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NIH RESEARCHERS CRACK THE GENETIC CODE

In pioneering experiments, two young biochemists have begun to decipher the RNA molecules that carry cellular blueprints

The enigma of genetic coding, considered a fundamental secret of life, may be on the verge of solution.

In just-published and about-to-be-published papers, several research teams are reporting experimental proof of what has been largely theory: the intricate process by which structure and function of living organisms are shaped. One group has begun to crack the DNA-RNA code—the key to the whole mystery. Soon they expect to decipher the entire set of instructions by which genetic messengers direct the manufacture of proteins—the basic stuff of life.

The major achievement in RNA research is the work of two young biochemists at the National Institute of Arthritis and Metabolic Diseases, Drs. Marshall W. Nirenberg and J. Heinrich Matthaei. Behind their work, however, is a whole series of investigations which has produced the basic theory and its preliminary experimental support.

Fundamentally, the theory states that the hereditary "blueprints" of cell structure and function are coded within the cell nucleus as long-chain molecules of desoxyribonucleic acid (DNA). These plans are transmitted, in a series of steps, to the cytoplasmic "assembly line" where they direct the synthesis of each cell's characteristic products.

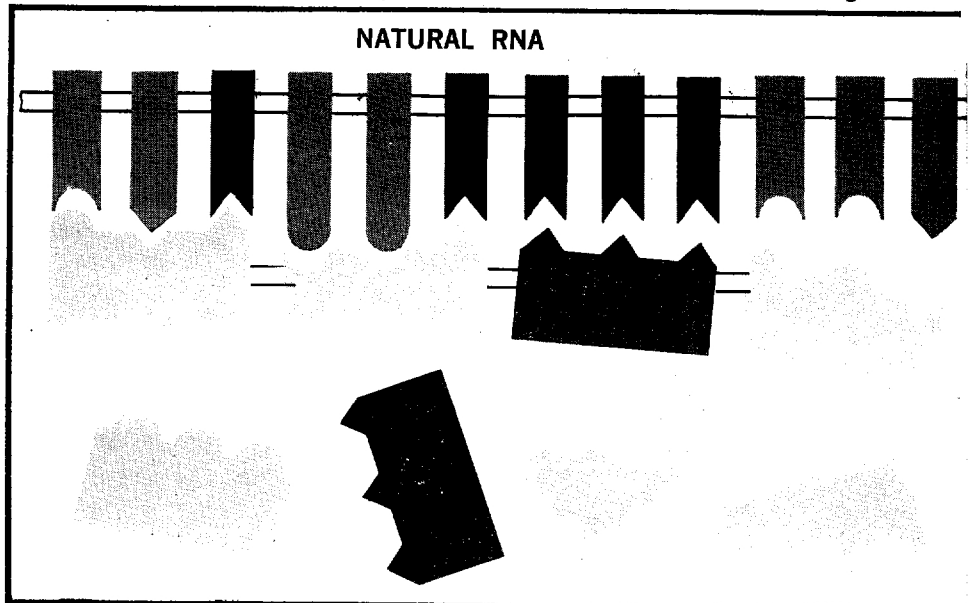
In all species, from bacillus to man, DNA molecules are organized around the same general plan, chains of only four nitrogen-containing units (bases): adenine, guanine, cytosine and thymine. The specific order of these bases, like the order of letters in words, is meaningful. In effect, the coded "message" of heredity is written in a four-letter alphabet.

DNA molecules can duplicate themselves. This property plays a key role, not only in the passage of hereditary characteristics from one generation to the next, but also in the development of multicellular organisms. The DNA in a fertilized human ovum reproduces thousands of billions of times to form the myriad cells of the mature individual. And each cell contains a complete copy of the genetic "specifications" for the human species, as well as those for the individual's unique collection of hereditary characteristics.

This duplicative process was reproduced in the test tube by Dr. Arthur Kornberg of the Stanford Medical Center, who won the 1959 Nobel Prize in medicine and physiology for the accomplishment. He prepared solutions containing the four DNA bases and other ingredients, added a dash of "natural" DNA as a primer—and found that the primer would assemble the bases into exact copies of itself.

