Iowa. The Army, Navy, Air Force, and a few other agencies, therefore, have been trying to support research abroad. They have been distributing basic research funds to key investigators in other countries, but this money is still only an infinitesimal trickle. When one realizes that in nations such as Portugal a scientist with the rank of associate professor earns about seven hundred dollars a year, it is obvious that a very small amount of money can go a long way. Science can be a tool of tears or of triumph, of destruction or creation. We need its creativity for our health, welfare, wealth, and strength. We need to be aware of its tears because there are powers in the world who would use it for its terror. But whether it is for constructive use and high purpose or for defense, discoveries can come only from basic research. Americans must get over the habit of assuming that basic research is being supported because it seems logical. It is not adequately supported. They must realize that the millions and billions in *applied* research have nothing to do with *basic* research and should not be confused. The public and only the public can insist, demand, and be responsible for a resurgence and an increase in basic research —without which this nation and those of the Free West will perish.

CHAPTER 12

THE FUTURE THROUGH A GLASS DARKLY

A constant refrain throughout this volume has been that the basic research man goes into the unknown; and because it is unknown, he cannot predict what he will find. However, once the first few steps forward are taken and some insight into the problem is obtained, it is often possible to make some predictions as to what future work may bring. Since these are only educated guesses and confirmation must await future work, they are presented here, in the words of St. Paul, "through a glass darkly."

Earlier chapters have pointed out many of the possibilities for the future. In this chapter a very few more projections are presented, but these can alter the life of man to such a degree that life on this planet will never be the same again. As with all mighty forces, these may be used for good or for evil. It is man's free will and moral fiber which will determine how these discoveries are used.

The first possibility for the future to develop from further basic research has to do with gravity. Most of us tend to ignore gravity because it is ever with us. Even when we fall and break a leg we seem unaware of the fact that we really did not "fall," but that gravity pulled us down. Airplanes have to fight gravity, and it is the primary difficulty in trying to lift rockets of great size. Gravity actually causes diseases such as varicose veins, many so-called "female disorders," sprains, and fractures and also makes a lot more work for the heart.

It is intriguing to contemplate what would happen to man if the gravitational force which constantly acts upon him could be reduced. Our most educated guess would indicate that in the many patients who are suffering from what is called "chronic heart failure" the reduction of gravity would be a tremendous boon.

What effect this might have on people who are partially paralyzed or who have muscular weaknesses, circulatory disturbances, pregnancy, and many unusual physiological situations can only be speculated on now. For all we know, many of the aspects of aging may be tied in with the body's constant fight against gravitational force.

Physiologists and space biologists are eagerly looking forward to the day when they can observe man under conditions of a gravity significantly weaker than that of earth. This situation will be upon us very shortly as man gets into space. Once there, depending upon a variety of circumstances, gravity can be pretty much tailored to fit the specifications of the space biologists. Should it be apparent that low gravitational forces are helpful, it would obviously be an enormous advantage to try to make a low gravitational field available to those who need it. Naturally, one cannot hope to send patients into space or maintain them there. However, should it be possible to create a situation in a home or a hospital where a lower gravitational field could be induced, one might have a powerful new tool that could be available to physicians for a variety of diseases.

Everything that moves fights gravity, not only directly, but indirectly, through the friction which is caused by weight on moving parts. Weight merely describes the effect of gravity upon mass. Of course, gravity has its uses, too. One of its many "virtues" is that it holds the molecules of air which comprise our atmosphere close to the earth as a blanket of air.

With too little gravity the air would dissipate into space, leaving an airless globe, as in the case of the moon. Gravitational force is in many ways similar to magnetic force. It is possible now to make an electromagnetic force equal and opposite to gravity. This, of course, does not cancel gravity —it merely opposes it. Anything caught in such a force field will not fall down but will stay suspended in mid-air. The amount of apparatus involved is massive and the objects which can be "floated" are quite small—but it can be done. This suggests the possibility that in the future we will be able to devise an apparatus which can produce so much force, equal and opposite to gravity, that it can raise itself off the earth. This would, in effect, be an anti-gravity machine. It probably would be a pretty huge affair and would be operated by atomic or thermonuclear energy. Consider what a revolution would ensue in transportation alone. Railroads, roads, and big landing strips would not be needed. Friction due to weight would be negligible. The enormous problems of rockets which now have to pull away from the earth's gravity, using tremendous amounts of fuel, would be solved. In order to pull away from the gravity of the earth, a huge thrust is needed. To keep the acceleration of a rocket sufficiently low so that man can stand the accelerative force, one must take off relatively slowly, and this requires still more fuel. For a rocket to return to earth, it must have the same amount of fuel it had at take-off in order to resist gravity and not burn up or crash. Current rocket fuels cannot provide enough thrust to take off slowly and land again. If there were no gravity to fight, all this would be obviated. The impact of an anti-gravity device on man and his economy would be incalculable.

We have already indicated that as basic research proceeds, the diseases of both mind and body will be conquered, one after the other.

