Life Without Father —the Future of Genetic Control

by James Bonner

One of the great triumphs of biology in recent years has been finding out in molecular detail how living things work. Here, briefly, is the take-home lesson about how a cell operates and what its strategy is—the strategy of life.

A cell in a very real sense is the smallest unit of living material, the smallest unit of an organism which can multiply itself and make two new objects like itself.

We know that the reason the cell is alive and can pass on its characteristics to its progeny is that each cell has in it a complete recipe about how to make all of the things that it takes to put inside the cell. This recipe is the genetic material, and it is written in the language of DNA.

Before the cell divides into two, the DNA must replicate itself to form two new identical copies of the recipe, so that each daughter cell can get a copy of the whole. In order for the DNA to replicate itself, it is necessary to have the building blocks for DNA-making.

In the good old days—or maybe I should say the bad old days—about 3.5 billion years ago, the first lonely little DNA molecule appeared in the aboriginal soup of the ocean made by random chemistry. That DNA molecule could replicate itself using the building blocks which were also present in the aboriginal soup, because in those far-off days there were no living organisms to eat up organic molecules.

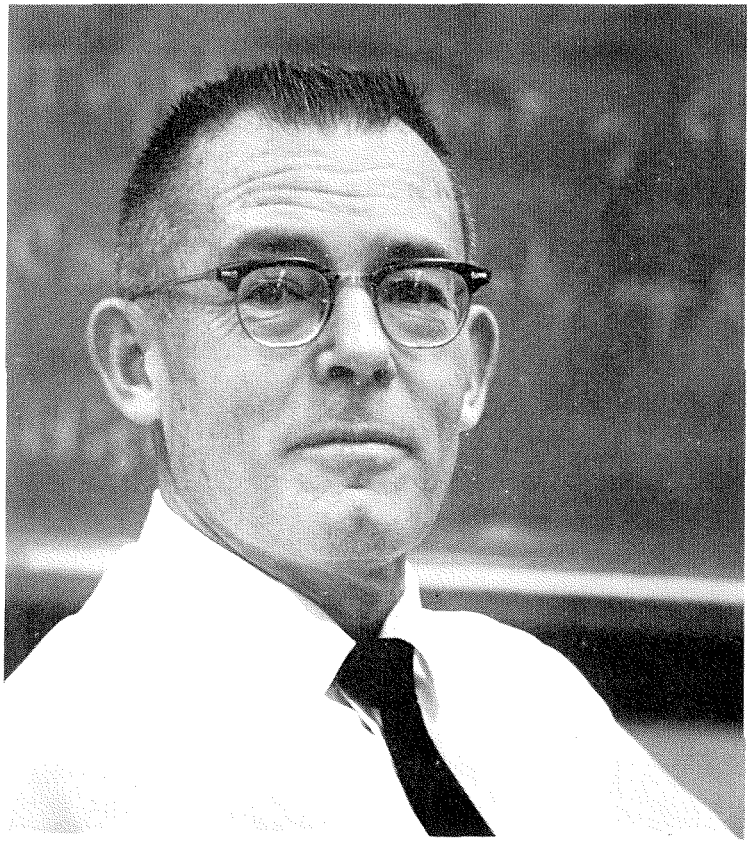
Today when a DNA molecule wants to replicate itself, it has to make the monomeric building blocks for replicating by itself. They are not available in the outside world. An organism has to make the material which it is going to use to replicate its DNA. And basically, in all cells and organisms, all of the machinery in the cell—except for the DNA itself—is merely machinery for making the building blocks so that the DNA can replicate itself.

This is the way the DNA goes about its task of making the building blocks so it can replicate: DNA is divided into message units (each message unit is a gene) and each unit contains information about how to make one particular kind of enzyme molecule—one particular kind of protein. The duty of those protein enzyme molecules (in a typical cell, there are a few thousands) is to transform the available kinds of food molecules into the materials necessary to make more enzyme molecules. And the machinery is there so that the duty of some kinds of enzyme molecules is to transform the available food into building blocks for DNA replication.

