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The Symbiosis of Clinical Practice and Basic Research: Joshua Lederberg on the Interface of Science and Medicine

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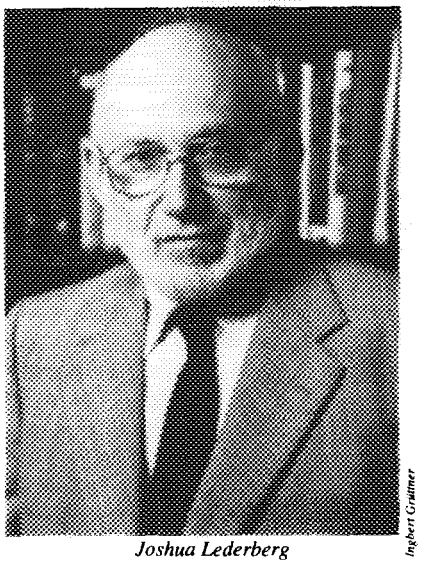
Joshua Lederberg, president emeritus of Rockefeller University, New York, has been a frequent contributor to *Current Contents*® (*CC*®). Most *CC* readers probably know him as an eminent geneticist and Nobel laureate in medicine (1958). In addition, Lederberg is a polymath who has produced insightful commentaries on a wide range of issues—for example, the sociology and history of science,[1,2] the nature of scientific progress,[3] new directions in print and electronic media for scientific communication,[4,5] and so on.

In a recent paper in the *Mount Sinai Journal of Medicine*, Josh addressed another of his concerns—the symbiotic relationship between basic research and clinical practice.[6] In particular, he discusses the impact of DNA research on clinical knowledge and practice.

His commentary is reprinted below. An essential point Lederberg makes is that the spectrum of basic research at one extreme and clinical application at the other is not a one-way street. That is, basic research is not always the exclusive source of knowledge from which technological and clinical applications later evolve. Just as often, clinical observations lead to major advances in basic knowledge. As an example, he cites the biological discovery of microbes as having been inspired by clinical observations of cholera, tuberculosis, and other major diseases.

Another major point is the danger to scientific progress Lederberg perceives from an excessively "reductionist" approach in research. He cites the massive human genome mapping project as an example. He sees the potential risk of a narrow focus on simply mapping the complete DNA sequence as a goal in itself. Rather, the map should serve as a springboard for major advances in clinical knowledge and practice as well as for a new revolution in basic biological research.



Joshua Lederberg

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As an example of this process, Lederberg discusses the first clinical application of basic DNA research—the development of prenatal diagnostic tests for sickle-cell anemia and thalassemia in 1978 by Yuet Wai Kan, University of California, San Francisco.[7] Incidentally, Kan's paper has been cited in over 300 publications. For his pathbreaking research in clinical diagnos-

tics, Kan was awarded the 1991 Albert Lasker Clinical Medical Research Award.[8] See his recent review in *JAMA*.[9]

In conclusion, Lederberg's paper is a timely reminder to basic researchers and clinical practitioners alike. That is, keep an open mind rather than a narrow focus to make the serendipitous associations and creative connections that lead to major advances both in basic knowledge and clinical practice.

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The Interface of Science and Medicine

JOSHUA LEDERBERG, PH.D.

MY ONLY CONTRIBUTION to the field of cancer was a paper I wrote 45 years ago, in which I defended the somatic mutation theory,[1] a theory that has proven successful. However, I can discuss with alacrity the interface of science and medicine, since I have had occasion to look into this question from time to time, both in a fairly systematic way and also as part of my daily work at the Rockefeller University. I am happy to share some observations about how I think the science-medicine interface has gone, how it may go in the future, and how it can be directed in its proper path in the future.

The SATT Model

My first response was generated in reaction to some propositions made at an earlier stage in the direction of the National Institutes of Health (NIH). I saw a report that tried to provide some justification for the research programs of NIH by the so-called SATT model. The basic notion is that we begin with the development of fundamental knowledge. We need a large basic science substrate from which technological and clinical applications will be

Adapted from the author's presentation at the symposium "Human Cancer: From 'Precurable' to Curable" commemorating the 65th birthday of James F. Holland at the Mount Sinai Medical Center on May 29, 1990. Address reprint requests to the author at The Rockefeller University, Suite 400, 1230 York Avenue, New York, NY 10021.

devised. The flow is all in one direction, from basic science to medical practice. And clinicians and patients would all bow down in great gratitude to the illuminations provided by the basic scientists. That may not be a bad idea, but not necessarily for the right reasons.

The "Can of Worms" Model

My own observations about what has happened in the history of science and medicine are best portrayed by what I call the "can of worms" model, in that progress is by no means linear, that no particular direction can be described, that there is constant interplay not only of the applications of basic knowledge to medical practice but of natural historical and clinical observation, both inspiring and provoking important discoveries. I venture to say that the most revolutionary discoveries have arisen out of observations that did not fit prevailing scientific doctrine, and required a reexamination of the fundamental concepts.

