Photo: The Rockefeller University-Ingbet Grüttner

Nobel Laureate Joshua Lederberg, PhD

Recipient of the Maxwell Finland Award for Scientific Achievement 1997

Weighing the process by which the boundaries of scientific knowledge are extended, Vannevar Bush, Franklin Roosevelt's science advisor, noted that there are those of great vision who grasp well in advance the materials needed, who can tell where they will be found, and who have an uncanny skill in bringing them into the light. "These are the master workmen," he said.

Although Joshua Lederberg is skeptical of efforts to delineate how science progresses, there is little doubt that he is one such master workman. This year's recipient of the Maxwell Finland Award for Scientific Achievement, he is president emeritus of The Rockefeller University in New York and is currently the Raymond and Beverly Sackler Foundation Scholar at the university.

For over half a century, Dr. Lederberg, by training a geneticist, has been at the forefront of biomedical research and a pioneering spokesman for innovative thinking about meeting the challenges posed by infectious organisms. As a 1958 Nobel Prize winner at the unprecedented early age of 33, he has seized the opportunity such an award offers to draw public attention to a wide variety of issues that affect human health and well-being; one of his most recent pronouncements has been his warnings about the need to combat newly emerging infectious agents.

Before he was appointed president of The Rockefeller University in 1978, Dr. Lederberg was chair of the genetics departments at the University of Wisconsin in Madison, and subsequently at Stanford University School of Medicine in Palo Alto. His research into the molecular mechanism of genes and their application in recombinant DNA technology today is cited in virtually every field of biology, and has revolutionized medical diagnosis and treatment.

As a 21-year-old researcher at Yale University, he startled the world of classical genetics with his finding that the bacterium, *Escherichia coli*, could reproduce sexually. Until then, and indeed for some time thereafter, it had been widely assumed that bacteria only reproduced by simple cell division resulting in two identical progeny.

In 1945, Dr. Lederberg was working toward a medical degree at Columbia University in New York under Professor Francis J. Ryan. He credits Professor Ryan for getting him interested in genetics. At the time he was working on what he calls a "fanciful project, namely the search for sexual processes in bacteria."

In March 1946, on the recommendation of Professor Ryan, Dr. Lederberg went to work on this "fanciful project" at Yale where Edward Tatum had developed nutritionally-dependent double mutant strains of *E. coli*. Dr. Lederberg believed these strains could be a suitable model for studying bacterial recombination, and he was granted temporary leave from his medical studies to pursue this project. Isolating the nutritionally-defective bacterial mutants necessary for his work was a tedious process, and Dr. Lederberg developed a simplified method of isolating them.

At about the same time, Bernard Davis at Harvard Medical School had also developed a similar method. "We decided that we wouldn't squabble about it, but publish the papers together back to back." Dr. Lederberg says. "These papers were rejected by the *Journal of Biological Chemistry* on the grounds that they 'did not add to existing fundamental biochemical knowledge.' Any way you look at it, it was bad judgment on the part of the *Journal of Biological Chemistry* to reject it."

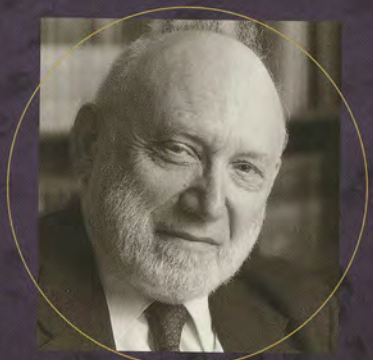

Photo: The Rockefeller University-Robert Reichert

However, the papers were eventually published, back to back as planned, in the *Journal of the American Chemical Society*. "Our work was really the foundation of the whole industry of obtaining these mutants for a wide variety of analytical and even industrial purposes," says Dr. Lederberg.

At Yale during the summer of 1946, Dr. Lederberg uncovered a system whereby two bacteria attach and form a connecting bridge through which one organism passes a chromosomal strand to the other, a process known as conjugation. The discovery helped to confirm the existence of bacterial genes, making them available for genetic research.

Dr. Lederberg earned his doctorate at Yale in 1947, and became professor of genetics at

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Wisconsin. Over the next decade, until he went to Stanford in 1959, he and his colleagues continued the work he had begun, exploring the ramifications of bacterial recombination.

