Symbolic model of life-giving DNA molecule. Scientists can see how first DNA might have been formed in primordial seas.

In today's most fascinating mystery story, scientists feel they are close to learning

THE SECRET OF LIFE

By MAX GUNTHER

"THIS century will go down in history as the century when life ceased to be a mystery," a famous biochemist said recently. "Life is only chemistry. It is complicated, yes. But we no longer have any reason to believe it is beyond human understanding."

Few people realize how close that understanding may be—or how broadly science is pressing its attack on the mystery. In a wide-windowed laboratory on the rolling "campus" of Washington's National Institutes of Health, for example, one group of researchers is working with a strange group of man-made chemicals. Dumped into a solution similar to the environment of a living cell in the body, these chemicals create the molecules of which living tissue is composed in exactly the way an animal or human cell does. The chemicals are, in effect, artificial genes, the units of heredity, and the experiments foreshadow a day when man, making genes at will, can fashion plants, animals or human beings to any desired specifications.

In a smaller, quieter lab at Johns Hopkins University, another scientist studies gene chemicals in the nuclei of frogs' eggs and compares them with corresponding substances in the cells of adult frogs. He is trying to find out why living things grow old. His studies may contribute to a fantastic lengthening of the human life span.

In the brightly lighted, bottle-lined laboratories of the Sloan-Kettering Institute for Cancer Research in the heart of New York City, biochemists are trying to discover why cell growth occasionally gets out of control. They believe that the answers here, too, may lie in the genetic chemicals. When found, the answers should lead to the defeat of one of man's most dreaded diseases.

These scientists and hundreds of others like them, all around the world, are chipping their way toward a breakthrough that may be the most far-reaching scientific discovery in all human history. For the two remarkable chemicals whose secrets they are unfolding are the basic genetic patterns that shape every living thing on earth.

One of the chemicals is DNA (deoxyribonucleic acid). The other is RNA (ribonucleic acid). Both are found at the very core of life, in the nuclei of cells—which is why they are called nucleic acids. Not only do they control all life; in a sense they *are* life. They are found *only* in living things, and they occur in *all* living things, apparently operating in precisely the same way whether in a single-celled microbe or in the cells of a dandelion, a cockroach or a man. These two nucleic acids determine what every living thing is, how it develops from conception to maturity, what it looks like.

