4.5 Billion Years of Protein Molecules: What Do We Know Now about How They Are Made?

The great successes of the last two decades of work in molecular biology have specified certain chemical components and processes shared by all known forms of life. In these recurring biochemical patterns, unchanged since their establishment before the earliest fossil records, lies the hope of discovering the key to both the astonishing diversity of biological species and the unique character of the individual, most evident in man.

Four nucleotides have been recognized as composing the chemical backbone of the genes of most forms of life, from the smallest one-celled organisms to man, whose brain alone includes 10 billion cells.

Just 20 amino acids compose the proteins of all known forms of life, but 20 seem to be more than enough. Combinations of these 20 in all possible sequences, Harold Urey once said, would produce so many different protein molecules that "not all the molecules possible exist now in the observed universe nor could they have existed during the last 4.5 billion years."

How far researchers have advanced in discovering how genes act to transform 20 amino acids into the almost infinitely varied forms of life will be reported in a variety of ways at the AAAS annual meeting in Montreal, 26 to 31 December.

Clement L. Markert, a developmental biologist at Johns Hopkins University, will give a lecture on the role of the genes in embryonic development as one of the AAAS "Moving Frontiers of Science" series (28 December). Another major event will be James Ebert's address on interacting systems in development (28 December). Ebert, an embryologist at the Carnegie Institution of Washington laboratories in Baltimore, will give this as the vice-presidential address of the AAAS Section on Medical Sciences.

What turns genes on and off? With discovery of the basis of the genetic code, this has become the next great question of molecular biology.

An increasing amount of work shows that genes may act or cease to act in response to certain proteins. Alfred Mirsky, for example, outlined a possible mechanism of genic inhibition by showing that cytoplasmic histone combines with about 95 percent of the phosphate groups along the DNA backbone.

Some of Markert's experiments have been concerned with this question. For example, he was able to arrest development of fertilized eggs by injection of a nuclear fraction which included histone. He has also shown that another, more acidic, protein interacts with the chromosomes, and affects genetic function at a critical step in embryonic development.

Other of Markert's experiments are part of the growing evidence that protein synthesis may be guided, not only by the DNA code, but also by mechanisms to be sought in the cellular cytoplasm. Demonstrating the presence of five isoenzymes of lactate dehydrogenase in mammals, Markert suggested that such multiple enzyme forms may be the result of cytoplasmic events that regulate primary gene activity and also determine the final functional structure of proteins.

Cellular Differentiation

What is known of the biochemical machinery of cellular differentiation will be explored in detail at a five-session symposium arranged by Ebert, Norman Kretchmer of the Stanford University School of Medicine, and Oscar Touster, of Vanderbilt University.

Participating in this symposium (28 to 30 December) will be men who are on the forefront of research in this field. They are:

Mahlon B. Hoagland and W. Eugene Knox, Harvard; Tore Hultin, University of Stockholm; Daniel Mazia and Fred Wilt, University of California, Berkeley; J. G. Gall, Yale; David Epel, University of Pennsylvania; Paul Gross, Brown; Stanley Cohen, Vanderbilt; Irwin Konigsberg, Carnegie Institution of Washington at Baltimore; Ruth Doell, Clifford G. Grobstein, and Norman K. Wessells, all of Stanford; John Papaconstantinou, University of Connecticut; Olga Greengard, Institute for Muscle Disease, New York; Sol Spiegelman, University of Illinois; H. O. Halvorson, University of Wisconsin; Maurice Sussman, Brandeis University; and Ulrich Clever, Purdue. Markert will give the summary.

