ADVENTURES

of the MIND

The Messages

About the Author

James Bonner, professor of biology at the California Institute of Technology, researches the biochemistry and physiology of plants, enzyme synthesis, and the nuclear-cytoplasmic structure of the cell. The author of several books on these subjects, Professor Bonner also is interested in the future of plant-animal relationships as they bear on the problem of supplying food for the earth's expanding population. No book-bound scholar, Professor Bonner spends many of his winter weekends in the California mountains serving as a ski patrolman for the National Ski Patrol System.

Biology is today on the edge of understanding how living things live. This almost-successful search for the principle, the logic, of life may someday enable us to control the step-by-step development of the human organism, to cultivate replacement organs and perhaps even to initiate life in isolated cells. A whole new world of medicine also awaits us across this threshold of understanding; among the most urgent problems which may yield to the new knowledge are the control of virus diseases and of cancer.

This new biology—for it is a new branching of an old discipline—is largely concerned with the molecular facts of life. One of the most complicated mysteries of nature is the way the tens of thousands of chemical compounds that compose a living creature work together to cause that creature to breathe, digest and leave descendants. But this mystery is being unraveled. Every day now brings new excitement as research biologists draw close to its final solution. For they have discovered that each cell of each individual contains a blueprint, an instruction manual, which gives the cell detailed instructions on what kind of chemicals to make from the available food, on how the cell shall divide or replicate itself, on the size and shape of the systems it shall form (that is, elephant or mouse)—in short, how the cell should become a part of a particular kind of living thing.

This cellular instruction manual, which biologists call "genetic material," possesses the extraordinary power of being able to print copies of itself. These copies are then passed on to the next generation. In this way living things leave their descendants directions on how to look, how to behave, how to be. The new biology seeks to read this genetic book and to find out what kinds of instructions it transmits, how

Biologists unravel the secrets of DNA, the remarkable substance that contains the genetic blueprints for all living organisms.

of Life

By JAMES BONNER

the genetic information multiplies itself, how it acts, how it enforces its decrees.

The gateway to this new understanding of the basic life pattern has been found in the study of the living cell. All creatures consist of cells and have in common cells which are very much alike. All cells are made of various standardized types of components. Living creatures may, in fact, be looked upon as a series of models made of a kind of tinkertoy, with standard interchangeable parts. For example, the largest and most spectacular part of every proper cell is a nucleus. This nucleus contains the genetic material, the chromosomes, each made up of many genes. The genes are made of a special gene substance found nowhere else—deoxyribonucleic acid, known to biologists as DNA. The DNA of the nucleus contains, in coded form, all the information required to assemble the individual cell—and indeed, to assemble all the cells comprising an entire organism.

That DNA contains—and transmits—genetic information, was first shown by O. T. Avery at the Rockefeller Institute more than fifteen years ago. His experiment consisted of the transplantation of genetic information from one type of bacterial cell to another. The laboratory transplantation of such genetic information requires only that a portion of the DNA of the donor cell be placed in solution, together with some of the receptor cells. The receptor cells, in a fraction of cases, incorporate the alien DNA into their own genetic complement so that it becomes a permanent part of their genetic information. In this way genes for resistance or susceptibility to an antibiotic, or for ability or inability to cause disease—such as pneumonia, with which Avery worked—may be transferred from one strain of bacteria to another.

DNA has two characteristics which suit it uniquely to its role of information bearer. The first is a structure so arranged that it can carry information. The DNA molecule is a long chain, made up of four kinds of links, or building blocks, whose chemical names we can symbolize by the four letters, *A*, *T*, *G* and *C*. The four links may succeed one another in any of many permutations and combinations to produce many different words, all written in a four-letter alphabet, the alphabet of *A*, *T*, *G* and *C*. The DNA molecule is thus a sort of telegram, written in DNA language, which carries messages indicating how a cell shall develop and proliferate. We might call DNA a do-it-yourself book of instructions to its host cell.

