

COMMENTARY

Science and Medicine at the Millennium

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It was 21 years ago almost to the day that I addressed the Western Society for Pediatric Research. On that occasion my title was: "Research, the Lifeline of Medicine." To my surprise the lecture was published in the *New England Journal of Medicine* (1). On rereading the 1976 lecture, I was struck that the problems we faced then are very much with us today and my feelings about them have not changed at all.

The Abstract of that paper cites an analysis reported in *Science* in that year by the late Julius Comroe and Robert Dripps of the key advances in the diagnosis, treatment, and prevention of cardiovascular and pulmonary diseases (2). After reviewing 4000 papers, they concluded that the preponderance of contributions came from basic research unrelated to the eventual application.

The concluding paragraph of the *New England Journal* paper 21 years ago stated: "Acquisition of basic knowledge is now threatened by strong social, economic and political pressures. These forces discourage financial support of basic research and question its importance. They drive scientists to undertake excessively complex problems in a gamble for quick payoffs. They make scientists into entrepreneurs and administrators. It is just such times that test the temper of a scientist. Whether a basic scientist or a clinical investigator, the investigator must adhere to the fundamental discipline of science by asking discrete and well defined questions. It is out of these small and numerous contributions of knowledge that we build the grand edifices of nature" (1).

That was twenty one years ago!

Now, in the last decade of a century and near the dawn of a third millennium, I would like to reflect

first on the history of medical science in this 20th century and then try to assess where we may be heading in the next. I want to apologize to those of you who will be aware of my repeated use of a hunting metaphor.

The first two decades of this century were dominated by the **microbe hunters** who tracked down the microbes responsible for the most dreaded scourges of many centuries: **tuberculosis, cholera, diphtheria**. There remained terrible diseases—**scurvy, pellagra, rickets**—for which no microbe could be incriminated. These diseases were caused by the lack of vitamins and so in the 1920s and 1930s the **vitamin hunters** replaced the microbe hunters.

In the 1940s and 1950s, the **enzyme hunters** discovered the key enzymes in metabolism that use the vitamins to produce the energy for cells to grow and function. Now, these **enzyme hunters** occupied center stage.

You may be aware that the enzyme hunters have been replaced in the past two decades by the **gene hunters**, the genetic engineers who use recombinant DNA technology to identify and clone genes, the blueprints for the enzymes. These **gene hunters** introduce their constructs into bacteria and plants to create factories for the massive production of hormones and vaccines for medicine and better crops for agriculture. *Biotechnology has become a multibillion dollar industry.*

Almost daily we see newspaper reports of discoveries by gene hunters of a defective gene responsible for some disease—diabetes, cystic fibrosis, Huntington's chorea, and Lou Gehrig's Disease—as well as genes for predisposition to colon cancer, breast cancer, alcoholism, hypertension, and mental illness.

In view of the *inexorable* progress in science, we can expect that the gene hunters will be replaced in the spotlight. When and by whom? Which kind of hunter will dominate medical science in the last decade of our waning century and into the next millennium? I wonder whether the truly novel hunters who will occupy the spotlight might be the *neurobiologists* and *neurochemists* who apply the techniques of the enzyme and gene hunters to the functions of the brain. What will we call them? Perhaps they will be known as the **head hunters**.

During this 20th century with its succession of hunters and golden ages in medical science, the current age of gene hunting is undeniably the most golden. We have an inexhaustible supply of genes and simple and efficient techniques to track and capture them. Genetic engineering and related biotechnologies represent the most revolutionary advance in the history of biological and medical science. The term revolutionary is generally overused, but not here. The effects of this advance on medicine, agriculture, and industry have not been exaggerated.

Yet even more revolutionary, but generally unnoticed, is a development, which, while lacking a name or obvious applications, will inevitably lead to even more remarkable and *unanticipated* practical applications. I refer to the coalescence of the numerous basic medical sciences into a single, unified discipline, which has emerged because it is expressed in a single universal language, the language of *chemistry*.

