

Senate Subcommittee on Government Research
Hearings on the human impact of advance in biological science

Testimony by Arthur Kornberg, March 8, 1968

This is the first time that I have been invited to appear before a committee of the Congress and I am eager to respond. There are important and urgent problems that Congress and the American people must face to assure progress of research in the service of man. In this brief statement, I will not try to present a detailed course on DNA and genetic chemistry. I am mindful of an exchange which took place between the late Honorable John Fogarty and Dr. Fred Stone of the NIH in a hearing in 1967 before an appropriation subcommittee of the House:

"Mr. Fogarty. 'What is the difference between DNA and RNA? I don't understand either one of them although they have been explained to me for 4 or 5 years now.'

"Dr. Stone. 'I share some of your confusion, sir. DNA is deoxyribonucleic acid. The other is ribonucleic acid. The difference between the two lies in a difference in the ribose sugar.'

"Mr. Fogarty. 'I don't know any more than when you started.'"

What I would like to convey to you is a broader insight into the significance of some recent research on genes and heredity. With respect to the Senate Joint Resolution 145, I would like to record my essential agreement with the opinions expressed by Dr. Joshua Lederberg, in testimony which he has kindly let me see in advance and which he will present later.

Although we have all grown weary of the much overused adjective "revolutionary," I believe we all agree that the changes in biology which have occurred during the past 25 years are nothing short of revolutionary. The nature of heredity, clouded in abstract language even 15 years ago, can now be described clearly in chemical terms. We understand how nature arranges heredity through ingenious applications of well-established laws of chemistry and physics. And because of these tremendous advances, the essence of biology has become comprehensible to the high school student and the non-scientist. This revolution in biology has introduced a new theme, a theme of "molecules to man."

During the past 100 years, starting with the work of Louis Pasteur, we have learned that straightforward chemistry explains the cellular combustion of foodstuffs to produce the energy that a cell needs to work and to grow. This knowledge has been of crucial importance in understanding human and animal nutrition and many metabolic disorders in man.

However, there were scientists, including Pasteur, who predicted that these processes of fermentation and combustion of foodstuffs absolutely required a living cell, that they would never be reconstructed in cell-free fluids.

But we know now that they were mistaken. Around 1950 many scientists were convinced that the far more intricate reactions surrounding the structure and operation of genes would never be understood or resolved in simple molecular terms. The events of the past 15 years have proved that these gloomy predictions were also wrong.

As you know, heredity resides in our genes. Our genes are, in turn, composed of complex molecules called DNA. About 10 years ago we learned how to synthesize DNA in the test tube with the use of a certain cellular catalyst or enzyme. This synthesis required that DNA be furnished as a master tape to instruct the enzyme how to carry out the assembly process. The DNA we synthesized had the chemical and physical characteristics of natural DNA but it lacked the genetic properties. During the past year we have been able to synthesize DNA which has the full genetic activity of natural DNA. In this work we chose one of the simplest creatures, a virus which has only 6 genes, to serve as the master tape to be copied. Human cells by comparison have many thousands of genes. At Stanford University, Dr. Mehran Goulian and I were able to synthesize a DNA copy which had the same chemical and physical properties of the DNA obtained from the virus itself. Together with Dr. Robert Sinsheimer at the California Institute of Technology, we found that the synthetic DNA was infective: it was able to enter cells and produce new viruses just as efficiently as DNA from natural viruses. I have mentioned the complexity of DNA molecules. In this case one molecule of viral DNA contains 5,500 building blocks in a very precise sequence; each building block in turn has 35 atoms.

We infer from these results that in the test-tube synthesis of the viral DNA there was an error-free duplication of the original viral DNA. Each of the 5,500 components in this viral chromosome was placed in exactly the right sequence. Were it not so, a defective DNA message would have resulted and viruses would not have been produced. With these techniques in hand, it should now be equally simple to synthesize the similar DNA of the polyoma virus. The polyoma virus causes a variety of cancers in rodents. Why synthesize this particular DNA? In order to modify it. We can do this by substituting modified constituents in the assembly process. This will result in subtle but significant changes in

the message carried by the virus. In this way it should be possible to analyze which of the genes in the virus is responsible for its cancer-producing properties.