The second unique property of DNA is its ability to produce exact copies of itself. DNA can so replicate because it is a twin molecule with two long strands, each composed of the building blocks *A*, *T*, *G* and *C*. These two strands are wound around each other to form a helix, a molecular barber pole. And it is a basic law of living matter that the sequence of the letters *A*, *T*, *G* and *C* in the one strand determines the sequence of letters in the companion strand. *A* in the one strand must be paired with *T* in the second, *G* with *C*, *T* with *A*, and *C* with *G*. The two strands are, as biologists say, complementary. We believe that when the DNA replicates itself, the two strands first separate, and that each then assembles upon itself its complement, using the chemical building blocks available in the cell. When the replication has been accomplished, we have two new double strands, each indistinguishable from the original, but bearing the same coded information as the original.

The double-stranded complementary structure of DNA, first recognized by James (*CONTINUED ON PAGE 105*)

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Watson of Harvard University and Francis Crick of Cambridge University, is a concept of great significance. It suggests the basic operation by which a living organism reproduces itself. And it appears that of all the substances in the organism, only DNA possesses this power of replication. All other substances are directly or indirectly made by the DNA. The DNA might be likened to a queen bee, hatching out workers who cannot leave descendants. Only the queen bee can proliferate—only the queen can produce the infertile workers and, from time to time, a new queen bee.

The DNA is then a set of self-replicating instructions, constituting the genetic material within the nucleus of the cell. But whence do the instructions come? How are they carried out? To answer these questions, the biologist leaves the central nucleus and he prospects in the surrounding cytoplasm of the cell.

A cell contains of course a multitude of parts. In addition to its nucleus, for instance, a plant cell possesses chloroplasts. These contain not only the chlorophyll which makes plants green but also the machinery for photosynthesis, which converts carbon dioxide and the energy of light into the plant material all of us nonplants use for food. All cells also contain units of a smaller order called mitochondria—the cellular powerhouses which burn the food and supply the energy for our muscular work, the operation of our nervous system and the process of chemical synthesis within the body.

All these cellular units are small, but they are large enough to be seen through a microscope, and biologists have been observing them for a generation or more. To find the direct linkage between the units in the cellular chain of command, biologists have had to descend into a still smaller world—a world observable only after the introduction of the electron microscope in the 1940's. On this minute stage—an area where the common unit of measurement is the angstrom, or the fractional part of one hundred millionth of an inch—the most interesting objects are the cellular enzymes and the microsomes.

One of the triumphs of modern biology has been the demonstration that each of the cell's chemical reactions is speeded on its course by a specific kind of enzyme with the sole duty of hastening that particular reaction. Because the cell carries on several thousand kinds of chemical reactions, it contains several thousand kinds of enzyme molecules. We know that the enzymes a cell produces are genetically controlled—that for each enzyme there is a gene in the nucleus which orders the cell to make that particular enzyme. Since there are about 10,000 kinds of enzyme molecules in a typical cell, there must be at least an equal number of genes in the nucleus of the same cell.

A striking example of this one-for-one relationship is an enzyme found in victims of the hereditary disease called sickle cell anemia, characterized by abnormal hemoglobin of red blood cells. We now recognize the cause of this enzymatic abnormality as a hemoglobin-determining gene different from the normal.

Among the many things we know about enzymes is that each consists of a unique chemical material. All enzymes are protein, that complex material which forms so large a part of all living matter, and all are made up of the same twenty kinds of amino-acid building blocks. An enzyme molecule consists of several hundred of these building blocks linked together in a long chain. What makes a particular kind of enzyme a unique material is the sequence of the building blocks. We may say, therefore, that an enzyme molecule is, like DNA, a message, but a message written in a twenty-letter alphabet—the alphabet of the twenty naturally occurring amino acids.

The cellular enzymes perform various essential tasks in the transformation of food into cell substance. But before an enzyme molecule can perform its task, it must first be assembled by the cell from the amino-acid building blocks. One of the exciting discoveries of the new biology is how the cell makes its enzyme molecules. It is a most logical arrangement. The cell contains superenzymes, called microsomes, for making ordinary enzymes. Though the microsome is about 100 times larger than the enzyme molecule, it is still so small that we can see it only with the electron microscope.

