A Scientist's Perspective

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I AM PRESENTING a general overview of the subject of biotechnology. My difficulty is to extract a few salient points.

Cells are the basic architectural constituents of all biological life, including human beings. The important point is that there is a vast variety of cells. Yet the biochemical basis of all of these cells is the same. This is known as the unity of biochemistry.

Curiously in science, sometimes more is known about a detailed biochemical process than about the organization of chemicals into the structures found in cells. It is remarkable that the accurate identification of the chromosome set in the human was not known until 1955. And yet at that time, scientists were already presuming that advances would occur in research in human development and in genetics. Those hopes came because the structure of DNA—the essential chemical constituent of the chromosome that embodies information—was already known in its physical and chemical detail. Understanding how DNA encodes information dates to 1953, when James D. Watson and Francis Crick published their very famous double helix structural model for DNA.

Human development and genetics

DNA has two functions in the cell. One is to replicate itself faithfully. In replication, the problems are (1) transmission of information from generation to generation and (2) how to ensure that every cell in the body has an appropriate quota of genetic information.

DNA's second function is to influence the structure and character of the cell and the organism. This is done through the medium of another form of nucleic acid called ribonucleic acid (RNA). RNA acts as the messengers of the blueprints of the cell that is present in DNA. This process of selecting parts of the DNA blueprint and putting them into RNA is called transcription. The RNA messengers then move to a structure called the ribosome, where they direct the process of protein synthesis. This process is called translation. The type and function of proteins manufactured on ribosomes provide the unique characterization of any cell. In short, DNA and RNA form a coding mechanism. The DNA is transcribed into an RNA copy, and the information in the RNA then directs the assembly of the amino acids into protein on the ribosome.

Proteins are chemically composed of twenty different amino acids. Proteins differ in the number of amino acids and their order in the protein chain. Each of the amino acids has a very distinctive molecular form. Consequently, after the protein chain is released from the ribosome, it has a built-in propensity to fold up into a very specific, three-dimensional shape. The linear sequence of information, which in itself is a reflection of the linear sequence of information in the RNA, then results in objects that have well-defined shapes and well-defined distributions of specific amino acids. Some of the amino acids will have charges on them; some will repel water, some will attract water; and the shapes themselves will permit attachment to external substances.

The relationship of DNA structure to the structure of proteins is reasonably well understood. Somewhat less is known about the details of how and why proteins fold up, but that they do fold into very well-defined and predetermined kinds of three-dimensional conformations is apparent. When they do so, proteins can perform biological functions. If the proteins attach to one another, they become structural elements like skin or collagen, (for example, hair). If they have chemical specificities, they can function as enzymes that catalyze metabolic reactions. By virtue of their very specific shapes, they can attach to specific molecules in the environment and function as antibodies; or grab onto oxygen and transport it throughout the body; or grab onto cholesterol and transport that through the body, and so on and so forth. These relationships concerning the transfer of DNA information to protein structure are the underpinnings of biotechnology. One can take advantage of this knowledge for further analysis of how cells work and how they produce various products.

A gene can be thought of as the segment of DNA that is responsible for the characterization of some particular protein. An average protein is a chain of one hundred amino acids. Knowing this, one can calculate that, in principle, there can be about 10 million genes in the human organism. To a rough approximation, using our alphabet to match the genetic alphabet, a set or a dozen sets of the Encyclopedia Britannica would be required in order to inscribe that much information. Therefore, if one is to understand the complexity of the human organism, one is going to have to unravel the identities of at least a hundred thousand different gene products. And then the fun begins. Each one of those gene products is worth a chapter, if not volumes, of further investigation. This provides a philosophical perspective that is one of the most important contributions of molecular biology. Human nature is a mechanism of such complexity that it is necessary to be very humble, indeed, about the ability to even understand small parts. Today there is only a glimmer of 1 percent of the knowledge of what the protein constituents of the human body do. Of the thousands of proteins inferred to be present, only a few have been isolated and definitely characterized. In large measure, these are known because of the power of the new tools of biotechnology. Today, there would not be materials like interferon or interleukin-2 if it were not for the intervention of biotechnology as a means of production.

From science to technology

What about biotechnology? In the early 1970s, besides the fundamental understanding of the structure of DNA, a set of tools for handling DNA was developed and allowed science to move into technology. The contributions of many investigators provided the tools to allow the cleavage of DNA at certain selected places in the DNA sequence. These tools are enzymes that are called restriction endonucleases. They function like a search routine in a word processor. The enzymes generate pieces of DNA, whose ends are of a specific nucleotide sequence, and that will form "complementary" pairs with other pieces of DNA generated by the same enzyme. The unity of biochemistry shows that the same rules of DNA structure are shared by bacteria, plants, yeast, algae, other animals, mammals, insects, and so on. So, by using restriction enzymes, a piece of DNA can be removed from one source of DNA and inserted into another.