Much of life can be understood in rational terms if expressed in the language of chemistry. It is an international language, a language without dialects, a language for all of time, and a language that explains where we came from, what we are, and where the physical world will allow us to go. Chemical language has great esthetic beauty and links the physical sciences to the biological sciences.

Yet when I entered medical school in 1937, the importance of chemistry was hardly noticed. It was a serious question whether genetic phenomena operated by known physical principles. Of course we now understand and examine genetics and heredity in simple chemical terms as DNA. DNA in the chromosomes and genes is easily analyzed, synthesized, and rearranged. Species are modified at will. It is no longer a question of whether we can sequence the 3 billion base pairs of the human genome, but rather when it will be completed and at what cost.

Let me reflect again, this time on the medical specialties. They too were quite discrete in 1941 when I chose to do my internship in internal medicine,

which was then to me the most intellectually challenging. However, today, *pediatrics* is arguably the most attractive of all the branches of medicine because of several things: the coalescence of all the biologic and medical sciences, the technology of genomics and genetic chemistry with its great impact on developmental biology, and the unremitting prominence of microbial disease so prominent in childhood.

In science today, we possess phenomenal capacities to acquire and integrate unprecedented quantities of sophisticated data. Yet, in this time of informational plenty, we are beset by serious problems which complicate our lives and threaten the foundations of our scientific enterprise. For the sake of brevity, I have selected *just three* among the many problems which warrant our concern, whether we be scientists, clinicians, or neither.

The three problems I want to consider are the *anti-science attitudes in society*, the *consequent lack of support for basic science*, and the *use and possible abuse of advances in science and technology*.

ANTISCIENCE ATTITUDES IN SOCIETY

The *first problem* is the rising tide of public fear, distrust, and rejection of science, both chemical and biological. The late Carl Sagan in "The Demon Haunted World" pointed out that *95% of Americans test out as scientifically illiterate* (3).

Chemistry has had a poor image for some time. "Better things for better living . . . *through chemistry*" had been the DuPont slogan for many years. The slogan informed the public of the value of plastics, detergents, and industrial chemicals for our individual and collective well-being. Then the logo was abbreviated to: "Better things for better living." The words "*through chemistry*" were dropped when the public became aware that chemicals, as is true of all things, natural or man-made, can be toxic too. A few months ago the largest banks in New York merged: Chase Manhattan and the even larger Chemical Bank. Not surprisingly, the new giant bank is simply the Chase Manhattan. There is no "chemical" in its name. In fact, the only times we hear something good said of chemistry these days are references, as in newspaper articles, to the good chemistry of a winning football team, or the improved chemistry between certain heads of state.

The image of biologists has not been doing well either. Hollywood has chosen them as their villains in recent years. Lacking communists as culprits, and

squeamish about racial bashing, some hit movies have demonized doctors and scientists—“Lorenzo’s Oil,” “The Fugitive,” and “Jurassic Park”. Never mind that well-controlled studies now show *Lorenzo’s oil* is of dubious value, that criminal activity by a major drug company as in “The Fugitive” is exceedingly uncommon, and that we all know the cloning of a whole dinosaur genome in “Jurassic Park” to be utter fantasy.

Perhaps Hollywood has taken its cue from Congressional committees and the headlines they generate that make it seem that science is wracked with fraud. Members of Congress and reporters fail to recognize that the practice of science defines rather strict boundaries for behavior that are effective in all but the very rare instance, one in a thousand or less. In the practice of science, the more startling the claim, the more it attracts attention, and if false, the sooner it is exposed.

And then there is the disillusionment with the failure of science to cure the ills of society. Vaclav Havel, the celebrated Czech author and statesman, and his followers, often blame science. Modern science has to them degraded the natural world and brought us to an abyss.

LACK OF SUPPORT FOR BASIC SCIENCE

This brings me to the *second problem*, the lack of adequate financial support for science, a poverty worsened by severe pressures to engage in targeted research, such as the treatment of breast cancer and AIDS or the development of technologies to improve the economy.