The functioning of a microsome depends upon a full set of built-in instructions. To make one particular enzyme—the hemoglobin molecule, for example—600 building blocks of twenty different kinds must be properly stapled together in the correct sequence. The building instructions are written in the microsome in coded form. The essential portion of the microsome is thus a coded directive about what kind of enzyme to make and how to make it. The building blocks of which the microsome is made are much like those of DNA, with the addition of a single chemical group essential to enzyme synthesis. The nucleic acid of the microsome, ribonucleic acid, or RNA, is more specific than the DNA of the genetic material in one respect—RNA can make enzymes; DNA cannot. But DNA can replicate itself, and RNA cannot.

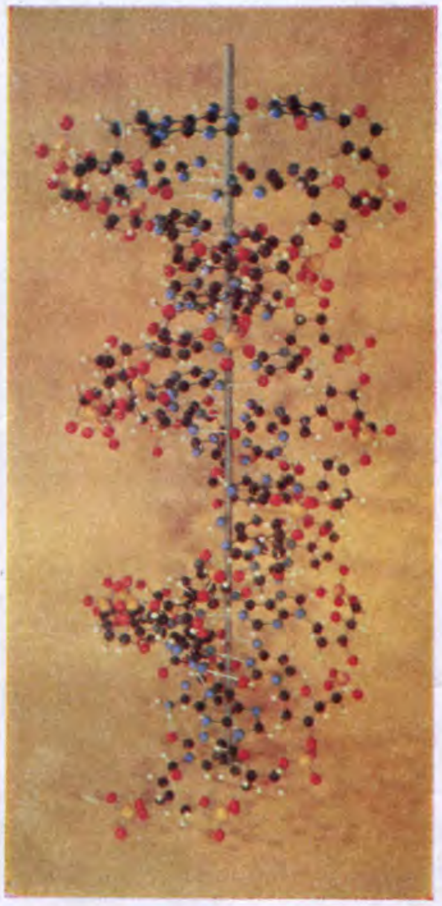
Microsomes, then, make enzyme molecules. But we also know that the DNA of the genetic material is the original source of the cell's information about what kinds of enzyme molecules to make. Clearly the genes somehow determine the kind of information contained in the microsome. Microsomes, in fact, are apparently made in the nucleus and then distributed throughout the rest of the cell. Further, it appears that the formation of microsomal RNA in the nucleus takes place only in the presence of the DNA, for if the DNA is removed, the cell loses its power to make microsomal RNA.

We do not know exactly how the genetic DNA makes the microsomal RNA. Obviously the next great step is to find out. We could, for example, put some DNA in a test tube and ascertain what else has to be added to cause RNA to be made. For the present we can say that the genetic material has two functions—(a) it can replicate itself or (b) it can synthesize RNA. This RNA is packaged as microsomes which go out into the cell and make enzymes.

The amount of information contained in the RNA of a single microsome is quite small compared to that contained in all of the DNA of the nucleus. We think, in fact, that it just about equals the information contained in a single gene. If this is true, a single microsome probably contains the message of but a single gene. One gene, therefore, would contain the information necessary to make one kind of enzyme. To get this information acted upon, the gene produces its special kind of microsome within the nucleus; the microsome then sifts through the nuclear membrane and out into the cell, where it manufactures the specified enzyme. Since the genetic material of the cell consists of several thousand genes, it follows that the cell contains several thousand kinds of needed enzymes.

The success of any organism is measured by the number of descendants it leaves. The cell that leaves the most descendants wins out and populates the earth. But the division of cells to make more cells requires the multiplication of the genetic material, the replication of the DNA. Each unit of genetic information, each gene, each chromosome, must double before cell division can take place. The two daughter cells, products of the cell division, each contain genetic information characteristic of the original parent cell—characteristic in amount and kind.

In terms of the cell, multiplication is the goal of life, and multiplication means replication of DNA. And now we can sense the logic which requires the presence in the cell of the varied things which it contains. The genetic material of the nucleus contains information. This information is somehow transferred to microsomes. The microsomes go out into the cell and use this information to make enzymes. Some of these enzymes make building blocks for making more enzymes. Others make building blocks for making more RNA to make more microsomes. But—and most importantly—a portion of the enzymes are those which make building blocks for DNA, so that the genetic material may multiply, so that, in turn, the cell may produce more cells. A cell is a device arranged by the DNA to provide for its own welfare, to provide it with conditions suitable for its own replication. We might even say the same thing for the whole living creature.