Other enzymes, called ligases, seal up the chemical bond which is formed when two pieces of DNA form complementary pairs. The final result is that the original DNA, and a piece of DNA that was cut from another source, are joined together. This new, chimeric DNA can then be taken up by bacteria. These bacteria can now be fooled into allowing the indefinite promulgation of foreign DNA. Of course, there are tricks about getting the bacterium to also perform the tasks of transcription and translation, which are needed to get a protein product.

That is the technical base of the recombinant DNA piece of biotechnology. It is important to remember what is easy and what is difficult. It is easy is to take DNA from any source and manipulate it so that in a population of 100 billion bacteria, each bacterium will have one each of the various stretches of DNA that were in the DNA source. This is a totally random process. This is relatively easy. What is more difficult is to first pick out that one bacterium that has picked up the particular DNA wanted. The second difficult task is to get that bacterium to produce the protein wanted. Third, and hardest of all, is to find something really useful to do with the product that has been made.

The discussion to this point has focused on recombinant DNA. But that is not all of biotechnology. Biotechnology has a long history that goes back to the primitive selection of plants for crops. The largest part of the world's food supply is still derived from the choices that our neolithic ancestors made seven, eight, nine thousand years ago. No really important new crops to date have been invented since that time.

Our staples are still rice and wheat. There have been geographic discoveries: the discovery of the New World brought the Irish potato to Ireland from Peru, the tomato from Mexico, and a wide variety of others that have been of indigenous origin. Our ancestors were uncanny in their ability to select and develop plant resources for that purpose.

Much the same has happened in the domestication of animals. The cat, the dog, the cow, the horse, and the goat, have been subjected to extensive, although informal and not scientifically sophisticated, patterns of breeding to achieve specific purposes. The current advances are part of a continuing progressive understanding, and there are many other technologies that are involved in biotechnology.

There is one technology about which there is some misunderstanding. The term genetic therapy is misleading. The current objective of the introduction of genetic information is not at all the alteration of germinal information (which dictates the transmission of characteristics to an offspring), but rather the modification of cells in the body of the individual. In this respect, genetic therapy is not very different from vaccination. For example, with live polio virus vaccination, one introduces genetic information from a foreign source into humans in an attempt to modify the behavior with a desired end. In this case, the desired end is the production of antibodies to polio virus. It is very important that already sensitive issues are not confounded by failing to make important distinctions. Germ cell alteration is something that would deserve the most critical attention.

I was asked to say a few words about what the issues are. I am a little loathe to do so, because I am an interested party. I cannot pretend to have a disinterest in the outcome of decisions about the continuation of modern biological science. As a scientist very much involved in laying some of the underpinnings of biotechnology, I have a commitment to engendering more understanding, and I am eager to see positive uses. I am also eager for there not to be any human disasters as a result of this research. I also have a financial interest in these outcomes. It is very important that I am not perceived as a disinterested party.

The consequences of biotechnology

What are the issues? One very important aspect is to enhance the scientific quality of biomedical research. Biotechnology is framed much too narrowly. The glamour of recombinant DNA has made many forget the many steps requiring hard work in the development of pharmaceutical products. After learning how to produce a product, it is hard to figure out what to do with it. The testing, validation, and discovery of a drug's side effects includes many more disciplines than recombinant DNA. This country is still not doing a very good job in this area. The laboratories of molecular biology are by and large not in sufficiently good contact with their clinical colleagues for the development of those applications of molecular biology research.

I think it is of the utmost importance that biotechnology be directed to the most important human ends. One important human end is the application of molecular genetics to the problems of parasitic disease. Malaria is the world's most important disease, and there are very significant, exciting, provocative ways in which to attack that by using the most advanced of our present technologies. However, currently, it is very difficult to find support for research in this area, from either federal or commercial sources. In agriculture, the situation is similar. There is little motivation for trying to do what would be of the greatest importance in terms of global welfare.

Opportunities exist for applications of biotechnology that may lead to a better understanding of environmental toxicity. Perhaps this country can establish a rational basis for decisions about environmental "clean-up." These priorities must be founded on scientific knowledge of how environmental chemicals relate to genetic structures.

Social consequence of success in this new field must be anticipated. Realities are sliding right by that have enormous implications for the future. The success of programs in biomedical investigation will have the most important consequences. Biomedical research can contribute to the alleviation of disease. The conquest of heart disease and of cancer is already wreaking a change in our demographic structure, in the relationship of old to young, and in the interval of progressive disability. Those are the important consequences of biomedical advance. Biotechnology cannot be isolated from the whole framework of biomedical application. The same is true for agriculture. The success of programs in enhancing the efficiency of food production key to the economies of the developed world is very likely to cause major disruption in world agricultural markets that must be thought about very seriously. Otherwise, the United States may discover that it has the technology and the land, that it can produce all the world's food, and nobody else can afford to do it because others cannot compete with this country. What a terrible situation that would be in a global economy. Yet society seems to be heading there like an express train.