So it is as simple as that. The DNA makes enzymes, and the enzymes take the food and make it into the building blocks so the DNA can replicate so there can be more cells.

Now, if we are a simple organism like some miserable bacterium in which all cells are identical, that is all there is to it. The bacterium has about 2,500 genes for making 2,500 different kinds of enzymes, and the majority of those genes are continuously and at all times during the life of the cell making all the kinds of enzymes contained in that cell.

But let's not look only at microorganisms. Let's look at impressive creatures like ourselves or pea plants. Pea plants are more impres-



"Maybe some day your doctor will say, 'Well I think your heart isn't so good now. We had better start growing you a new one, and in two or three years it will be grown, and we can plumb it in.'"

—JAMES BONNER

sive than we are because they have twice as much DNA per cell as we do. The reason they have all that genetic information is that they have to know more organic chemistry, because pea plants (and indeed all plants) have to be able to synthesize all of the materials required for making cells out of the simplest of materials—carbon dioxide, inorganic nitrogen, a few inorganic minerals, and sunlight.

Even the cleverest physicist or chemist cannot make all of the building blocks that he requires. He has to eat plants in order to get the amino acids which he needs for making enzyme molecules.

In complicated creatures such as ourselves, there are about a trillion cells living together in harmony. These cells are of many different kinds—epidermal cells, nerve cells, muscle cells, and all the other kinds it takes to make us work.

It is odd when you think about it, because each of us starts out from a single cell—a fertilized egg which divides into two, then into four, and then multiplies and multiplies. And gradually, during the course of development, the cells which were originally all alike start to become different from one another and turn into specialized cells.

This problem of how a complex adult creature arises by the multiplication of a single cell is the problem of development and differentiation. Before we understood the nature of cell operation, about all that could be done was to observe that there *is* such a phenomenon as development and differentiation. That is the science of embryology. Today, however, we can try to find out the molecular basis of what it is that causes cells to become different from one another during the course of development.

When we look at the developmental process in the light of our new knowledge of molecular biology, we find that in higher creatures (like us) all the different kinds of specialized cells have the same amount and kind of DNA. This means each cell contains *all* of the genetic information about how to make the whole creature. This isn't immediately obvious, so let me tell you about a clever experiment that shows dramatically how this is so. In this experiment my former colleague John Gurdon, now at Oxford University, uses *Xenopus laevis*, the South African clawed toad. He takes the cells of the lining of the intestine (specialized cells that are never going to divide again but are just going to sit in there and make digestive enzymes for the toad, ultimately die, and never leave any progeny) and scoops out the nucleus that contains all of the genetic material. He then takes that genetic material and puts it into the cytoplasm of an egg of the toad. He has previously scooped the nucleus out of this egg.

When this body-cell nucleus is put into the environment of an egg, with all of the egg goodies in it, it thinks that it must be an egg nucleus, and so it starts to make more DNA and to divide. And from this egg containing the genetic material from a body cell develops a tadpole and then the adult *Xenopus laevis*.

So then, all of the genetic information about how to go through the whole developmental and reproductive cycle of an adult animal is contained in the specialized body cell.

Since there are many different kinds of specialized cells in an adult organism, each containing all of the genes for making the whole organism, it is apparent that in a given kind of specialized cell most of the genes must be turned *off*—that is, not making their gene product.

For example we have the genes for making the two hemoglobin proteins polymerase and ligase. Those genes produce the hemoglobin proteins only in a very restricted number of cells—those that give rise to the red blood cells. Those same genes which are present in each of our body cells are turned off everywhere else. How lucky! Otherwise we would make hemoglobin on the outside of our bodies.

In order to find out about how the developmental process works, we see immediately that we should focus our attention upon what makes it possible for some genes in the cell to be turned off (repressed), and in other cells to be turned on (derepressed). Next we need to learn how a gene that is turned off can get turned on again. And finally, to study development we ought to find out something about how the programming of genetic activity works. Clearly there must be, in the genetic material of the organism, some further system that provides that the right genes be turned off and on in the right place in an orderly sequential way, so that the right specialized cells end up in the right places to make an adult organism.