While he was at Wisconsin, Dr. Lederberg was developing what was then a novel theory concerning the mechanism of the immune response. "I was working on the genetic control of enzyme formation in bacteria," he recalls, "both because it was a crucial question in how genes operate and also because bacteria had become the ideal experimental objects for this sort of study as a result of my previous findings."

Current theory at the time was that antibody generating cells make an infinite number of antibodies. But the cell genome is finite, so antibody formation could not be under genetic control. There had to be another explanation for antibody formation. In 1957, Dr. Lederberg spent a few months working with Sir MacFarlane Burnet, director of the Walter and Eliza Hall Institute of Medical Research in Melbourne, Australia. "Mac described to me his clonal theory of antibody formation in which the production of antibody generating cells is the unit of selection," he says. He credits Professor Burnet with the insight that the number of antibody types was finite. "It's just that it's a rather large number," Dr. Lederberg says. "I learned once again—don't believe everything you are told."

Back in Wisconsin, Dr. Lederberg completed work on his theory of antibody formation and presented it at the J. Howard Mueller Lecture at Harvard in 1958. "I remember," he says today, "the paper was greeted with total disbelief." The lecture was published in the journal, *Science*, the following year.

In 1958, Dr. Lederberg was awarded the Nobel Prize for his studies into the organization of genetic material in bacteria. Inevitably, such an award turns the bench scientist into a public figure whose thoughts, opinions, and advice on the issues of the day are eagerly sought, if not always listened to.

For two decades Dr. Lederberg was a member of the National Academy of Sciences committees on space biology and on the boards of the National Aeronautics and Space Administration's lunar and planetary missions, serving on the Mars Viking lander team. He voiced warnings about the need to make certain that astronauts did not carry back dangerous microbes with them.

More recently, Dr. Lederberg has been a leader in drawing attention to the threats posed by emerging infections. In 1995,

through his efforts, a national policy for dealing with such emerging infectious diseases was adopted by the White House. One of his concerns is the possible re-emergence of an influenza epidemic paralleling that of the 1918-19 epidemic. Referring to the plans now in hand by a number of government agencies to deal with the possibility of a pandemic of influenza, Dr. Lederberg says that he is pleased that there is now an effort being made to mount a response.

One issue that Dr. Lederberg worries about is the need to stimulate development of new agents against disease in a society that places a very high emphasis on safety. "From a social health perspective we may be paying such a high price for safety that we're making sacrifices in efficacy. The bias is toward guaranteeing perfect safety when in fact there is no such thing," he says.

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"When it works, our system of drug and vaccine development works very well," he says. "But basically it's a system whereby the regulator, the Food and Drug Administration, is the policeman on one side and the advocates of a drug for profit are on the other. It's assumed that the balance of these interests will take care of the public concerns and needs, and in many respects it has. Certainly it's much better than any centralized managed system has ever done," Dr. Lederberg says.

"To be blunt, who's going to invest a hundred million dollars to develop a vaccine and prove its safety and efficacy if there isn't a market for it? I think we need some more objective third party involvement in the development of agents of need." Dr. Lederberg looks to some sort of public subsidy to support what he calls a new paradigm of development and regulation for dealing with public health requirements beyond those that our present system offers. "I don't want to kill the goose that lays the golden eggs; it's done a marvelous job. But it can't do all of it," he adds.

Perhaps it is inevitable that eradication of disease has become synonymous with the eradication of the causative organisms. Smallpox is a good example. But, Dr. Lederberg says, "I came into microbiology with a philosophy similar to that expressed by C. B. Van Niel of Stanford University in Palo Alto, who said that in investigating bacteria, more would be found by those who love them, or at least respect them, than by those who hate them. So much of medical microbiology is devoted to extirpating the parasite and only incidentally trying to understand it and its relationship to the host. I think we always do better if we stand back a bit and try to look at things from a more dynamic point of view."

Dr. Lederberg cites a remark he attributes to Rene Dubos: "'It's better to learn how to live with microbes than to think about how to extirpate them.' We need think about what changes we need to invoke in ourselves in order to live healthy lives in a microbe infested world."