The most outstanding example I can think of is in the foundation of my own field. Oswald Avery was a biochemist who was commissioned in the 1910s to study the biochemistry of pneumonia at the Rockefeller University. He became an expert on the specific soluble polysaccharide which was the characteristic antigen that defined the different serotypic variants of this organism. This was a necessary basis for the development of serodiagnostic reagents and of serum therapy.

Then came the bombshell. In 1928, Fred Griffith in London described an experiment which was ignored by most people, since they could not grasp its significance. He showed that an extract of one pneumococcal type could alter the serologic character of the cells of another.[2] Avery proceeded to investigate that particular phenomenon from 1928 till 1944, and in effect established that the foundation of genetic influence appears in a molecule which nobody at that time suspected could possibly have those characteristics.[3] This molecule is deoxyribonucleic acid.

Everything we do today in molecular genetics and molecular medicine stems from that source. I do not think those experiments could have been performed except in the context of a clinical observation. The motive, the drive, the financing, the resources for an inquiry so far out of the context of general genetics would have been absent. But in the setting of a medically important and necessary investigation, the experiments were possible. The tools were there: background information, natural and historical information about pneumococcus, and so forth. Probably the most revolutionary discovery in modern biology arose by this "can of worms" model.

Medical-Scientific Progress

Medical-scientific progress over the last century can roughly be divided into three phases.

Microbe Hunting. Modern scientific medicine began with discoveries about infectious diseases that reached their flowering just 110 years ago, with the work of Louis Pasteur and Robert Koch, and the identification of specific bacteria as the etiologic agents of a variety of diseases. There again an important biological discovery was founded, provoked, inspired, and substantiated by clinical observations, whether the discovery was cholera, tuberculosis, or anthrax. Out of that arose one of the two or three major biological revolutions of the 19th century. I don't want to put down Darwin and Mendel as equal competitors, but the recognition of the world of the microbe, the development of experimental tools for the isolation of specific microbiological agents, the concept as we now know that the etiology of each infectious disease can be traced to some specific pathogenic entity, a different species of microorganism, constituted a biological revolution.

From the 1880s until the 1920s and 1930s, 90% of medical progress consisted

of the systematic exploitation of that fundamental insight—the "microbe hunting" that Paul de Kruif described so vividly.[4] It was a rather clear paradigm, a highly reductionist one. For every disease, find the bug that causes it, isolate it, use it to develop a vaccine, and in due course use that knowledge for the development of chemotherapeutic agents. We had a highly reductionist approach within that particular sphere. One could start with scientific knowledge of the microbe and from that develop important, necessary, and effective modes of management of disease. This has of course reached its culmination, and 90% of the battle has been won. But we must never forget that it is an eternal battle, and we live with constant reminders at the present time that infectious disease is far from conquered.

Constitutional Disease. Roughly by the time of World War II, we had the beginnings of the antibiotic industry, a fairly well routinized set of procedures for the development of vaccines, and we rather knew what to do about infectious disease. The new horizons were constitutional diseases.

The NIH was founded on the ideological groundings of the work on infection, but then faced a much more difficult problem, trying to deal with the complexities of the human host. When questions such as cancer, psychiatric disorders, and heart disease arise, the answer is not so simple as locating a bug and stamping it out. Investigative protocols are more complicated because you cannot conduct experiments with billions of people overnight, as you can with microbes, without facing ethical, technical, and economic constraints.

Intrinsic biology is also very much more difficult. Trying to drive a wedge between a tumor and its host is intrinsically far more difficult than trying to do that between an alien bacterial invader and its host. It has taken a very long time. During that interval, a great deal of medical progress was made, albeit in the empirical mode. It is hard to point to any important drug that was not discovered by serendipity or empirical observation. That applies to the vast majority of chemotherapeutic agents used in cancer.

In large screening programs based on limited rationale, one cannot predict which compound is going to work. One learns ex post facto that some things work better than others. One can do meticulous science in terms of calibration and validation of findings, but one cannot confidently operate from any theory which can predict the next step. The latter is what I mean by rationale.

DNA as Key to Therapeutic Advantage. The breakthroughs that led to the third phase started emblematically in 1944 with Avery's discovery. The knowledge of the role of DNA as the central storehouse of the blueprints of the cell was and is the key to how to approach questions of the distinctions within the human organism and its cells which can be used for therapeutic advantage.

The first clinical application of this knowledge goes back just about ten years ago to Y. W. Kan developing diagnostic procedures for the prenatal diagnosis of sickle-cell disease and thalassemia.[5] This was the first time that a clinically significant procedure depended on one's knowing the structure of DNA. My criterion is: Could you have done it without knowing about the double helix? Nothing prior to that time did require that specific knowledge and information. The 1980s have seen a veritable explosion of knowledge in this direction and the rebeginnings of rationally based therapy, using drugs designed not with perfect predictability but rather founded on some specific theory of the nature of the interaction of the chemical entity with the targets, the receptors, and the cell they are supposed to address.

