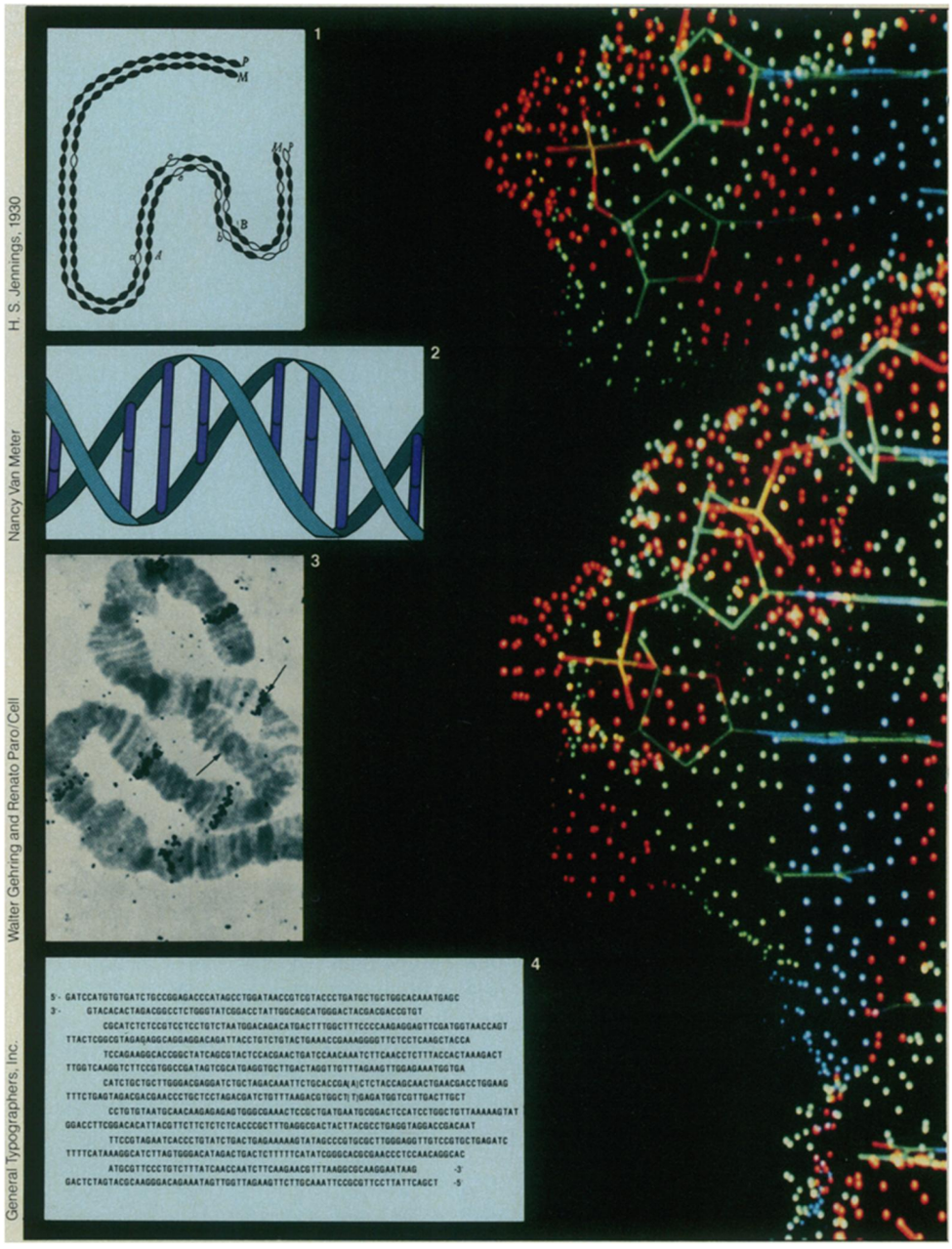
THE GENE IDEA

Scientists' image of hereditary units has gone from the abstract to the biochemically concrete over the last sixty years

BY JULIE ANN MILLER

"But ever in our thoughts the question rings, what are these units [of heredity] ...? How the pack is shuffled and dealt, we begin to perceive: but what are they — the cards? Wild and inscrutable the question sounds, but genetic research may answer it yet."