Cytoplasmic DNA

During the last two decades of intensive work on nuclear DNA, other researchers have found evidence that certain genetic characteristics are transmitted by hereditary factors not contained in nuclear chromosomes. In a symposium (27 December) organized by S. Granick, Rockefeller Institute, a number of researchers will report finding DNA in organelles of the cellular cytoplasm—in chloroplasts, mitochondria, kinetoplasts and kinetosomes. They are: A. Gabor, David Luck, William Trager, all of the Rockefeller Institute; Gerald Seaman, Hunter College; Hewson Swift, University of Chicago. Other units of cytoplasmic inheritance will be discussed by Piotr Slonimski, Gif-sur-Yvette, France; Tracy Sonneborn, University of Indiana; A. C. Taylor, Rockefeller Institute.

F. M. Burnet once said: "The greatest prize in the future of biochemistry is an understanding of the environmental conditions necessary for the replication of the virus molecule." When it comes, part of the prize may be knowledge of how to check cancer. Increasing evidence indicates that cancer may occur when an invading virus interacts with the DNA of normal cells. Lasker award prizewinners Renato Dulbecco and Harry Rubin, for example, have suggested that the DNA of polyoma virus may be integrated into the DNA of recipient cells, while the RNA-containing virus found in avian leukosis acts by nonchromosomal mechanisms.

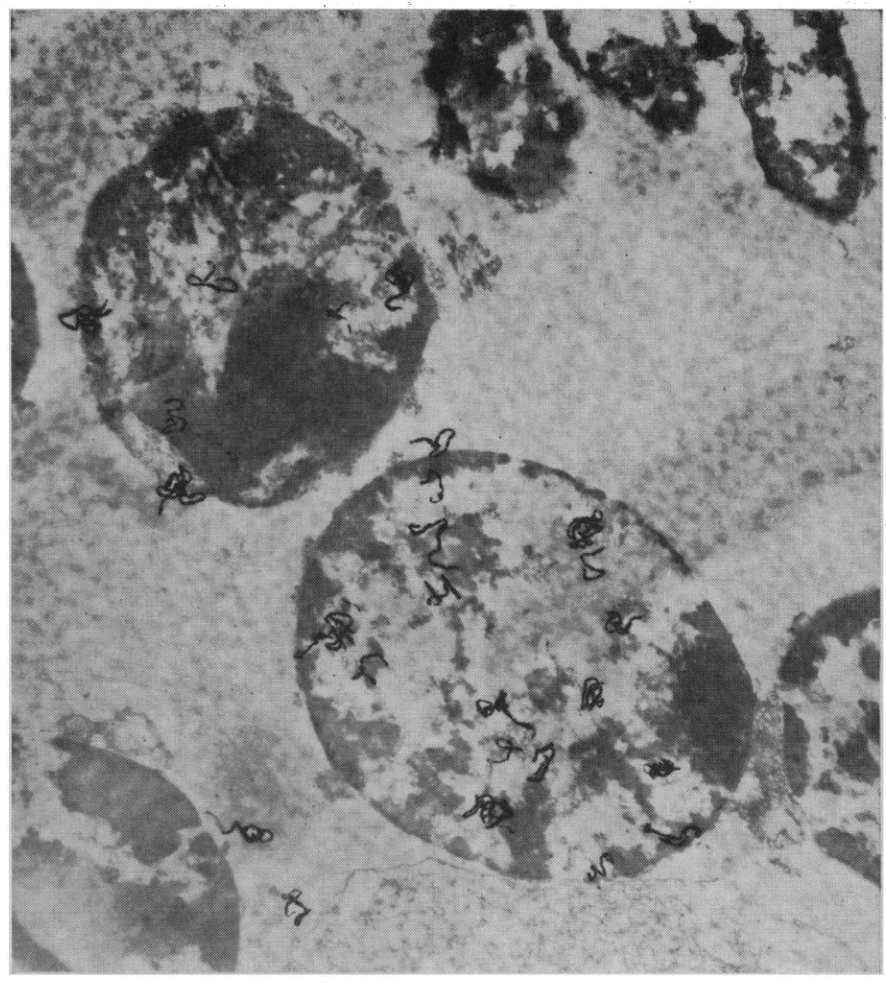
Three medical researchers who have assembled important parts of the evidence suggesting a viral origin of cancer will discuss this question at a "Frontiers of Microbiology" symposium (30 December) arranged by Jacob Gershon-Cohen, Albert Einstein Medical Center, Philadelphia. They are:

► Joseph Beard, Duke University Medical School, who isolated a unique strain of leukosis virus causing myeloid leu-

kemia and other neoplasms in chickens. Since 1950 he and his associates have carried out systematic studies on the biological, biophysical, and biochemical properties of this agent and of other avian tumor viruses.