The details of the work I just summarized for you were reported in the Proceedings of the National Academy of Sciences in December. Because I thought they might be of public interest, I informed our press officer at Stanford and he in turn got in touch with local newspaper reporters. A reporter who interviewed me asked whether we had in fact created life in the test tube. At first this question irritated me. What's wrong with my saying "enzymatic synthesis of viral DNA?" Why use another vocabulary and call it "creation of life in the test tube?" I then realized that the reporter was simply asking a question in language that would be asked by the average citizen. Semantic problems flourish when there is lack of understanding. Understanding, in turn, diminishes when problems of language persist. So we talked for some time. We spent several hours going over the background, the details and the implications of the work. Finally he said, "As I understand it, you obtained DNA from a virus to serve as a master tape." "Right." "You added these building blocks from available supplies on the shelf." "Correct." "And then this particular enzyme that you had purified from cells assembled these building blocks to copy the master tape DNA." "Right." "So what did you do?" I paused and said, "I just watched with admiration." He then paused and said, "I guess I would, too." He wrote a fine story in the newspaper the next day but the banner headline ran: "Living Virus Core Created."

In discussing our work with interested citizens, and I believe it imperative that scientists should, we must find a common language. It will not do for me to tell the reporter that for years scientists have had no interest in the question of whether viruses are living because they know exactly what viruses are. The state of living or dying understandably interests people and we should use such a question as one means of beginning an educational dialogue between scientists and their fellow citizens.

I think you appreciate that it is difficult to define the term 'living' to the satisfaction of both the scientist and the interested citizen. We all will agree that bacteria which swim about, multiply and are fully self-sufficient are living. But scientists, if persuaded to make a yes or no judgment about viruses, would not all agree that viruses are living. This is because viruses are not self-sufficient and must invade a bacterium or animal to multiply. Yet if you were to examine the simplest of the bacteria and the most complex of the viruses you would find no sharp line separating them. We know that the DNA of a virus is as effective as the virus itself in infecting a cell and leading to the production of hundreds of new viruses. We know that this DNA can be assembled in the test tube from simple, well-defined chemicals. Understood in these terms, then, we can agree that the viral core is a very primitive or simple form of life, and has been synthesized in the test tube.

The term 'creation' is a problem in itself. The reporter finds it an easier word to use than 'synthesis.' But applied to DNA, the word creation upsets some scientists. Assembly of the DNA molecule in the test tube from its component building blocks followed the plan dictated by DNA obtained from nature. All DNA is an exact copy or a slight modification of the DNA that preceded it. We can argue that the creation of DNA is nature's genetic engineering job that has been going on for the last 2 billion years and will continue as long as life remains on earth.

What really startles and intrigues people is that genetics or heredity is simply chemistry. It is a young and difficult branch of chemistry. After 20 years of work on DNA in laboratories throughout the world we can begin to reconstruct some of the very simplest patterns of DNA duplication in the test tube. In the next 20 years this work must be made more precise, varied and extensive. Genetic engineering would then come more into prospect. This prospect fascinates people. It also frightens them and I understand why it does. Any knowledge or any invention can be used for good or evil. Fire, the wheel. Gun powder, nuclear power. They serve us and destroy us.

What will genetic engineering bring?

We can look forward to the correction of genetic defects, the cure of diseases due to defective or missing genes. At some future date, many years hence, it should be possible to cure a patient with an anemia due to defective hemoglobin. Current treatments consist only of blood transfusions and cannot cure the disease. Assume that at some unspecified future date the gene for human hemoglobin were identified, separated from other genes and reproduced in quantity in the test tube. How could we deliver this gene into blood-forming cells of the patient? It should be possible to include this gene in one of the many viruses which infect but do not harm us. Such a harmless virus, as Dr. Stanfield Rogers has suggested, might be exploited as a vehicle for delivering genetic information into cells where it is needed.