Model of segment of a long, chainlike DNA molecule showing helical structure and linkage of four basic chemical compounds.

In the logic of the living cell, then, the RNA and the enzyme molecules all originate with DNA. The DNA originates from itself, using its own body as a model. Where did the first DNA come from? The question of the origin of DNA thus is the question of the origin of life.

No one has yet synthesized life. It should, however, be possible. One would have to make some DNA and then put it in a soup containing the *A*, *T*, *G* and *C* building blocks that DNA needs to reproduce itself. The DNA should then be able to reproduce and make more DNA. Ultimately the replicating DNA would use up one or another of the ingredients—say, *A*—and replication would cease. Thenceforth only the occasional DNA molecule which had acquired information on how to make *A* from some other precursor would be able to reproduce.

This acquisition of new information by a DNA molecule is known as mutation. Geneticists believe that mutation consists of little errors which occur from time to time in the replication of the DNA. Possibly a *G* is inserted where an *A* should be, or one letter is left out entirely, or an extra letter is put in. Once made, the error is ruthlessly replicated during the course of DNA multiplication—just as a printing press replicates all of the errors of the typesetter.

In any mutation, the altered DNA molecule will contain information slightly different from that of its parent. Often this new and randomly acquired information will serve no purpose. Occasionally, useful new information will be acquired. The properly mutated molecule will have a selective advantage over its nonmutated mates—it would be able, in our first example, to make *A* building blocks from some appropriate precursor and continue the production of the slightly different kind of DNA. This is natural selection at work. In time the system will run out of something else, such as the precursor of *A*. Only those DNA molecules will survive which have, by mutation, acquired the capacity of making the precursor of *A* from still another precursor.

Thus we can imagine that, as the DNA molecule reproduces and mutates in a soup containing all imaginable substances, mutation and selection will gradually enrich the soup with those DNA molecules which possess more and more sophisticated synthetic ability.

This is the kind of model most biologists today believe to be a reasonable one for the origin of life on our earth. [See HOW LIFE BEGAN, by E. A. Evans, *The Saturday Evening Post*, November 26, 1960.] They conceive that aeons ago the oceans were a sort of primordial soup, containing an almost infinite variety of organic compounds which persisted because there were no creatures to feed upon them. The first living creature to appear in this soup must have been a simple organism, no more than a molecule constructed by random organic chemistry, yet a molecule capable of replication and mutation, so that it could adjust to changing circumstances. It must have been a molecule of DNA. And, over the ages, this aboriginal DNA molecule gained the ability, by mutation and selection, to house itself within membranes and to produce cells. From cells arose, likewise by mutation and selection, the wonderful array of living things.

A single cell is, of course, just the beginning of a complex creature such as man. Each of us, however, does develop from a single cell—the fertilized egg. The fertilized egg cell divides into two cells. Each of these divides into two, and so on. As the process continues, individual cells begin to differentiate into different types of cells—structural cells, glandular cells, secretory cells, reproductive cells, nerve cells. We know such differentiation consists basically of differentiation in enzymatic constitution—different kinds of cells containing different kinds of enzymes that, in turn, produce different structures and functions.

But this leads to a paradox. Each enzyme is apparently produced by a particular kind of microsome, derived from the DNA—quite possibly the DNA of a single gene. We know that all cells of a creature have (*Continued on Page 107*)

(*Continued from Page 105*) the same total complement of DNA and thus have all of the genes characteristic of that creature. Accordingly we should expect all cells to contain the same enzymes and therefore the same characteristics. How do cells of a single creature develop into different types?

The inescapable conclusion is that all genes do not always make their characteristic microsomes, their characteristic RNA. As an extreme example, take the cells which produce hemoglobin. In these cells all genes except those concerned with the production of microsomes for the synthesis of hemoglobin are inert; they are inoperative. Conversely, in the adult organism the gene for making hemoglobin is inoperative in all of the cells except those in the bone marrow which are concerned with the making of red blood cells.