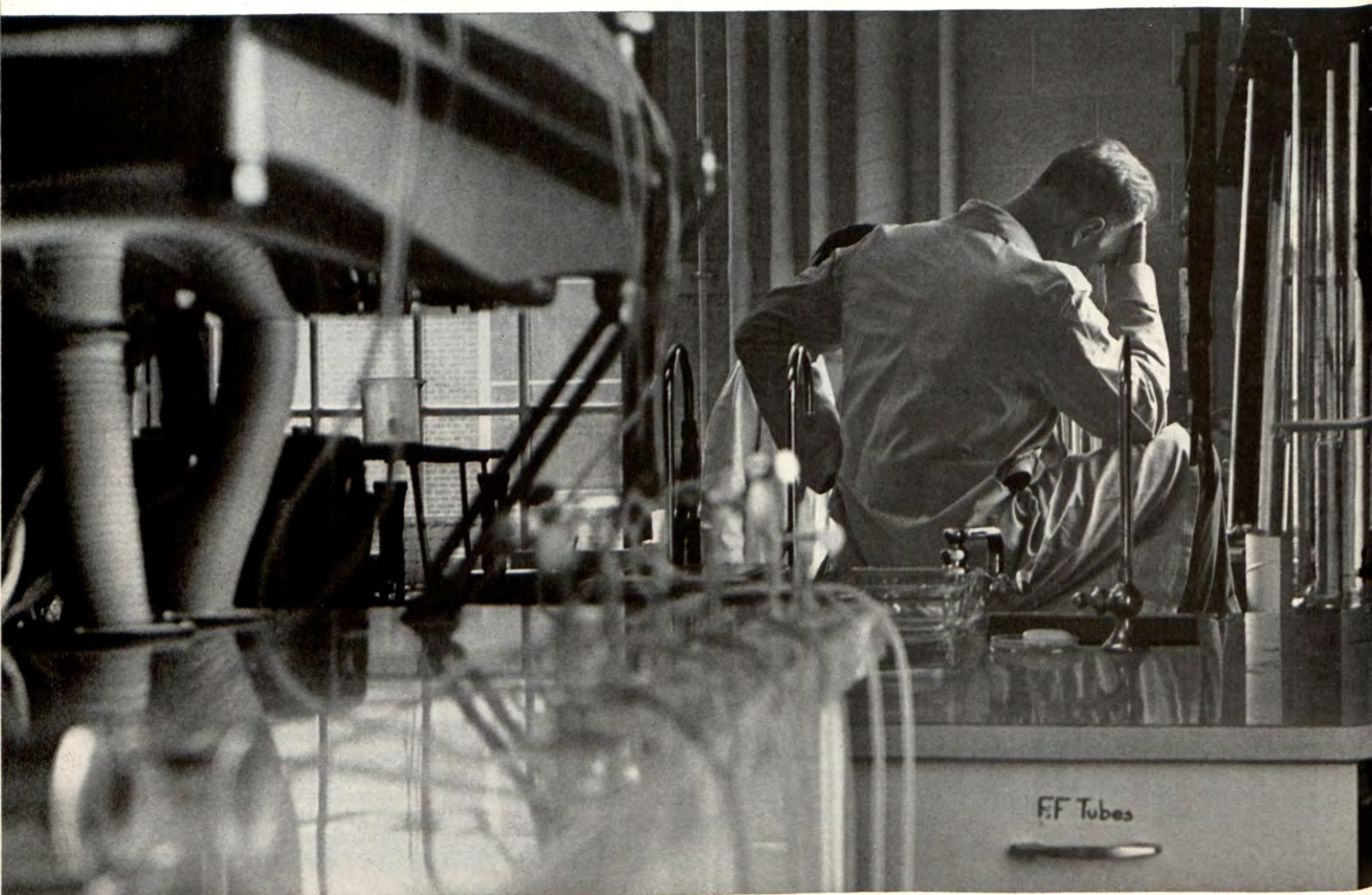
The nucleic acids were first discovered—in white blood cells and fish sperm—by an Austrian chemist named Friedrich Miescher in the late 19th century. Miescher had no idea what function the substances served. But gradually, decade by decade, clues came from various parts of the world.

The great scientific detective story reached an important turning point in 1944. In that year Dr. Oswald T. Avery and a group of colleagues at the Rockefeller Institute were working with the pneumonia germ, the pneumococcus. Most pneumococci, the virulent ones, are encased in a gelatinous coat or capsule, but occasionally there appears a harmless freak or mutant strain without a coat. These mutants have failed to inherit the ability to make coats or to pass on the coat-making trait to their offspring. But when the Rockefeller scientists extracted long threads of pure DNA from a culture of ordinary pneumococci and added it to a culture of the coatless germs, a strange thing happened. The coatless germs suddenly began to make coats. More important, their progeny did also, and so did the generations that followed.

For some scientists, that settled it: DNA was the controller of heredity, the carrier of the patterns on which living things are built. Moreover, it could be transferred as a pure chemical from one group of organisms to another, changing the latter's pattern of heredity. But other scientists raised questions. In particular, they found it hard to reconcile the simplicity of DNA with the complexity of a living creature. DNA had been shown to be built of only four different kinds of molecular subunits, called nucleotides. Each nucleotide has as its main component, or "base," a single substance. The four are adenine, thymine, guanine and cytosine, usually designated by their initials, A, T, G and C. How could something so simple form a pattern for a creature with billions of varied cells?

Gradually a theory evolved that answered the question. All living things on earth require protein molecules for their growth, and each protein, in turn, is composed of one or more of about 20 amino acids. According to the theory, DNA uses its four bases as letters in an alphabet with which it spells various "codewords." Hundreds of thousands of these words, arranged along the spiral-shaped molecule, specify the order in which amino acids are chemically hooked together to make proteins and build a living thing.

The double-helix shape of the DNA molecule itself—a long, twisted ladder of which the four nucleotides form the rungs—was discovered by three



Sitting in his laboratory at Johns Hopkins University, Dr. Clement Markert ponders the course of an experiment. One problem that fascinates him is why living cells grow old.