Obviously this programming of gene activities must reside in the genetic material, because our adult form is hereditary, and everything hereditary is contained in the DNA.

During the last few years, biology has made a considerable amount of progress in understanding all three of these aspects of the developmental process. This is, in part, because the functions of the cell are divisible and separable from one another. We know how to remove the genetic material from the cell and put it into a test tube—out in public where you can see what it does and where you can diddle with it and find out about the chemistry and physics of this material.

We have found that in any given kind of specialized cell of a higher organism *90 percent or more* of the DNA is turned off and unavailable for expressing itself by making its protein products. It is turned off by one kind of enzyme—one of many thousands of kinds of enzymes in a cell—whose duty it is to sit on the DNA and make that DNA be turned off. These repressive proteins are very similar in all organisms, from humans to the lower organisms.

In addition, we have found out something about how the switching of gene activity is controlled. We know that there are small molecules which can enter a cell and cause genes which were previously turned off to be turned on again. One example of such molecules are the hormones. The hormones are simple chemical substances which have only a few dozen atoms in them, so they are simple enough to be studied by chemists.

Hormones are made in a particular spot in the body, and then they go to other spots called "target organs" where they evoke certain effects. For example, the adrenal cortical glands make the hormone cortisone. The cortisone enters the bloodstream, goes to the liver, and says, "Liver, make me some of each of the following 12 enzymes." There are 12 genes in the nucleus of each cell in the liver which have been repressed and which are then derepressed by the arrival of the cortisone. So the cortisone does its work by entering the cell and, after a series of intermediate steps, complexing with the genetic material and removing the repressors of the genes which are to be derepressed.

We know that many different classes of small molecules besides hormones have the same effect. They can enter the cell and transform the genes from the turned-off to the turned-on state and vice versa.

There is one other important concept in the programming of gene activity that contains two basic principles. The first is that in some

instances, when a particular gene is turned on, the product of that gene can then go and turn on a second gene. So there are chains of a successive turning-on of one gene, resulting in the turning-on of a sequence of genes.

The second principle is illustrated by the following: Suppose we want to study about how the orderly development of an organism occurs. I have found that a good way is just to imagine that you are a cell and think about what kind of instructions would enable you to divide and divide and turn into something sensible.

We know that cells in the developing organism are continuously monitoring their environment and seeing what kinds of things are out there, and as a result they are turning on the right genes to develop into the kind of cell appropriate to that environment.

Let me just give you a very simple example of how this *developmental test* works in a particular organism. A potato tuber is made of cells just lying doggo waiting for somebody to come along and eat them. Essentially they have all their genes turned off. But if you cut a thin slice out of a potato tuber, the cells at the edge of the slice all get busy and start dividing trying to make a new skin.

We can imagine the cells in the potato tuber each day monitoring the outside and saying, "Aha, there are potato cells everywhere, and it says here I'm not supposed to do anything." But one day they look out and the cells at the edge say, "Aha! I have potato cells on one side and nothing on the other side. And in that case, it says here, 'Go to page 47—or to gene 47. There are the instructions on how to turn on the right genes for becoming new epidermal cells.' "

It does no good to preserve
the other parts of the body intact
if the head goes to wrack and ruin.

The way potato cells tell whether they are on the inside or the outside is that they are continuously producing a diffusible substance; as long as the potato is whole, that substance diffuses very slowly. Its high concentration is what turns off the genes of the tuber cells. But as soon as it is cut, the substance diffuses away from the cells on the edge. That results in the turning-on of the correct genes for the epidermis.

Even more dramatically, if a single potato cell is put all by itself in a nutrient solution that contains the embryonic growth goodies that plant embryos grow up in, that single cell will turn into an embryo, develop into a seedling, and go through the whole life cycle of growing into a higher plant.

We know enough about the developmental process to realize that it will one day be possible to know *so much* about it that what is left to find out won't be interesting. We will know enough about the developmental process to be able to use this information in very specific and useful ways.