I will remind you of the story, retold on several occasions, of the surgeon who, while jogging around a lake, spotted a man drowning. He dove in, dragged the victim ashore, and resuscitated him. He resumed his jogging, only to see another man drowning. After he dragged the second one out and got him breathing, he saw two more drowning. He also saw a colleague, a professor of biochemistry nearby, absorbed in thought. He called to him to go after one while he went after the other. When the biochemist was slow to respond, he shouted: “Why aren’t you doing something?” The biochemist said: “I am doing something. I’m desperately trying to figure out who’s throwing all these people in the lake.”

This *parable* is not intended to convey a lack of regard for fundamental issues among clinicians nor a callousness among scientists. Rather, it portrays the reality that a serious problem, a war on disease,

must be fought on several fronts. Some contribute their special skills to the distressed individual while others try to gain the broad knowledge base necessary to cope with present and future enemies.

Five years ago, Dr. Bernadine Healy, then Director of the NIH, developed a *Strategic Plan for Medical Research*. Such plans are fundamentally flawed because discoveries are commonly serendipitous. The best plan over many decades has been no plan. For lack of essential knowledge, timetables for assaults on particular disease targets have had little meaning. Nor could we have anticipated the confrontations with novel diseases, such as AIDS, Legionnaire’s disease, septic shock, and drug-resistant tuberculosis.

Medical research is still more a game of pool than billiards. You score points regardless of which pocket the ball goes into. This was eloquently explained recently by Dr. Harold Varmus, the present Director of NIH in addressing the Conference to Establish a National Plan on Breast Cancer. He made it clear that a *specific disease* model is far too narrow a target to encompass the complexities of a disease process, such as cancer or AIDS.

A well-designed plan, by its very nature, cannot lay the groundwork for the utterly novel techniques that make possible major transformations in the acquisition and application of knowledge. The success of the NIH that has changed the face of medicine in the post-World War II period was not planned. This extraordinary success is owed to channeling a major fraction of the budgets of the Heart, Cancer, and twenty other disease institutes to noncategorical, basic research. Had this money been spent instead in palliating these various diseases, the current advances in preventing and curing them would have been squandered. How tragic that the NIH, with a budget of only 1% of the health care dollar and the best investment for improving the quality of medicine, is faced each year with arbitrary and devastating cuts for research and training.

The breakthrough of recombinant DNA technology and genetic engineering was based on the discoveries of enzymes that make, break, and seal DNA. All these basic advances were made in academic laboratories built and supported almost entirely by funds from the NIH. For thirty years, my research on the biosynthesis of the building blocks of nucleic acids, their assembly in DNA replication, and the training of over a hundred young scientists, was funded with many millions of dollars, without any promise or expectation that this research would lead to marketable products

or procedures. No industrial organization *had*, or *would ever have*, the resources or disposition to invest in such long-range, apparently impractical programs. We carried out these studies to satisfy our curiosity. Yet to my great pleasure, such studies of the replication, repair, and rearrangements of DNA have had many practical benefits.

The pathways for assembling DNA from its building blocks have been the basis for the design of most drugs used today in the chemotherapy of cancer, AIDS, Herpes, and the treatment of autoimmune diseases. These studies are crucial to understanding the repair of DNA, so important in the aging process, and for understanding mutations and the origin of some cancers.

It may seem unreasonable and impractical, call it *counterintuitive*, even to scientists, to solve an urgent problem, such as a disease, by pursuing apparently unrelated questions in basic biology or chemistry. Yet, the pursuit of curiosity about the basic facts of nature has proven throughout the history of medical science to be the most practical, the most *cost-effective* route to successful drugs and devices.