If heredity can be controlled, who will decide who gets what traits?

scientists in the early 1950's. Doctors James D. Watson of Harvard, Francis H. C. Crick of Cambridge, England, and Maurice H. F. Wilkins of Kings College, London—whose work won them a joint Nobel Prize in 1962—first published their findings in 1953. Since then, they and others have added further details to man's knowledge about the way this molecule transmits its genetic message.

DNA is the master pattern. It stays in the cell nucleus and doesn't directly participate in protein-building but seems to delegate this to its companion substance, RNA, which is also built of four bases. The most widely held current theory envisions "messenger" and "transfer" types of RNA, which pick up information from the nucleus-bound DNA. Carrying codewords, RNA molecules migrate from the nucleus to the sites within the cell where new protein is to be made. There they gather amino acids and direct their bonding-together as instructed by the DNA blueprint.

Not only does the DNA molecule direct the patterning of RNA and hence the making of protein; it also has the unique ability to make an exact copy of itself—the characteristic which permits cell division and hence growth. Each time a cell divides to make two daughter cells, the daughters possess precisely the same DNA that the parent cell had.

You yourself began life as a single cell in whose nucleus was a genetic code describing just how you were to be built. That same information is now located in the nuclei of cells throughout your body and will be passed on to your children.

Much work remains to be done before science has a sharply detailed picture of the way nucleic acids play their roles. "The whole field of molecular biology is in a state of flux," says Dr. John H. Heller, executive director of the New England Institute for Medical Research. "It's a young field. Theories rise and fall daily. But that's one of the things that make the field exciting." Most other scientists in the field share Heller's excitement. There is a feeling among them that any day may bring some final and fantastic breakthrough.

In terms of money and mind power, the drive to crack the nucleic-acid secrets is one of the greatest scientific hunts ever undertaken. At the Sixth International Congress of Biochemistry last summer, 6,000 scientists from a score of nations crowded into the New York Hilton Hotel to talk and listen, and no other subject was mentioned one-tenth as often as DNA. A feeling of suspense permeated the meeting rooms and corridors. "We cannot sleep!" said young Soviet biochemist A. S. Spirin. "We must know more!"

"This is going to be the biggest science story of the century," said the Rockefeller Institute's Dr. Vincent Allfrey "—bigger than nuclear fission."

It seems likely to most scientists that man will soon learn to steer heredity with a precision hardly dreamed of before. "It may be possible to cause mutations that result in certain characteristics which we may consider useful, such as larger brains," says Doctor Allfrey. "We can imagine such a deliberate mutation right now. And if you can imagine something, usually you can do it."

To this end and others, molecular biologists are now tackling the job of deciphering the DNA code. They want to know precisely what each word of the code means in terms of the living tissue that is eventually built.

One group of scientists working on the problem scored a major victory early this year. A team from Cornell University and the U.S. Department of Agriculture, led by biochemist Robert W. Holley, figured out the precise structure of a small RNA molecule.

In a grueling, three-year test of scientific patience, they first isolated about a 30th of an ounce of RNA from 200 pounds of yeast. This was a type of "transfer" RNA. Its special function was to help incorporate the amino acid alanine into the yeast's protein structure. Doctor Holley and his teammates dissected the RNA molecule piece by piece until they knew precisely how it was made. It turned out to be built of some 70-odd units of the four RNA bases, plus certain other units whose function isn't yet clear. Part of this code message—nobody knows which part—presumably says, "Alanine." Other parts must specify how the alanine molecule is to be joined to neighboring molecules in the yeast protein which is to be built, and still others probably give further instructions.

Asked about the importance of this discovery, Doctor Holley seems as much interested in the method as in the result. "We hope the methods we've used will help other scientists work out the structures of other nucleic-acid molecules," he says. What Doctor Holley's team has done, in effect, is to point out a way in which genetic code messages can be read clearly. There remains the problem of finding out precisely what the messages mean.