Our problem in this branch of science today, and for the foreseeable future, is not too much but too little knowledge. I see no ethical or moral problems that are different in kind or quantity that face us today with this new knowledge of genes and gene action. I do see the need for congressional action, to mobilize the talent and resources throughout the world to exploit the opportunities to expand our knowledge of the molecular mechanics of man.

We have been and continue to be the objects of nature's genetic engineering. Often we are its victims. May I remind you what happens if a single building block in any gene in the DNA is altered either by an agent such as X-rays, by radioactive fallout or by an error in the cell's copying process. The chances are 1,000 to 1 that any alteration in the gene will make the highly refined and evolved cell defective. In the case of human hemoglobin we have recognized over a dozen distinct blood disorders which

are due to a single alteration in the gene which carries the message for hemoglobin. Such changes are called mutations and the unfortunate individuals that carry these changes are mutants.

We desperately need more information about the molecular anatomy and behavior of genes to understand and cope with nature's genetic engineering. Despite the promising leads and insights into gene structure and action that I have cited, knowledge of genetic chemistry is really pitifully weak. Scandalously little support or encouragement is given to chemists to work in this area. We know that molecules determine what we are as men and how we behave. Yet we know less about the molecules of our chromosomes and our brain than we do about the molecules in Australian wool. This is because Australian wool growers have for many years recognized the value of basic research in the composition and chemical properties of wool. I believe it urgent that we expand our research into the molecules, genes and cells of man. This is the soundest investment I know of to bring us closer to a deeper understanding of growth and aging, of our nervous system and behavior.

I make a special plea now because the 1969 budget enacted by the Congress actually cuts back rather than expands this essential basic research. In recent months graduate students have completed their training in our laboratories with superb qualifications. These are young men and women who should be exploiting their talents and training to the fullest. The experiences of many of these investigators has been depressingly similar. They have applied for NIH or National Science Foundation grants and had these grants approved with high priority ratings. But they have been informed that monies were not available to fund these grants. It seems clear that support for nucleic acid chemistry and other areas of basic research, never adequate, has in 1968 dropped below the critical point. For the investigators who want to work in the field, this is discouraging and frustrating. For the medical practitioner who hopes one day to have the advantage of fundamental findings in his clinical practice, the implications are tragic. It is difficult to understand why this erosion of support has taken place. Is it because the government which must carry the lion's share of the burden of support for scientific investigation in this country does not believe in such basic research?

The remarkable progress of the past 20 years stems from laboratories all over the world financed by the Congress in programs superbly administered by the NIH, the NSF and other federal agencies. In these programs we have the organizational mechanisms to do the job. We must provide them with the means.

In concluding, may I repeat what I said at the outset. The revolution in biology has introduced a new theme, a theme of molecules to man. This theme could become a miraculous bridge across the gulf between the humanistic and scientific cultures. For the first time in recent history, physicists, chemists and biologists are finding in the operations of heredity,

problems that fascinate them all and which they can discuss in a common language. The granulation of science, which Maxwell deplored even a century ago, has visibly coalesced around the theme of molecules and genes. This area of science also happens to be of intimate concern to man and society. And I insist that basic facts of heredity and what we do with this knowledge can be understood by non-scientists and discussed in a common language with scientists. Twice before in the history of western civilization, the scientist-philosophers, the humanists and the politicians found common grounds for broad intellectual discussions. There was the Golden Age of Pericles and there was the Renaissance Period. I see the prospect of a new period of enlightenment in which we can begin to understand the molecular foundations of human nature. The American people and the Congress that represent them have a trust to make this prospect a reality.