Investigations that seemed totally irrelevant to any practical objective have yielded most of the major discoveries of medicine—X rays were discovered by a physicist observing discharges in vacuum tubes, penicillin came from enzyme studies of bacterial lysis, and the polio vaccine came from learning how to grow cells in culture. *Cisplatin*, a widely used drug in cancer chemotherapy, came about from studying whether electric fields affect the growth of bacteria and then observing an inhibition traced to the unexpected electrolysis of the platinum electrodes. As I have mentioned, genetic engineering and recombinant DNA depended on reagents developed in exploring DNA biochemistry. All these discoveries have come from the pursuit of curiosity about questions in physics, chemistry, and biology, apparently unrelated at the outset to a specific medical or practical problem.

A few years ago, a meeting in Washington celebrated the bicentennial of the U.S. Patent Office. From discussions among the inventors and corporate and government officials gathered there, a remarkable truth emerged. It was agreed that the age-old aphorism “Necessity is the mother of invention” is usually wrong. Generally, the reverse has proven to be true: *Invention is the mother of necessity*. Inventions only later become necessities!

Time and again, inventors created things that had to wait many years to be recognized for their practi-

cal value. Nobody really needed the airplane, the FM radio, or television. The study of quantum mechanics led to the transistor, not the reverse. Take xerography as another example. It took Chester Carlson, the inventor of the Xerox process, six years to interest a company in his invention and twenty years before the first commercial copier was produced. FAX machines were invented 30 years ago, but it took a deteriorated postal service, among other factors, to make them the necessities they are today.

Quite clearly, even industrial inventions emerge from a creative process. As such they are haphazard rather than goal-oriented. The process of invention conflicts with prudent business strategy. A pioneering invention, almost by definition, is profoundly different from what the company has been doing. It is commercially unproved, and, therefore, riskier than the established business.

The lessons to be learned from this history should be crystal clear. It is crucial for a society, a culture, a company, and a medical school, to understand the nature of the creative process and to provide for its support. No matter how counter-intuitive it may seem, basic research is the lifeline of practical advances in medicine, just as pioneering inventions are the source of industrial strength.

The future is invented, not predicted. Great innovations, whether in art, literature, or science, seldom take the world by storm. They must be cultivated to be understood and understood before they can be properly appreciated.

How can we convince people to support basic research? Perhaps the analogy of rearing a child would help. We accept the uselessness of an infant, and the cost of *education and support* for more than twenty years, in the hope of producing a useful citizen. In the same vein, we need to explain that basic research also follows a tortuous and uncertain route. It is an *investment* that needs to be supported for a long time to produce the practical advances for medicine and industry.

Of course it is important that basic discoveries be promptly and wisely applied to solve practical problems. The recent applications of biotechnology to medicine have given us major insights into diabetes, cancer, and other metabolic diseases. Will these approaches and techniques be equally effective when applied to the human brain and behavior? I am sure they will.

Accepting that consciousness is a matter of *chemistry and neurons* is hard for many to accept, including physicians. We must remind them that the same

chemical language that describes the functions of the heart and liver surely applies to the operations of the brain.

Already, major advances are being made in understanding the chemical basis of several degenerative brain diseases. The dogma that nerve cells cannot regenerate may soon be overturned. At least four major growth factors have been discovered that promote the survival and growth of nerve cells and are being clinically tested. I am confident that the “**head hunters**” who are now applying biotechnology to brain functions and diseases will soon be making startling advances in the understanding of sleep, memory, moods, mental illness, and other nervous system states, including consciousness.

USE AND POSSIBLE ABUSE OF ADVANCES IN SCIENCE AND TECHNOLOGY

Finally, I want to consider the *third of the problems* I mentioned: the use and abuse of advances in science and technology. Now and for decades into the next millennium, we will be confronted in medicine between the need to advance its scientific base and the art to apply it. There can be no argument that knowledge beats ignorance. Identifying the genetic lesions responsible for sickle-cell anemia, thalassemia, cystic fibrosis, Huntington disease, and Tay-Sachs disease has vastly improved our capacity to avoid them. There can be no argument that we must continue to do hard science, to understand mechanisms, and develop technologies in order to monitor and sustain health and to combat disease. Equally daunting will be our capacity to cope with the avalanche of data and technologies that emerge from this scientific enterprise.