Many researchers have been trying to do just that. Among these are Dr. H. G. Wittmann in Germany and Dr. Heinz Fraenkel-Conrat at the University of California, who have been working with tobacco-mosaic virus. A virus is a tiny wad of DNA or RNA (it can be either) wrapped in a protein capsule. Its method of propagation is to get into a living cell of plant or animal and superimpose its own genetic code on that of the host cell. The cell obediently begins making new viruses according to this new blueprint. Colds, polio and other human ailments are caused by viruses that upset cells' genetic machinery in this way. The tobacco-mosaic virus, an RNA type, causes a browning and crinkling of tobacco leaves.

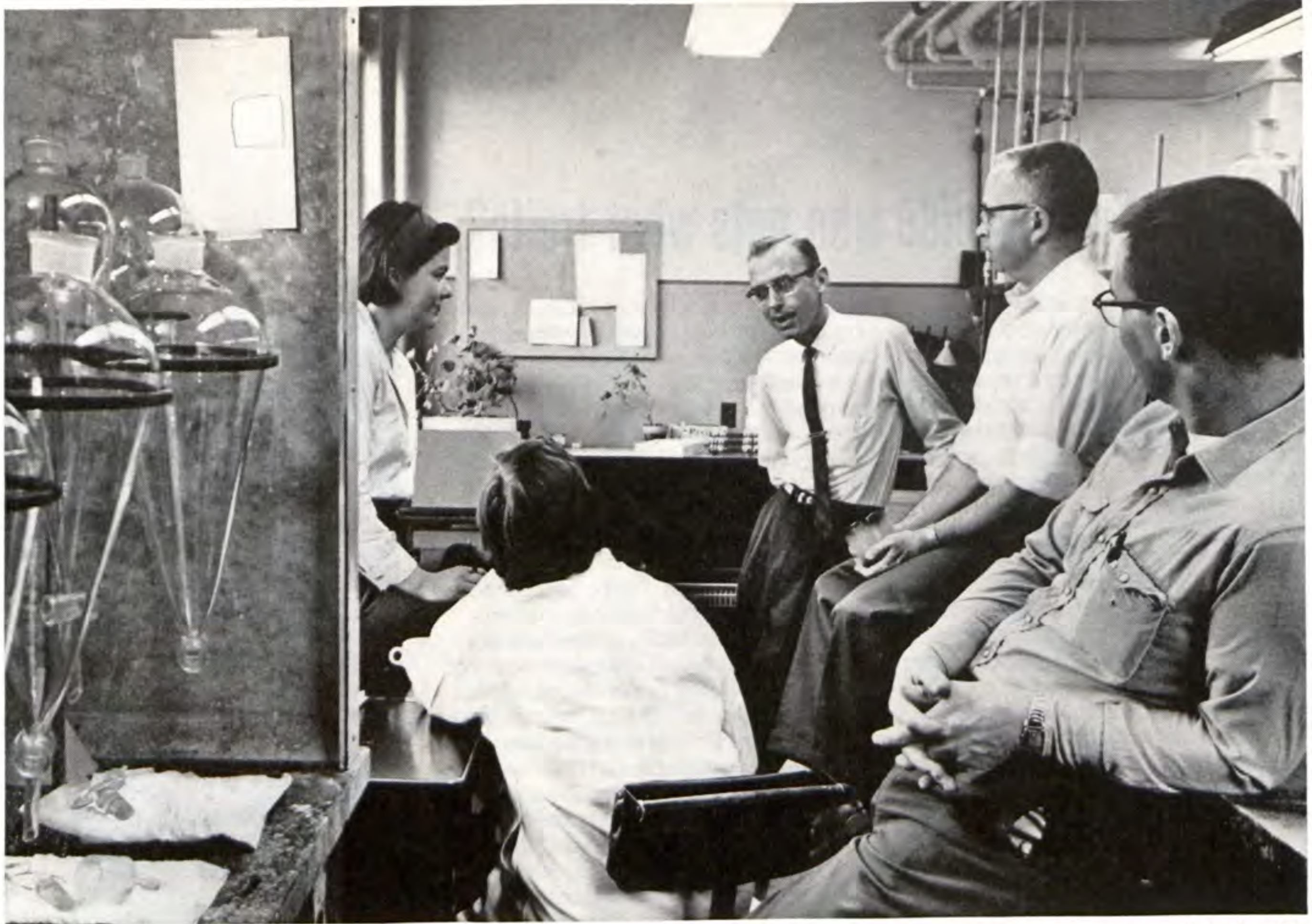
Doctors Wittmann, Fraenkel-Conrat and others have analyzed the protein in the capsule of this virus and have identified its amino-acid components. They even know the order and geometrical pattern in which the amino-acid molecules are put together to make each protein molecule. Knowing this, they have a basis for studying the nucleic-acid code. Their method is to isolate the virus's RNA and to make small, precisely known changes in it, using substances such as nitrous acid. They then infect tobacco plants with this changed RNA. The cells of the plants' leaves make new viruses—viruses whose capsules are composed of proteins differing slightly from normal.