— William Bateson,
British geneticist, 1906



The closest science has come to discovering the "secret of life" has been the elucidation of the gene. Sixty years ago, scientists recognized that the heredity of all organisms is controlled by a large number of distinct structures or substances in a cell. But the composition of these units of inheritance and the means by which they act, although the subject of many theories and much controversy, were unknown.

Now, the composition of the gene is not only known, but known in such detail that a particular gene can be synthesized by chemists and made to perform its function in a living cell. In the 1920s genetics was hardly considered a legitimate field of biological study. Today, genetics is an important aspect of all biology.

Speaking at a meeting in 1921, American geneticist Hermann J. Muller, whose work on fruit flies over more than 15 years had demonstrated the connection between genes and chromosomes, summarized then-current genetic knowledge:

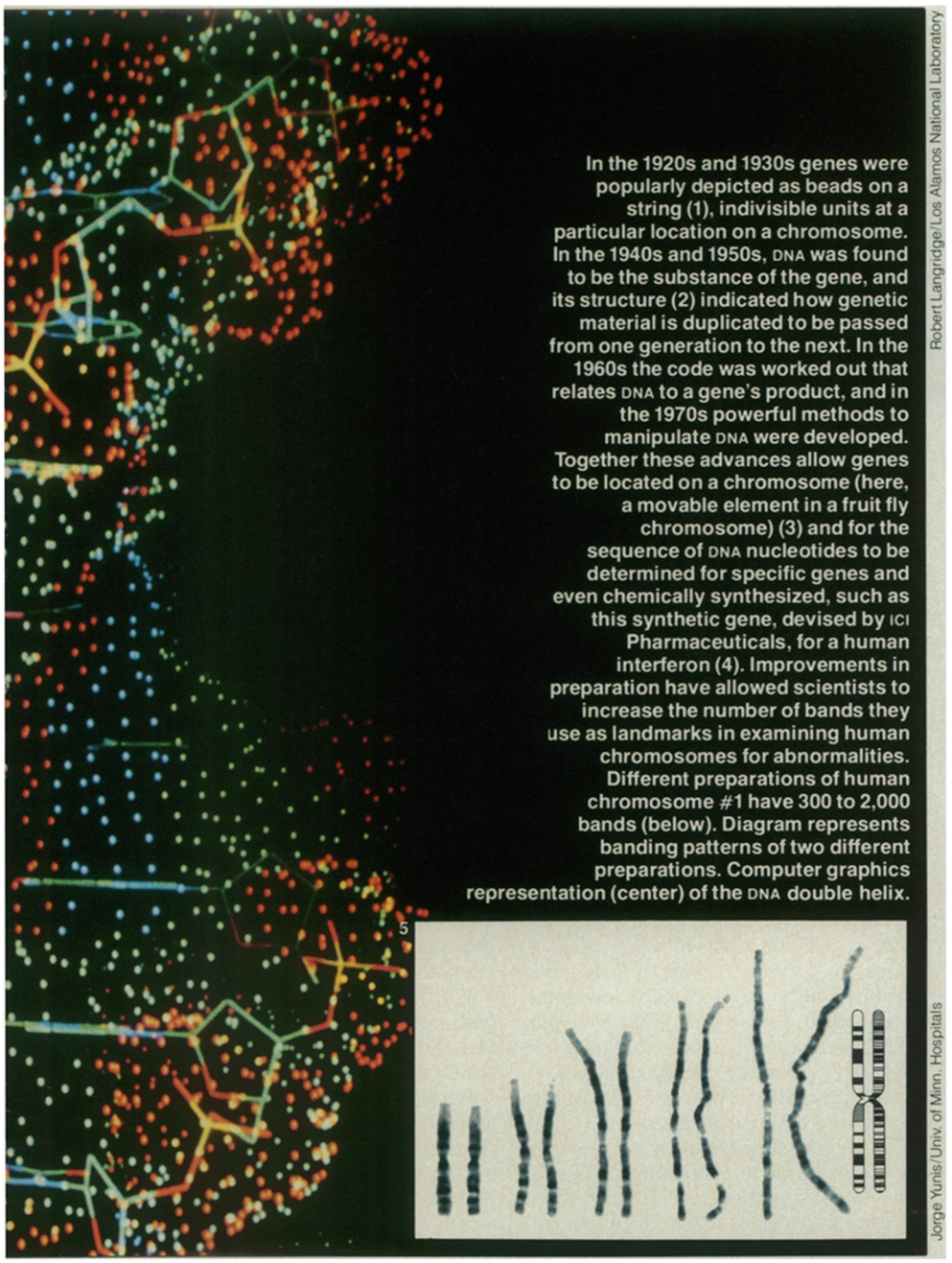
- Genes are definite but unknown substances.
- Genes are very small.
- Genes are different than the materials they cause to be produced.
- Genes can mutate, and this variation is the root of evolution.