Let me cite some examples: We know that many lower organisms have embryonic cells left at the base of the limbs which, if the limb is lopped off, can then regenerate a whole new limb or a whole new organ. And we know now how to take a cell—as in the case of the toad or the potato—and change its stance of gene activity to make it think it is a fertilized egg. So in the future we should be able to reset the genetic program of a cell to any desired point to make that cell or group of cells turn into a new organ. Maybe someday your doctor will say, "Well, I think your heart isn't so good now. We had better start growing you a new one, and in two or three years it will be grown and we can plumb it in."

In a very real sense the regeneration of organs with the same genetic constitution as that of the potential recipient would, of course, have all sorts of advantages. We'd get around the whole host-rejection phenomenon.

One of the most troublesome problems in the longevity of human beings is concerned with the nerve cells which make up our brain. Each of us is endowed with ten billion nerve cells in our brain. They are given to us in embryonic life. In later life we never make any new ones. After the age of 35 or so they start to die off at the rate of about 100,000 a day. You don't notice it for a few days, but ultimately you do. Loss of memory and the senility of old age are due to this continuous dying-

off of the nerve cells of the brain. They die because of little accidents in the circulation that deprive them of oxygenation. Maybe some of them get fallen on by fallout and all sorts of accidents like that. And it does no good for our National Institutes of Health to preserve the other parts of the body intact if the head goes to wrack and ruin.

We might try to fight this process. There are other cells in the cortex of the brain that are not nerve cells. So with our new knowledge of how to control the developmental process, we might hope to be able to judiciously turn the

The normal expectation would be that some better kind of creature will come along and make us extinct.

required number of both cells into the pathway that causes them to develop into new neurons and to replace the 100,000 that die each day by a new 100,000 neurons. Of course these new neurons would not contain any information—they would just be new empty neurons. But we are told today that we should spend one-third of our total time in continuing adult education or we will become obsolete. So maybe to have 100,000 nerve cells dying each day, removing obsolete information, would actually be a good thing. We could use the new nerve cells to help us learn all of the new information we have to keep constantly acquiring in order to avoid obsolescence.

Then, most importantly, I would expect that our information about the developmental process, and indeed our whole new knowledge of the molecular basis of heredity, could be used to control man's evolution.

Since the beginning of life on earth, there have been more than 100 million different species of plants and animals invented by evolution. And 98 percent of them are now extinct. The normal expectation for a species such as our own is that we will ultimately become extinct too. That is the *statistical* likelihood, and it is not a very tasty prospect. We know from the works of anthropologists that there have been other species which have preceded us—like Neanderthal man—and he is extinct. He lived contemporaneously with *Homo sapiens on earth, and we probably* extincted him.

So the normal expectation would be that some better kind of creature will come along and make us extinct, were it not for the fact that we are the first species of organism to understand and, hopefully, to be able to control and direct our evolutionary processes.

Among the steps which our human species might take to improve its genetic endowment and its chances for survival are these: One is the controlled breeding of human beings in order to disseminate more widely the best genes. Another is to undertake vegetative reproduction of those individuals who possess desired characteristics. There is nothing to prevent us from taking two body cells from that same donor and growing two identical twins having the genetic constitution of the donor of the body cell. In fact, there is nothing to prevent us from taking a thousand.

Also in principle there is nothing to prevent us from growing any desired number of genetically identical people from individuals who have what we asses as highly desirable genetic characteristics. They won't, of course, have the learning and the wisdom of the donor. Learning and wisdom have to be acquired. Our genes give us the structure of our brain, not its thought content.

Those are some ways in which our knowledge of developmental and molecular biology could be used to improve our human race by improving its quality of genes. By the same token, as we acquire more information about the operation of the brain and about the optimum methods of teaching and training and educating and optimum modes of personality formation, we will, of course, extend these kinds of control of the environment over our young to expose them to the optimum influence for development of stable, intelligent, highly educated, highly motivated individuals. And when the time comes when we pursue these policies, we will have, indeed, a new and super species of human being.

In any case, it really appears to be within our power—if not today, then in the very near future—to cause our species to develop along any lines which we deem desirable.