By analyzing the new protein each time and relating the change to the known change in the RNA—and by doing this often enough with enough different mutations—Doctors Wittmann and Fraenkel-Conrat hope eventually to write a kind of two-column list. In one column will be highly detailed RNA specifications. In the other one will be types of protein. And because any given set of codewords apparently means the same thing whether found in a virus or a man, these studies are expected to reveal the way in which

Dr. Heinz Fraenkel-Conrat (top) has been using tobacco-mosaic virus in his studies at the University of California.

Dr. James D. Watson (lower picture) won Nobel Prize in 1962 for his part in discovery of DNA molecule's structure.

PHOTOGRAPHS BY CHARLES HARBUTT



Dr. Robert W. Holley (center) and fellow researchers relax briefly in a laboratory of U.S. Department of Agriculture at Cornell University.

protein is put together in a human being.

Other scientists are approaching the decoding problem in another way. Early in the 1960's two scientists at the National Institute of Arthritis and Metabolic Diseases, Dr. Marshall W. Nirenberg and Dr. J. Heinrich Matthaei, worked out a system for making and testing a synthetic, simplified version of RNA. Their idea was to put this RNA, with known code letters, into a "broth" containing the amino acids and other substances used by a cell to make protein. They hoped the synthetic RNA would act like a genetic blueprint in a live cell, directing amino acids to bond together in a certain sequence to make a certain type of protein. If the idea worked, they reasoned, it would mean they were on the way to writing a genetic-code dictionary.

According to the current theory, this code consists mainly of three-letter words, 64 of which can be made by the four-letter alphabet in all possible combinations. Each amino acid is thought to be specified by one certain word (or, in some cases, by more than one), while the order in which these words are arranged along the tape-like DNA molecule determines the type of protein produced.

Doctors Nirenberg and Matthaei began their experiment by making a strand of synthetic RNA containing only one base, uracil—"U" for short. Thus the strand could spell only one three-letter word, UUU, and its code would simply be a long chain of identical words. If their theory was correct, this strand would direct the manufacture of a protein consisting of only one variety of amino acid.

It did. When the synthetic RNA went into the broth, a crude, simple kind of protein was formed, and it was made entirely of the amino acid phenylalanine. "We now have the first word in our dictionary!" Doctor Nirenberg exulted. "It is spelled UUU, and it means phenylalanine."

This was widely hailed as the first concrete step toward cracking the genetic code. Researchers around the world promptly went ahead to find codewords for other amino acids. One major difficulty was how to determine letter sequences in artificial codewords. A scientist might, for example, mix a batch of synthetic RNA using two thirds uracil (U) and one third guanine (G), but he could not reliably tell whether the word he had spelled was GUU, UGU, or UUG. Despite this and other difficulties, however, British and American scientists have now found the three-letter codewords for all the known amino acids.

Other researchers are meanwhile seeking different avenues from which to attack the secrets of DNA. At the University of Wisconsin, for instance, two biochemists from India, Dr. H. Gobind Khorana and Dr. T. Mathai Jacob, have worked out a method of building whole synthetic nucleotide chains step by step, with the bases—that is, the code letters—in known sequence. "When we are more sure of what we are doing," Doctor Jacob says, "we will see whether we can correlate these chains with specific proteins."