Let us consider for a moment the problem of aging. Why, for instance, does one species of animal live for two years, another for thirty, another for seventy, and another for a hundred or more? Our best guess is that this is dependent upon genetics and, hence, the information as to when an animal should die is specifically coded into the molecules of the cells of each different species.

Normally in youth we find that cells repair damage by making new cells. The new cells are faithful replicas of their parent cells. In aging, two things happen. First, the process of repair or of making new cells is progressively diminished. One can see this in the rate of healing of fractures in elderly persons versus young ones. Second, the cells are unable to reproduce exact likenesses of themselves when they do reproduce. Thus one might say that instead of repairing themselves with new virile parts, the cells use older, more ineffective, and not quite functional parts.

What, if anything, can be done to limit or slow down the deterioration of body and mind as individuals age? It is quite possible that we will not be able to extend the life span of man very significantly, because this type of information may be a characteristic of the species. Certainly, looking at the longevity picture of many species, some such species-specific force would seem to be inherent in life. It might be said that this was simply a reflection of the rate of deterioration until death finally occurred.

However, there is evidence on the other side as well. This type of evidence has been obtained in lower species of animals such as mice. For instance, a recent experiment in which mice were raised on top of an atomic pile and, hence, exposed to a certain amount of radiation of a particular type, demonstrated that the longevity of mice was definitely reduced. These animals did not die from any disease that could be pinpointed. Instead they just died after a shorter life span.

This does not, of course, rule out the possibility that deterioration was early. But if it was, it was in a system of cells or molecules within cells that we have not been able to discover.

However, even if man's life span is genetically coded into him as an intrinsic part of life, there is still something that we may hope to do to retard the deterioration of the individual's body and mind as he becomes older.

As previously mentioned, when one is young there is a wonderful reparative series of processes that are automatically called upon every time there is damage or the cells die. Obviously there must be some kind of feed-back mechanism which identifies destruction or failure and stimulates new healthy cells to repair this damage.

This feed-back mechanism is certainly not understood. We do know about such things as growth hormone and a variety of other hormones which are stimulated by a specific chemical situation that occurs when there is need for extra amounts of a hormone. It may be some such model which is involved in the normal repair processes in youth.

It is not only possible, it is inevitable that sooner or later we will be able to find the chemical or other mechanism whereby this feed-back control works. Once this is known, there is no reason why we cannot hope to reproduce it and help maintain youth for a far longer period.

Today there are many places and institutions where one must retire at the age of sixty-five. As one of my friends recently stated, "This is statutory senility." There is no reason why man must deteriorate at an arbitrary rate at a certain time in his life.

If basic research is given the opportunity, it goes without saying that we shall in due time not only be able to preserve and extend man's space of life to its optimum, but we shall be able to maintain his body and his brain in such a state that he can perform fruitful and productive work for many decades beyond his current potentiality.

Thus far, we have spoken about correcting abnormalities and diseases, preventing decay due to age, and increasing the tools, powers, and devices of man. But is there anything we can do about man himself? Can science and basic research in particular make not only a better world for man to live in but better men to live in this world? We think so. In so doing, we do not feel we are playing God. Indeed, we feel we are using our God-given gifts of mind and purpose to explore His universe and follow the Commandments of the Gospel. I, for one, feel that I could be doing no more Christian work than pursuing basic knowledge of God's cosmos and trying to use this knowledge not only to increase man's physical comfort, but also, if possible, to adduce this knowledge so that man can actually make himself better.

As life on this planet has gone forward, we have seen the vast sweep of the evolutionary process. We have been able to trace how the horse evolved from the tiny eohippus to the racing steeds and work horses of today. We have been able not only to trace the evolutionary process but to reproduce and accelerate it for our own needs in the vegetable and animal kingdom. Evolution has two major methods which forge new or modified species. Both methods depend upon survival of the fittest. If a species of animal lives in an environment which is friendly, he will live and thrive. But if his environment begins to change, the species may be in for trouble. These changes can be alteration in climate, exhaustion of food supply, or a new threat from predatory animals. Let us take, for an example, animals who browse on tree foliage. Now, let us assume that the low trees which provided food began to die out. Only taller tree foliage would be available. As the animals tried to reach these leaves, only those with the longer necks could make it, and they would survive. The rest would starve. As those with the longer necks mated, their offspring would tend to have long necks, and if the process continued long enough, one might wind up with a species such as the giraffe.

Thus, natural selection of those best suited for survival would cause the evolution of something new which differed from the old. The other phenomenon is the occasional appearance of a mutant, or freak. Most of these do not survive or cannot reproduce. Every so often, however, it is the very freakish characteristic of the mutant which permits it to survive better. This may be size, speed, intelligence, or any number of things. If two such mutants were to breed and their offspring bred true (i.e., maintained the same "freakish" characteristics from one generation to the next), a new species would have been created.