The question of how new genes arise puzzled scientists. Muller announced a great advance in practical terms in 1927 when he reported that X-rays (which had been described in 1895) could induce mutations in fruit flies. These experiments also removed any residual doubt that genetics has a physical basis. (SCIENCE NEWS reported on this finding in 1927: "It has been proved...that in the germ-cells of the flies, X-rays affect the little particles responsible for heredity in much the same way as a shot-gun fired at a pile of pebbles would affect the pebbles. The hereditary particles become permanently transformed in all sorts of unexpected ways and the sudden changes known as 'mutations' are produced in them." [SN: 8/26/27, p. 91])

Experiments in barley by L. J. Stadler published the next year confirmed Muller's results, and together with the fruit fly work they opened the experimental use of deliberately created mutations, an approach that still dominates much of genetics.

The image of genes as distinct physical substances was tantalizing to scientists who wanted to know just what the substance is. Because genes govern complex functions, the best candidates for genetic material were molecules that are big and complex. Both proteins and nucleic acids meet these criteria. Before 1944, most scientists favored protein as the genetic material. It was already known to be important in many activities in the cell and, with its 20 amino acid subunits, there is room for extensive variation.

On its side of the argument, deoxyribonucleic acid had the advantage of being confined to the cell nucleus, where the chromosomes are. But because it has only four possible nucleotide building blocks, it was considered excessively monotonous.



In the 1920s and 1930s genes were popularly depicted as beads on a string (1), indivisible units at a particular location on a chromosome. In the 1940s and 1950s, DNA was found to be the substance of the gene, and its structure (2) indicated how genetic material is duplicated to be passed from one generation to the next. In the 1960s the code was worked out that relates DNA to a gene's product, and in the 1970s powerful methods to manipulate DNA were developed. Together these advances allow genes to be located on a chromosome (here, a movable element in a fruit fly chromosome) (3) and for the sequence of DNA nucleotides to be determined for specific genes and even chemically synthesized, such as this synthetic gene, devised by ICI Pharmaceuticals, for a human interferon (4). Improvements in preparation have allowed scientists to increase the number of bands they use as landmarks in examining human chromosomes for abnormalities. Different preparations of human chromosome #1 have 300 to 2,000 bands (below). Diagram represents banding patterns of two different preparations. Computer graphics representation (center) of the DNA double helix.

Robert Langridge/Los Alamos National Laboratory

Jorge Yunis/Univ. of Minn. Hospitals

Evidence that DNA is the substance of genes was first presented in 1944. But many scientists were very slow to accept the results. Oswald Avery, a New York microbiologist, demonstrated that coat characteristics of the bacterium that causes double pneumonia could be altered genetically by material containing as pure a preparation of DNA as any available. Enzymes that destroy proteins did not interfere with this transformation, but enzymes that break apart DNA eliminated the activity.

The doubters of Avery's results included a group of young scientists who had after 1943 begun working with some of the simplest organisms available, viruses that infect bacteria (SN: 4/25/81, p. 268). In 1952, members of this group performed the experiment that was quickly accepted as the definitive evidence that DNA is the substance of genes. Alfred Hershey and Martha Chase showed that when bacterial viruses or "phage" infect bacteria, their protein coat remains outside. The injected material, which changes the operation of the bacterial cells, is predominantly DNA. (In the same 1921 speech in which Muller described the state of genetics, he suggested that phage might be a useful object of genetic study, but that suggestion was taken then as a joke.)

Any good definition of a gene should include not just what it is chemically, but also how it determines, as Muller put it, "the nature of all cell substances, cell structures and cell activities." At the same time as the chemical nature of the gene was being determined, biochemically inclined geneticists focused on the chemical nature of gene action. George Beadle and Edward Tatum proposed that a gene is responsible for producing a single biochemical event, which in turn produces a trait of an organism. This idea was given the slogan "One gene—one enzyme."