Because molecular biology is a field in which few outsiders feel informed—and because the concepts involved in today's work with DNA are so staggering—laymen find it hard to comprehend the fact that nucleic-acid research is literally dealing with the stuff of life. But when a biochemist can take a handful of laboratory chemicals and transform them into a substance that will, in turn, make protein, he is only a short step away from being able to create life artificially.

On strictly moral grounds, the thought of man's having this power has caused a certain amount of uneasiness among both scientists and laymen. "You can see why people might be worried," says Dr. Edward H. Ahrens of the Rockefeller Institute. "If we ever reach a stage where we can exert a highly detailed kind of control over life and heredity, we'll be in somewhat the same position we were in when we harnessed atomic energy. We'll have something that can be either good or bad, depending on how it is handled." For example, if it becomes possible to control human heredity, who will decide which traits should be inherited by whom?

On religious grounds, recent discoveries concerning the nucleic acids have proved disturbing mainly as they apply to the mystery of creation. Scientists can now tentatively reconstruct the steps by which a universe originally made of nothing but hydrogen could eventually have spawned life.

"DNA is the only large molecule we know that can duplicate itself," says Dr. Allen Fox, geneticist at the University of Wisconsin, "and we can see how the first DNA molecules might have been formed in the sea." In fact, researchers at the University of California and elsewhere have made chemical "models" of the early earth environment as they think it was, have shot electrical charges through these models to simulate lightning and showered them with radiation to simulate intense sunlight. In the resulting broth they have found substances they believe could be precursors of nucleic acids.

Reactions to this version of genesis vary widely. One was expressed by a British scientist who talked out his feelings in a New York hotel room one night recently. "It seems pretty certain to me that life resulted from purely random chemical events," he said. "What's more, I feel certain that in another decade or two we ourselves will be able to create life. I no longer find it necessary to believe in God."

Many theologians, however, do not seem upset by the revelations of nucleic-acid research. Catholics, for example, hold that, no matter how science explains the origin of life, one huge question will always remain: where did the original hydrogen come from? Says Msgr. George A. Kelly, spokesman for Cardinal Spellman in the Archdiocese of New York: "It seems to this nonscientist that human ingenuity will likely reach out to capture more and more of God's power. This is perfectly proper, since God made man the 'lord of creation.' But when a biochemist is able to create matter and energy out of nothing, and this is what Catholics mean by creation, then I would say he is approaching the power of God. And when he has the power to endow life with an immortal soul, then I would like to talk to him."

Another controversial aspect of nucleic-acid science, particularly in view of the world's overpopulation problems, is the possibility that this research may lead to a great lengthening of the human life span. The aging process in living things has never been well understood. Age seems to result from a progressive malfunction of individual cells, and this may stem from malfunctions in the nucleic acids which control all the cell's mechanisms. If the nucleic acids functioned as perfectly in adulthood as they do in childhood, each cell might continue to work indefinitely and life would conceivably be eternal. The question is: Why don't the nucleic acids keep functioning well? A molecule such as DNA doesn't "wear out" the way a car does. What breaks it down?

One theory is that DNA molecules are gradually damaged by cosmic rays and other stray radiation. But another theory focuses attention on a kind of timing mechanism in living things. "There is evidently some sort of 'switch' incorporated in genetic material," says Dr. Clement Markert of Johns Hopkins University. "This switch turns genes on and off at certain times and locations in the body, and if we knew just what this switch is and how it works, we might have a clue to the nature of aging."

When a human sperm and egg come together, they form a single cell that incorporates the DNA of both. This cell divides into two new cells, these two divide in turn, and swiftly there is created a blob of cells all precisely alike. But at some point in the embryo's growth, the cells cease to be alike. Somehow they differentiate, proceeding along separate chemical pathways to result in a human being with hundreds of different types of cells—muscle, blood, skin, bone and so on.

"We want to know how this happens," says Doctor Markert. "As far as anybody has yet determined, the DNA in a muscle cell, for example, is no different from that in other cells of the same individual. It contains all the information necessary to make eyes, skin and other tissues. But why did that particular piece of DNA result in a muscle cell? Apparently only part of the genetic information is being used. Only part of it is 'switched on'—the part needed to make a muscle cell."