Man has used selective breeding in animals to produce new types of dogs, faster race horses, and fatter cattle. He has used the occasional mutants when they appeared to create characteristics that were felt desirable. More recently, he has been using radiation on seeds to produce new mutants, some of which have turned out to be disease-resistant, have greater yields per acre, and so on.

But where does man himself stand in the evolutionary process? As far as we can see, he is standing virtually stock still. There are several reasons for this. First, man has modified his own environment so that it is hospitable for almost everyone. No longer does our environment weed out the weak and permit only the strong to live. Indeed, man sends his strongest to war to be killed, and by medicine and special institutions permits the weak or defective to survive. Man could, of course, try to breed selectively, but this is repugnant to him. Man insists on free choice in picking his mate (or the family does in choosing a bride or groom for their son or daughter). But, other than breeding men like cattle or race horses, which man himself will not permit, is there any hope? Basic research has come up with a series of discoveries which make such a hope bright with promise.

Hereditary characteristics are transmitted from one generation to the next by genes. Whether it be blue eyes, red hair, or a long neck, there is a gene for it. Genes are molecules. They have a precise structure. Thus there is a precise molecular structure for blue eyes and another for brown eyes. Basic research has been able to learn quite a bit about the gene molecules. The search is becoming intensified month by month, and our knowledge is increasing proportionately. We know, for instance, that in a given type of bacteria, some will be killed by penicillin and others will not. Those immune to the effect of this antibiotic have "children" and "grandchildren" who are also immune. It has been shown, therefore, that the ability to resist penicillin is hereditary. Basic research men have succeeded in isolating the molecules that carry this immunity and have transplanted them to bacteria which are susceptible to penicillin. Thereafter, those cells that formerly succumbed to penicillin will be resistant to it and, even more important, so will their "children" and "grandchildren." In effect, a hereditary molecule has been successfully transplanted from one cell to another, and after this transfer the recipient keeps on transmitting the new heredity molecule for succeeding generations.

The implications which this has for man are overwhelming. Consider the fact that in the reproductive process in man there are tens of millions of sperm. Each sperm has its own set of genes and no two sets in any two sperm are exactly alike. One sperm may have genes to make a strong body and a weak mind, or vice versa. Some genes carry hereditary diseases. Other genes—by their structure—will carry a susceptibility to disease, physical or mental. Of these millions of sperm, only one will make contact with the ovum. Since it has been shown that we can transplant the genetic type of molecule from one cell to another, the following possibility now exists: We should eventually be able to identify genes which carry certain hereditary factors. We may then be able to transplant all the best genetic characteristics which a father has to offer into one or more sperm. The same may be done for ova. Think what this can mean.

Let us suppose that there is a difference in brain structure in the fanatical and vicious person as opposed to the gentle and reasonable one. Both types of individuals are frequently born to the same parents. In the same family with a generally similar background, one can assume that the difference between the two children is either a matter of brain structure or brain chemistry. Structure is definitely controlled by genes. But even if the personality is due to brain chemistry, this, too, is usually dictated by genes. Thus we may have available to us a means of genetically reducing man's inhumanity to man. We may be able to ensure that love will be the dominant factor in the human race that is to come, instead of hate. Over the millennia, man has been led by power-hungry, angry, ruthless, or insane men to war and slaughter. A new race of men with brain structure and chemistry of the right type would never follow such a leader. Couple this with the ability to use the genes which dictate the highest possible intelligence and we may develop into a new race which is not Homo sapiens, but Homo superior. We could give to our children the optimum in physical strength and health. They would not have hereditary disease or be susceptible to ordinary disease. Their brains could have the intelligence of an Einstein and be predisposed to work for the good of their fellow men instead of for their destruction.

Man has been able selectively to breed strains of vicious dogs and strains of loving, loyal dogs. These become characteristics of the breed and hence are hereditary. Since this is hereditary, it must be carried by genes. We should be able to take the very best that each man and his wife have to offer genetically so that the perpetual hope of all men can be realized—that our children will be better than we are. This could continue from one generation to the next, with each new group of children carrying farther and higher all the best hopes of mankind. We have controlled our environment. Now let us begin to think of controlling ourselves. The agnostic may call this human engineering; those with faith may call it divine engineering that follows the precept: "Ye shall know the truth, and the truth shall make you free."

Today and for the centuries past, man has not been free. He has not really been able to achieve "life, liberty, and the pursuit of happiness." He has let himself be dominated by evil men and evil systems, and by surges of hate, vindictiveness, avarice, and crime. The "truth" is that we have in our bodies the seeds of greatness that we and all mankind have always hoped would grow. But the seeds of weakness, disease, and depravity are in us, too. The choice is now before us. Man's spirit must be the guiding force. Man's intelligence can discover the way. Man's basic research can provide the guideposts.

Thus far, Homo sapiens has made instruments for destruction with which he can annihilate himself. He now must choose whether or not to put equal energy, wealth, and effort into changing himself into Homo superior. This may well be the last chance he will have.