So far as is known, DNA functions only in the nucleus, like an original blueprint kept in the foreman's office. From its headquarters, the DNA transfers its genetic information to ribonucleic acid (RNA), which constitutes the "working drawings" used in the cytoplasmic factory.

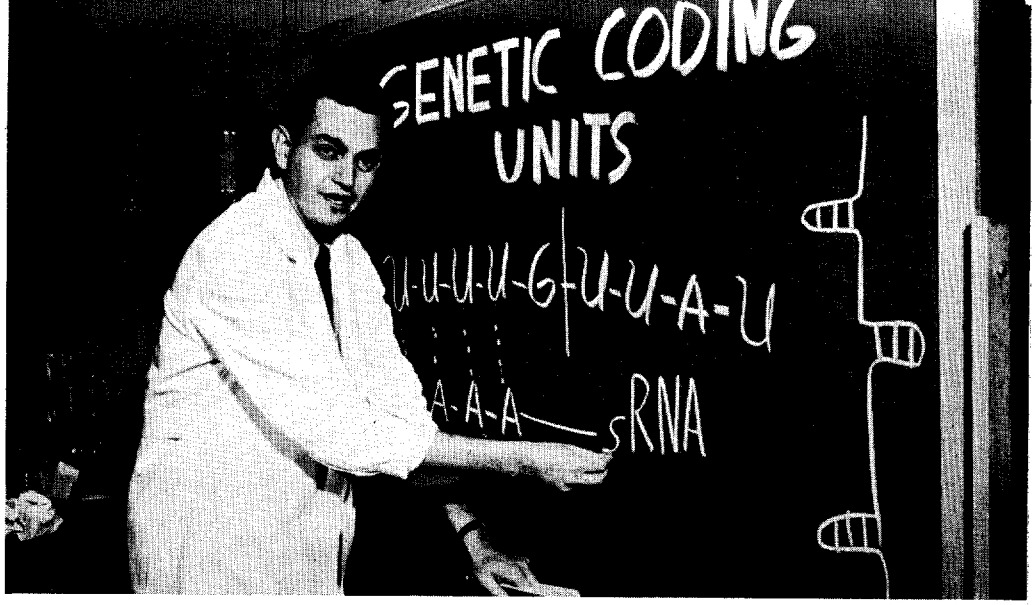
RNA, like DNA, also consists of chains built up of four bases. Three of the bases—adenine, cytosine and guanine — are the same as those in DNA, but instead of thymine, RNA has uracil. (Dr. Severo Ochoa of the NYU College of Medicine shared the 1959 Nobel Prize with Kornberg for



BIOCHEMICAL CODE depends on sequence of four kinds of units (gray) in RNA molecule. Various sequences select different amino acids (colof) for protein synthesis.

developing methods of synthesizing RNA.)

At NYU, the University of Chicago, and the University of St. Louis, researchers are now studying transmission of coded information from DNA to RNA. One NYU team, Drs. John Furth and Jerard Hurwitz, told the American Association for the Advancement of Science that they have now transferred, *in vitro,* the letter-for-letter nuclear code to a material which is known to pass through the nuclear membrane into the cytoplasm.



DR. NIRENBERG spells out an explanation of his work in biological cryptanalysis.

Exactly as Predicted

They prepared a solution containing quantities of the four RNA bases —unassembled components of the long molecules—and a special enzyme obtained from *E. coli.* Then they added various species of DNA. The DNA, presumably acting as a sort of template, assembled the bases to form RNA molecules. And in each case, the proportion of the bases in the synthesized RNA reflected the proportions in the DNA, precisely as the theoretical model predicted. For example, for every hundred adenine units in the DNA, there were a hundred uracil units in the RNA.

Not only the proportion, but also the order of the bases was transferred. In one experiment, the two investigators used a synthetic DNA in which every other base was adenine. In the RNA, every other base was uracil.