It would appear, then, that part of the cellular system controls the activity of the genes within the nucleus, determining whether a given gene may produce its characteristic microsomes. We do not yet understand the nature of this control. Perhaps certain genes are responsible for it. Perhaps part of the information in the DNA directs the use of the rest of the information. Perhaps a portion of the DNA

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Small Wheel:
Will Travel

Of all clichés, trust this the
least:
"The squeaking wheel is
soonest greased."
I squeaked, all right, but
what a waste!
I wasn't greased; I was
replaced.

Irene Magee

... ...

sends out signals informing each gene when it should be operative and when inoperative.

If biologists can learn how to turn the genes off and on, they will have taken the first step toward controlling the development of the fertilized egg into an adult organism. With such knowledge we could remedy defects as they appear in the developing child, replace worn-out organs and perhaps even initiate embryonic development in cells removed from the adult body.

Many current medical problems will yield to our increasing knowledge of cellular activity. We already know that some kinds of viruses are essentially pieces of DNA which can enter a cell and there replicate, foraging on the host cell for nutrients as they make more viruses. This is true of the bacteriophages, the viruses which attack bacteria. Other kinds of viruses, including those of influenza and polio, are more complex and consist essentially of portions of RNA.

Though we do not yet know how these viruses multiply, we do know how to attack the problem. We must find out whether the host cell's DNA is necessary for the production of the RNA of the virus—as it is for the production of microsomal RNA—or whether the virus RNA, unlike the microsomal RNA, can multiply itself. Such knowledge might help us arrest the growth of disease viruses without harming the host cells.

As for cancer, though we can now describe the various forms of this disease and though we know there are many different agents, viruses and irritants which induce cancers, we still do not understand the basic mechanism which transforms a normal cell into a cancerous one. Possibly a cancerous cell is one in which a large number of genes are operative, genes which would remain inert in the normal course of development. Some part of the carcinogenic process may cause the cancerous cell to start producing microsomes for producing enzymes which that cell does not ordinarily produce. Perhaps, to use an exaggeration, a cancerous cell is a cell in which all the genes are operative. We do not yet know the answer—but we expect to find it.

The new biology I have described is largely concerned with the molecular facts of life. Our progress has enabled us to make more clearly the boundary between molecular biology and the biology of even more complex matters—human behavior, for example. A fertilized egg cell develops into a creature—a human being, for instance—in response to instructions contained in the genetic material. Written down in the DNA is a vast amount of information—instructions on how to make all the cells and tissues and arrangements needed to assemble a man. Part of the instructions contained in the DNA of a human being direct the construction of a vast network of nerve cells, the brain and its associated sense organs.

Once assembled, this neural network is capable of receiving, through the sense organs, information about the outside world. It is also capable of storing, processing, sorting and acting on the information it receives. Though DNA contains instructions on how to make a human brain, it does not put information into this brain. The brain starts off with a clean slate. Each of us gathers his own information and acts upon it in accordance with what we learn and feel. Neurobiology, the biology of the neural network, is supramolecular biology. Its study is a challenge for the biologists of the future.

But the biology of today is molecular biology—life seen as the ballet of the big molecules, the dance of the DNA. The new biology promises much for human welfare; it has already provided much understanding. Through it we have learned that each living creature is, biologically, a cellular instruction manual written in symbolic genetic language, the language of the DNA. The DNA makes the RNA; the RNA makes the enzymes; the enzymes make the building blocks for making all three. The molecular logic of the animate world rests on this tricycle of life.

THE END

For readers who would like to pursue the subject further, the following books are recommended:

Swanson, Carl P.
The Cell,
Foundations of Modern Biology series
Prentice-Hall
$1.50

Gerard, Ralph W.
Unresting Cells
Harper
$4.50

Hutchings, Edward, Jr., Editor
Frontiers in Science
Basic Books
$6.00

Butler, John A. V.
Inside the Living Cell
Basic Books
$3.50

The Physics and Chemistry of Life
Edited by *Scientific American*
Simon and Schuster
$1.45