► Ludwik Gross, Veterans Administration Hospital, New York, who was first to show that leukemia, which develops in certain strains of mice, is caused by a filterable virus transmitted from one generation to another directly through the embryo. By serial cell-free passage in newborn mice of a virus isolated from leukemic mice, Gross developed a consistently potent virus strain, which induces leukemia and lymphomas in mice and rats.

► Leon Dmochowski, M. D. Anderson Hospital, Houston, who observed spherical virus particles in the leukemic organs and extracts of these organs from leukemic mice, and virus particles similar in appearance in the lymph nodes, bone marrow, and circulating blood of leukemic patients. He will report on how far work has progressed in isolating these particles and using them in experiments to determine their relationship to human leukemia.



All genes do not act all the time, as was assumed before recent work. A new piece of evidence that a high percentage of cellular DNA is inactive at any given time is the above electron micrograph of calf thymus nuclei. Autoradiography is used to detect active DNA (by means of tritium labeling, sites of RNA synthesis become visible.) Active DNA sections all show as part of diffuse chromatin, visible as white masses in the photo above. Some 80 percent of DNA is known to be in the condensed chromatin, seen as dark nuclear portions. This electron microscope autoradiograph (× 21,000) is by V. C. Littau, Rockefeller Institute (1).

Virus, Fungus, or Bacterium?

One of the smallest living entities, a fragile organism with a cumbersome name, is a subject of debate among microbiologists, a fair number of whom have devoted their working lifetimes to studying it. This is the pleuropneumonia-like organism (PPLO), which has been found in both animals and man. Its name is the result of the uncertainty that surrounds it.

Is PPLO a harmless member of the abundant flora of the human body cavities? Or does it produce pneumonia and certain other diseases, in the presence of which it is often found? Is it virus, fungus, or bacterium?

Studies intended to answer these questions have been difficult because PPLO lacks the rigid cell wall characteristic of bacteria. Its plasticity not only makes PPLO difficult to see under the microscope but also permits it to take many different shapes.

Microbiologists pursued PPLO as an independent organism for some years before the discovery that penicillin destroys the cell wall of many bacteria. If protected (in culture) against death by osmotic shock, some bacteria survive without their cell walls and, on discovery, look very much like PPLO. This raises the possibility that PPLO may be, after all, not an independent organism but simply the survival form of various bacteria.

Since traditional methods of microscopy, culture, and immunology have not provided a sure answer, biochemistry here, as elsewhere, has joined the team. Biochemists are analyzing the lipoidal composition and the nutritional requirements of PPLO and are comparing both with those of organisms known to be bacteria stripped of their cell wall by penicillin.

How far recent studies have succeeded in identifying PPLO and determining whether it is the cause of such major problems as chronic respiratory disease will be reported at a second "Frontiers of Microbiology" symposium (30 December), arranged by Charles Panos, biochemist, Albert Einstein Medical Center, Philadelphia. Other participants are Raymond J. Lynn and Paul F. Smith, both of the University of South Dakota, and York E. Crawford, U.S. Naval Hospital, Great Lakes, Illinois.

This is only a sampling of the reports on recent advances in the life sciences and in other major fields of science which you can expect to hear at the annual meeting. Plan now to attend.

Reference

1. V. C. Littau, V. G. Allfrey, J. H. Frenster, A. E. Mirsky, *Proc. Natl. Acad. Sci. U.S.* **52**, 93 (1964).