The idea that a gene acts by producing an enzyme had been suggested intermittently during the early part of the century, but Beadle and Tatum in the 1940s provided a clear formulation of the idea and overwhelming experimental evidence, first with fruit flies, and later with the bread mold named *Neurospora.*

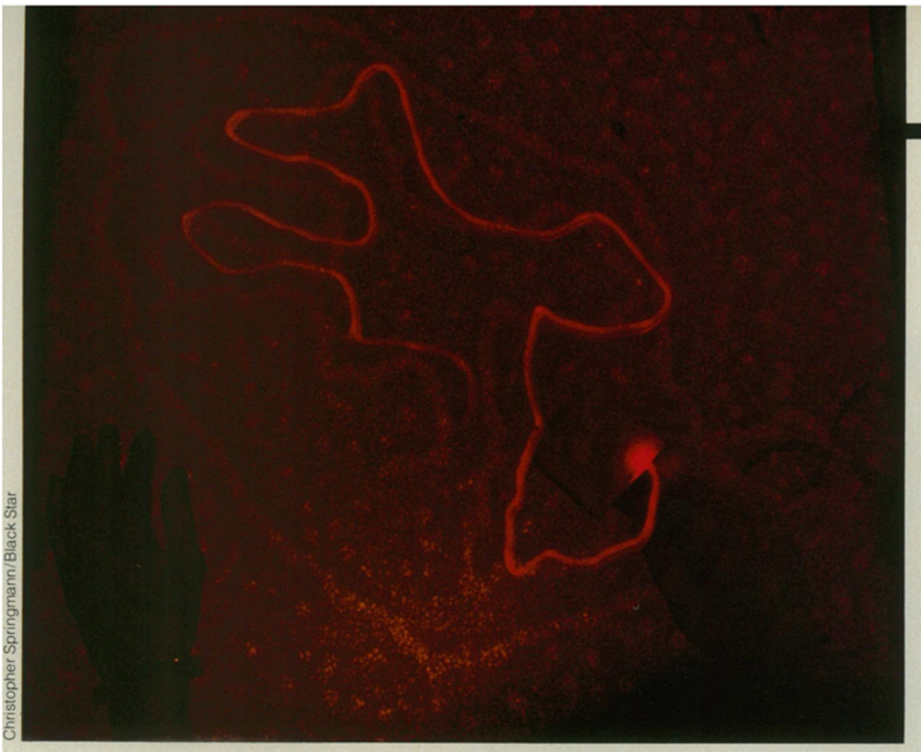
The most dramatic advance in genetics was, of course, the description of DNA.

"We wish to suggest a structure for the salt of deoxyribose nucleic acid (DNA). This structure has novel features which are of considerable biological interest." With this understatement in 1953, James D. Watson and Francis H.C. Crick of Cambridge, England, announced the double-helix model of genetic material. They continued "... It has not escaped our notice that the specific pairing [of nucleotides] we have postulated immediately suggests a possible copying mechanism for the genetic material." (As reported in SCIENCE NEWS [SN: 12/19/53, p. 387]: "Scientists have new key to duplication of life patterns within cells in proposed chemical structure for DNA, desoxyribonucleic acid. Suggestion has implications for cancer.")

Watson and Crick's suggestion of the DNA structure was accepted immediately by most biologists, and a burst of experimentation around the world soon confirmed the model.

Still all the new and exciting information about the structure of DNA did not reveal how it carries the instructions for making and maintaining a cell, but the linear structure of both DNA and proteins did suggest a simple relationship between the nucleotides in DNA and the amino acids in protein.

A new view of the gene arose from work using increasingly refined techniques to locate the sites where chromosomes



Christopher Springmann/Black Star

Computer calculates length of a DNA plasmid, outlined with red light. Plasmids are the vehicles for transferring genetic material in much gene-splicing work.

break and rejoin. Less sensitive observations of such recombination had earlier revealed the linear arrangement of genes. In the early 1950s Seymour Benzer looked at viruses and discovered that recombination could occur not only between genes but within genes. Therefore, genes are not indivisible units; they can be broken in many places.

Benzer's work opened the way for demonstrating a direct relationship between the location of a mutation in DNA and the location of the resultant amino acid change in a protein. Groups in the United States and England using different organisms and different experimental methods demonstrated that a gene's nucleotide sequence is indeed colinear with the amino acid sequence in the protein determined by that gene.