This is only the first step. Once the coded plans reach the cytoplasm they are translated into action—synthesis of enzymes and other proteins. The properties of these proteins are determined by the sequence of their hundreds or thousands of component units. Each of these units is one of the 20-odd amino acids, and biochemists have speculated that each amino acid is specified by a different genetic "code word"—a group of three or four bases in the RNA molecule. A sequence of several thousand such "words" could specify the complete structure of even the most complex protein. But the pivotal question has been: Which word signifies which amino acid?

The answer to this is the major contribution just now emerging from the laboratory of Drs. Nirenberg and Matthaei. For the first time, they have brought about controlled RNA manufacture of amino-acid chains in the test tube. And by utilizing known sequences of RNA bases, they have succeeded in equating certain sequences with certain amino acids.

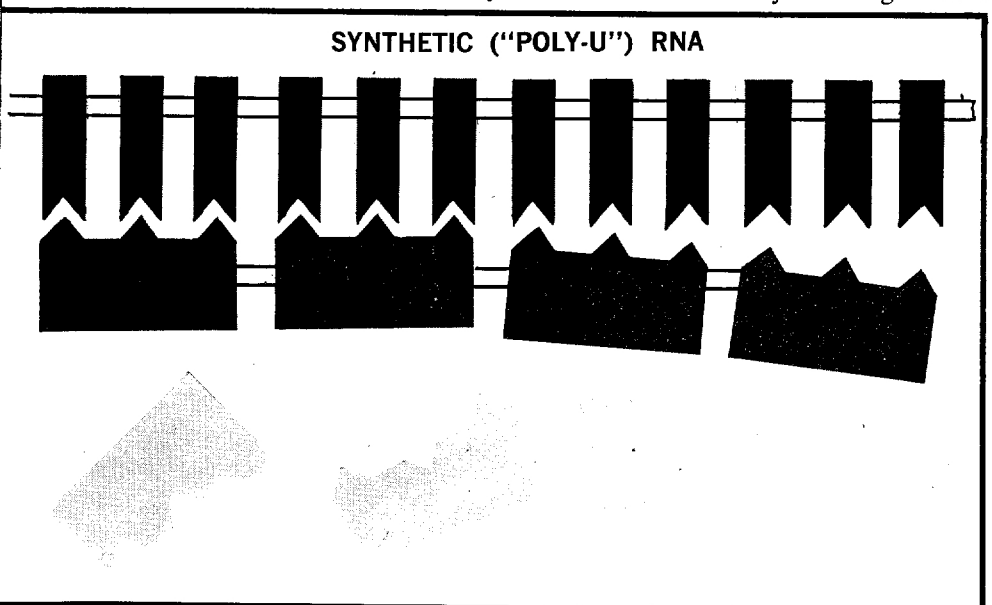
Drs. Nirenberg and Matthaei are using *E. coli* solutions containing the 20 amino acids, energy-rich adenosine triphosphate (ATP), ribosomes (tiny intracellular particles where proteins are synthesized) and cytoplasmic fluids (cell sap).

To this mixture they add "poly-U," a synthetic RNA containing only one kind of base: uracil. The RNA triggers the formation of amino-acid chains (polypeptides). But most significantly, out of all available amino acids, the poly-U selects just one — phenylalanine—to incorporate in the polypeptide. Evidently, the code word U-U-U (uracil-uracil-uracil) translates as "phenylalanine."

Within a few months, the NIAMD researchers expect to report on the code sequences associated with at least 15 different amino acids.

Nirenberg and Matthaei's techniques, which have yielded such exciting results, are now being taken up by half a dozen other groups. At least two Nobel laureates—Ochoa at NYU and Fritz Lipmann at Rockefeller Institute—are heading research teams that are tackling protein synthesis. Ochoa's group, including Drs. Carlos Basilio, Joseph F. Speyer and Peter Lengyel, has already achieved a preliminary picture of RNA sequences associated with 14 amino acids. For each sequence they have determined the names and proportions of the bases, but not their order.

Dr. Nirenberg predicts that "within another six months or so most of the genetic code will be cracked." ■



DECODING EXPERIMENT uses RNA with only one kind of unit, uracil (dark gray). This simple sequence forms chains of only a single amino acid, phenylalanine (dark color).