In Western societies we are faced with caloric plenty and overeating. Obesity, through its link to several diseases, is estimated to cost more than \$70 billion a year, not to mention the human costs of lowered self-esteem and clinical depression. Clearly, we need to learn how to temper food intake and administer the new fat hormone when indicated. We are offered cheap megavitamin pills and we must learn how to use or resist them. As physicians, we will need to guide our patients to the intelligent use of the enormous quantities of genetic, chemical, and physical data that descend on us. We must be wise in responding to the complex genetic readouts of deficiencies and predispositions. I like the injunction that I think can be attributed to Osler: “Ask not

what disease the person has, but rather which person the disease has.”

To begin with, we must not allow profit-driven companies, utterly disinterested in the acquisition of new knowledge, to manage health care in our nation.

Just as daunting in the guidance of patients will be our actions as a community to conserve the use of expanding technologies. Will we urge annual tests to monitor a genetic predisposition to diabetes, atherosclerosis, hypertension, cancer, and twenty other diseases? Will we prescribe ever more vaccines, pills, and injections? Will we order analyses in the whole range of electromagnetic radiations? If we do, we will do harm. We will cultivate a nation of unhappy hypochondriacs, insecure in their jobs and insurance, and we will exhaust our economic resources.

I am convinced that for the foreseeable future we should continue to respect the resilience and recuperative powers of the body and mind. We should also respect the efficacy of practices honed by common sense and experience.

In this frame of mind we must, as physicians, be guided by the age-old dictum: “Do no harm.” I came across an account of a certain Dr. LaMettrie, a famous physician and philosopher of the Enlightenment period in the 18th century. At a feast given in his honor by a grateful patient, he consumed an enormous quantity of truffle pastry, fell ill, and promptly died. Voltaire pronounced it a great occasion since, for once, the patient had killed the doctor.

SCIENCE AS ART

In the course of this talk, I have focussed on three problems: *the antiscience forces* in society, the lack of support of *basic research*, and the *use and abuse* of science and technology. I could add more problems to this list. However, instead, I want to recognize what deserves the most emphasis and what unites us all. It is our unconflicted and overriding devotion to the culture of science. We must make it clear to the public that science is great, although scientists are still people. As people, they are no different from others: dentists, lawyers, artists, or businessmen. Scientists are just as prey to the human failings of arrogance, greed, dishonesty, and psychopathy. What does set them apart from others is the discipline of science, a practice that demands exact and objective descriptions of progress, evidence that can be verified or denied by others.

It is the discipline of science that enables all of us ordinary people, whether we be chemists, biologists,

or physicians, to go about doing the ordinary things, which, when assembled, reveal the extraordinary intricacies and awesome beauties of nature. Science not only permits us to contribute to grand enterprises, but also offers a changing and endless frontier for exploration.

I have been asked whether the computer revolution and other advanced technologies have altered the way we do bioscience research these days. Can research now be engineered and pursued by formula? Not yet. The technical tools are indispensable, but the practice of science remains in essence an art form and its province is Nature. Sir Karl Popper, an eminent philosopher of science and society, who died last year in London, said that “next to music and art, science is the greatest, most beautiful and most enlightening achievement of the human spirit.” I would place science first.

We probe the inexhaustible mysteries of Nature from a variety of directions, and with different intensities and styles. These probings are determined by our emotions, our moods, and our cultural heritage, much as these influence the artist. The major discoveries in science are more often intuitive or serendipitous than the result of logical analysis.

The machines we use produce images and compositions of objective precision. But this should not obscure the fact that we use these machines as tools, with tastes as distinctive as the way that painters use their palettes, composers their notes, and authors their words in creating their images of Nature. Seneca, the great Roman statesman and philosopher, once said, “All art is but imitation of Nature.” What we try to do in science is to get ever closer to Nature. In *the art of medicine*, we try to find for the individual a harmonious niche in Nature.

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