Now the challenge became one of cryptology—how do the nucleotides of a gene specify the amino acids of a protein? The problem initiated a furious, but brief, race. The genetic code was cracked in 1961 by biochemists Marshall Nirenberg and Johann Matthaei, who were the first to assign a triplet of nucleotides to an amino acid. Within five years, the efforts of other laboratories revealed the rest of the code. The genetic code turned out to be identical for all living organisms, bacteria to humans (although recently mitochondria, structures within cells, have been found to use a slight variation [SN: 9/15/79, p. 185]).

At this point the gene had gained its modern image as a sequence of nucleotides within a DNA molecule that encode the amino acid sequence of a protein according to a recognized key. The DNA also may be translated directly into RNA components of the cell.

If scientists knew so much about the structure of a gene, could they build one that works? The first functioning artificial gene was synthesized by Har Gobind Khorana. And when it was reported in 1976, it was hailed as supplying the ultimate proof that the whole theoretical edifice of DNA genetics is correct (SN: 9/4/76, p. 148).

While most of the recent excitement in genetics has been the manipulation of genetic material, a few big surprises have turned up that influence the very image of the gene. One is the discovery that, at least in certain viruses, the genes can overlap. An important step in decoding the genes was the realization that non-overlapping triplets of nucleotides represent amino acids in a protein chain. In 1976, however, British scientists found a virus in which the same stretch of DNA encodes more than one protein (SN: 11/13/76, p. 310). Another new aspect is that the chromosome is not a static sequence. Some genes rearrange during development (SN: 12/11/76, p. 372) and other pieces of DNA, thought to include regulatory segments, can move in and out of sites along the chromosome. Such controlling elements were described in maize more than 30 years ago by Barbara McClintock, but received little attention because interest was focused on microorganisms.

The biggest surprise in recent genetics was the structure of mammalian genes. To some extent scientists were blinded to interesting avenues of research by the oft-stated belief that "if you understand the bacterium, you understand the elephant."

In recent years the interest of many biologists has shifted back up the evolutionary ladder. In 1977 studies of mammals and the viruses that infect them revealed that many genes are not simple stretches of nucleotides colinear with the amino acids in the protein they encode. Instead, the coding sequences are interspersed with stretches of DNA that are not represented in the final protein.

Another landmark in recent genetics must be considered the introduction of the technique for splicing genes of different organisms. The beginning of recombinant DNA technology is assigned to the 1973 discovery that it is possible to cut DNA molecules with one set of enzymes, join the pieces with another enzyme and introduce the spliced material into a cell (SN: 6/11/74, p. 348). The practical aspects of the technique have spawned the still-expanding genetic engineering industry, with its promise of new and less expensive drugs and useful chemicals.

The recombinant DNA techniques also proved so powerful for laboratory research that they soon became standard procedures. Together with methods for determining rapidly the exact sequence of nucleotides, they allow scientists to identify specific genes on chromosomes and to learn their nucleotide sequences.

This accessibility of genes has opened new vistas in medical research, although substantial improvements in patient therapy are still in the distance. The gene-splicing techniques can provide large enough amounts of biologically active rare material for scientists to investigate therapeutic applications. On another front, much progress is being made in identifying the causes of inherited diseases. In an increasing number of cases, inherited disorders are being described, not only at the level of a defective protein, but as a specific nucleotide change in a gene. And more and more human genes are being assigned locations on the human chromosomes. In 1971 only 3 human genes had been mapped; today the chromosome positions of more than 400 human genes are known.

With recent improvements in staining chromosomes, many inherited abnormalities can be visualized as alteration in the banding pattern. Such analyses of genetic material, plus improved detection of proteins affected by inherited disease, allow prenatal screening and diagnosis of an ever increasing number of disorders. In 1951 there were about 10 genetic counselors in the United States; by 1975 there were more than 300 counseling centers.

Today important questions remain, such as how genes are regulated during the normal development of complex organisms. But even with questions unresolved, genetics has come a long way from the period described by the late French geneticist Jacques Monod. In *The Eighth Day of Creation,* Horace Judson quotes Monod: "You know, the gene was something in the minds of people ... which was as inaccessible, by definition, as the material of the galaxies." Now the "secret of life" is a matter of chemical structures and processes accessible to scientists. □