That kind of reductionism is much in vogue today, and to some degree it is well founded. There are astonishing developments in our knowledge that simply were

not available thirty or forty years ago. I used to be quite impatient, as I have been working in this general area since the 1940s. When were the fruits going to come? Where were we going to see specific useful, clinical applications of the kind of knowledge that other molecular biologists and myself were having a great deal of fun developing? And what good would they be?

Intermediary metabolism, with its energy interconversions, mutual interconversions from nutrients into building blocks, has been the subject of extensive investigation during this past half century, and much of its details have been elucidated. There are about four hundred entities of these interconversions, each of which requires a few or a half dozen enzymes. To deal with that scope of intermediary metabolism probably takes about five thousand genes, genes which are reasonably commonly shared among most organisms on earth and whose structures are to some degree actually conserved from one species to another.

Not every cell has every one of the steps. Humans are quite deficient compared even to *Escherichia coli* and certainly to green plants. We require some of these materials as nutrients in our environment. Our assumption is that we have in the course of evolution lost some of those synthetic functions that were originally present in the primordial cell. The fact that a scheme of intermediary metabolism exists at all is the triumph of biochemistry, or premolecular biology if you like, with the development of that kind of insight. Of course we had to have this foundation to do other things, such as therapeutic intervention.

The other reductionist paradigm can be expressed in terms of a physicochemical approach to DNA itself. Here we do not have a map quite as coherent as I can give you for intermediary metabolism; we don't even know the size of the human genome to one significant figure. It's more or less 3 billion nucleotides. This is an approximation, and there may be variations from cell to cell. A reductionist project is currently in operation to try to get down every one of them, spending about $3 billion.[6] It can't be done at that price today, but with a little extrapolation this human genome project can be completed for about a dollar a base pair. Out of that, it would be hypothetically possible to build about ten million genes, which is roughly the information content of a few copies of the *Encyclopaedia Britannica*.

We now know that only about 1% of that information is coding information. Maybe another 4% or 5% play some role in the regulatory functions. About 90% of the DNA has no discernible function and may in fact not have one from the perspective of the organism; that percentage exists not because it serves any purpose of the organism, but because it serves some purpose of the DNA. Once a piece of DNA has been smuggled into the genome, it is difficult to see any special procedure by which it can be eliminated. DNA will tend to accumulate in any genome up to a certain point, just out of the dynamics of the molecular basis of replication of that DNA within that chromosome, and may not necessarily have any functions.

We know today that the vast majority of mutations that occur in DNA are not subject to any great natural selection but have indifferent results, either not causing a change in the corresponding amino acid, or causing a change that for the most part does not make much difference. Particular genes in closely related species have a lot of variation in protein composition but that variation does not seem to alter their functionality. The stringent NeoDarwinians among us, including myself, used to think that everything we saw was a consequence of a specifically oriented natural selection. I think we have had to abandon that position. There could be a lot of drift in that composition.

At any rate, we end up with the coding of about 100,000 proteins that are neces-

sary to make up the entire body, about 5,000 of those being the housekeeping entities. As a crude guess, any given eucaryotic cell is probably expressing about 10,000 proteins, using 10% of the total genome in a given cell. About half of these proteins are the housekeeping proteins common to most cells, and the other half unique to that particular cell. So there is room in the difference between the 10,000 proteins expressed in one cell and 100,000 available for all the diversification of gene expression which is involved in differentiation, adaptation to different circumstances, and so forth.

We have just scratched the surface; that is to say, we are only a couple of percentage points into a simple complete cataloging of the architectural units of the body, the variety of different proteins involved in its structures, the vast repertoire of enzymes, the enormous variety of growth factors and other control factors.

DNA and Coping with Human Diseases

The agenda for the next two decades is exciting. We know the direction of a large part of biomedical research. It is going to be the exploration of this catalog of DNA information. I not only don't quarrel with that, I am excited about the kinds of prospects it can generate.

What I am concerned with is an excessive reductionist approach: "That's all we have to do." Nothing can be further from the truth. If we were given the complete DNA sequence of a particular human being today, it would still not advance our pragmatic knowledge of how to cope with any specific human disease. It might help a couple of people who are already far down the track of locating specific genes to have some dictionary against which they can match their results. But they can still get their results without the benefit of the complete panoply.

My fear is that in the great excitement of this new wave of knowledge, we may lose some of the convergence, the feel for the organism, the natural historical context, the excitement and provocations that come from clinical observation which in my view will be necessary not only to further clinically important needs but even to give us the most important revolutionary findings within biology itself.

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