As the individual grows to adulthood, other switches operate at certain

Partway to the Fountain of Youth: A frog's egg that never grows up.

times—at puberty, for example. The information required to make cells take on new functions at puberty was in the DNA at the individual's conception. What switched it on?

Doctor Markert and other scientists believe that a clue to the answer may lie in certain proteins found in adult, but not embryo, cells. To demonstrate their presence Doctor Markert has extracted these special proteins from cells of an adult frog and injected them into a frog egg. The egg divides and grows normally until the embryo reaches a certain stage of development. Then it stops. It is not dead, but the adult protein has simply switched off its development.

Doctor Markert is reluctant to speculate on whether studies such as his will lead to a longer human life span. But he allows that it is "reasonable" to hope so. One biologist at the biochemical congress commented, in fact, that it is "not really fantastic" to think in terms of a human life span stretching across two centuries.

Nucleic-acid studies will also give man new weapons in his battle with disease. Many of the most dreaded and baffling human illnesses are genetically caused—by unexplained "misspellings" in the DNA code. Mistakes of this kind may occur in the sperm or egg cells and result in diseases that are passed from parent to child—hemophilia, for instance. Similar mistakes, occurring during development of the fetus, result in birth defects such as Mongolism.

Some extremely complicated and so far incurable diseases may be caused by a single "misspelling" or other mistake in an individual's DNA code. What can be done about it? "There is a wild hope that we may someday learn to superimpose a correct code on a wrong one," says a scientist at the National Institutes of Health. Conceivably a supply of correct DNA would somehow be introduced into the patient, perhaps by infecting him with artificial viruses.

Scientists studying the nucleic acids also speculate, of course, about the contribution their research may make to the quest for a cancer cure. Dr. Aaron Bendich of the Sloan-Kettering Institute for Cancer Research writes that some human cancers, like certain known animal cancers, may be caused by viruses. These may be latent viruses, he suggests, lying in the cells and waiting for some triggering action. Other cancers may be caused by random DNA mutations.

If there is a human cancer virus, scientists would naturally like to find it so they can prepare a defense against it. The search has been going on for over a decade, without success. One reason for the difficulty could be that the virus, if it exists, is a comparatively rare one. "Conceivably it may take only a single virus particle to start a case of cancer," says Dr. David Axelrod of the National Institute of Allergy and Infectious Diseases. "That one virus gets into a single cell and alters the cell's information code. The cell divides, passing the faulty information along to its progeny, and they to theirs. By the time doctors find the tumor and examine it, the virus has disappeared."

Dr. Robert Huebner, chief of the institute's Laboratory of Infectious Diseases, has been working on a method of detecting "chemical footprints" of viruses that have attacked cells and disappeared. Hopes are high around the institute that this research will eventually lead man to the hiding place of the elusive human cancer virus.

It may also lead to other viruses. "Viruses which we don't yet know about may cause many common genetic abnormalities," says Doctor Axelrod. Some may act like *rubella*, the virus that causes German measles. If a woman is infected by *rubella* while pregnant, her baby may be born with defects such as eye deformities or an improperly built heart. The disease is usually little more than a nuisance to the mother herself—in fact, she may never know she had it—but effects on the genetic code of the fetus can be disastrous. It is possible that other birth defects, even some hereditary diseases, are caused by a virus that infects the mother without her knowing it.

The number of avenues of nucleic-acid research is enormous. The National Institutes of Health alone now support more than 500 projects bearing directly on DNA and RNA, plus hundreds of others that are indirectly related to the subject. "It is hard to think of a single branch of medicine, biology or any other science dealing with life in which DNA-RNA studies aren't important," says Doctor Ahrens of the Rockefeller Institute.

Where the studies will lead is a fascinating question. For example, researchers are trying to find the genetic mechanism by which the body recognizes and rejects an alien protein—an invading virus, or a skin graft from another person. When they do, man may learn how to switch the mechanism on and off at will, perhaps making possible grafts of whole preserved organs and even of entire limbs.

But all this is just speculation. The present-day facts are fascinating enough—that scientists are probing into life's basic causes and have already made what may turn out to be the greatest scientific discovery of all time. They have found the key of life. □

At the New England Institute for Medical Research, Dr. John H. Heller and a laboratory assistant discuss problems in an experiment.