BIOLOGY

Virus Cell Reproduction

$1,000 AAAS prize awarded for concerted attack on key problem in biology, the biochemical processes which enable living cell to reduplicate original.

See Front Cover

➤ A CONCERTED experimental attack on what is probably the key problem in biology, the biochemical processes which enable a living cell to produce new living material which reduplicates the original, won for Dr. Barry Commoner of Washington University, St. Louis, the $1,000, 26th Newcomb Cleveland prize of the American Association for the Advancement of Science at Boston.

This process is the fundamental basis of all reproduction. Tobacco mosaic virus offers certain key advantages for experiments designed to penetrate the secret of this still unmastered problem. This virus is capable of being reproduced.

When a very minute amount of the virus is inoculated into a tobacco leaf, within a matter of days large amounts of new virus appear in the infected tobacco cells. In this respect, the virus behaves like any other reproducible part of the cell, such as a chromosome.

The virus also resembles the agents of normal inheritance in that, like the chromosome, it also exerts a profound influence over the chemical and other characteristics of the cell. So, when a tobacco plant is infected with the virus, the flowers produced are streaked with color instead of showing the solid color of a normal flower. The shape and color of the leaves are also affected.

No Direct Cell Relationship

For these reasons scientists have come to regard viruses, such as tobacco mosaic, as sort of free-wheeling genetic agents which, once inserted into an appropriate living cell, are able to imitate very closely the behavior of the cell's ordinary reproductive machinery. The virus acts, however, without any direct relationship to the cell's nucleus.

Unlike the ordinary reduplicating agents of the cell, tobacco mosaic virus possesses certain very important experimental advantages which permit biochemical experiments that cannot as yet be accomplished with agents such as those found in the chromosomes.

Tobacco mosiac virus can be taken out of the infected cell and isolated as a pure single substance—a nucleoprotein. As such, it can be kept in solution for years, and most important, will still be capable of being reproduced if put back into a tobacco cell.

The fact that the virus can be taken out of the cell, handled as a chemical, and then put back into the new cell without losing its biological powers is what distinguishes it from the cell's own reproductive agents, and leads to the enormous experimental advantages.

Dr. Commoner's research efforts have been designed to take advantage of these experimental opportunities, and to find out, in precise chemical terms, the specific processes which occur inside the cell when the virus is reproduced. The experiments have involved a large degree of teamwork and are the product of the efforts of a number of collaborators and students.

Dr. Commoner stressed the fact that many of the experiments would have been impossible for one or two persons to carry out alone.

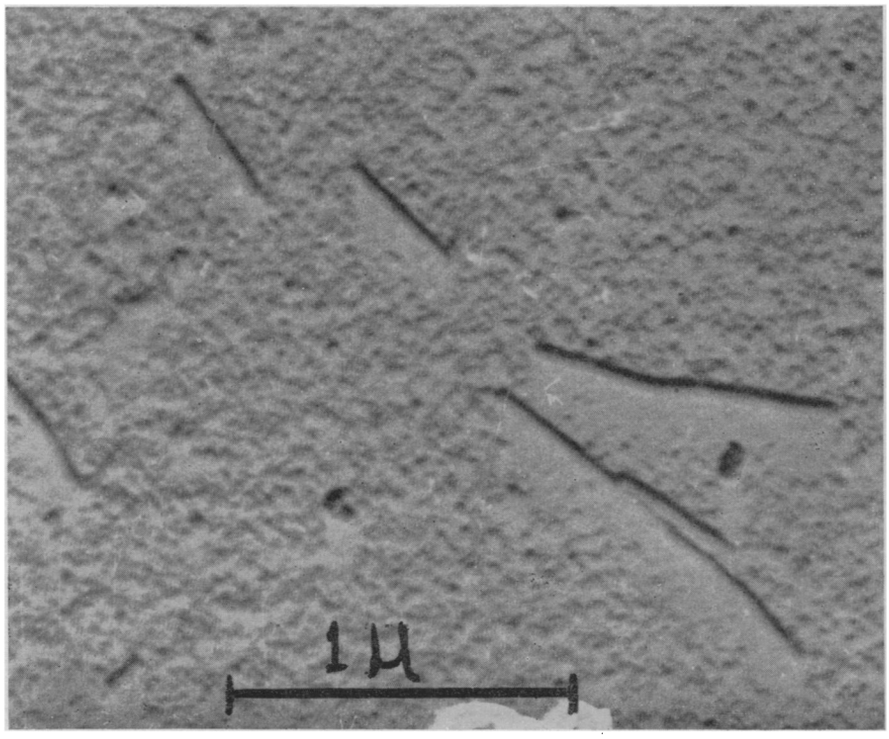
The fundamental approach, adopted by Dr. Commoner and his collaborators at Washington University, was to make detailed quantitative comparisons between the biochemical processes which go on in otherwise identical pieces of infected and uninfected tobacco leaf. By comparing the chemistry of the two tissues, it is possible to sort out from the complex scramble of cellular metabolic processes, those specific reactions which are linked to the reproduction of the virus.

Since the chemical composition of the virus is so well known, it is possible to scan the metabolism of the infected cell to find out from where the material required to form the new virus comes, and what biochemical processes are involved in its final assembly into virus. Dr. Commoner and his associates found that the new virus formed in an infected cell is made from the simplest form of nitrogen available to the cell. This is ammonia. The cell avoids the use of ready-made intermediates, such as amino acids and proteins.

Isotopic Nitrogen Tracer

By using isotopic nitrogen as a tracer, it was shown that the virus is not produced in a single synthetic operation, but by assembly of previously synthesized subunits. The first subunit formed is the nucleic acid component of the virus. A little later, several separate units of the protein of the virus are formed. Finally, the nucleic acid and protein units are assembled to form the rod-shaped nucleoprotein molecule which is the actual virus.

It was discovered that the infected tobacco



TOBACCO MOSAIC VIRUS—Enlarged approximately 55,000 times, this electron micrograph shows the molecules of this reproducible virus, which is regarded by scientists as a sort of free-wheeling genetic agent.

cell makes a small amount of protein which may represent free protein fragments of the virus. These proteins were found to be close relatives of the virus; because of their ability to react with the blood of rabbits which had been immunized against the virus.

Dr. Commoner pointed out that this early information constituted only part of what was needed to be known about the biochemistry of virus reduplication. He stated that reduplication can be thought of as two consecutive processes: (1) The cell is instigated to set up the biochemical apparatus required to make the virus. This apparatus is lacking in the normal cell and is induced in the infected cell by the entry of the virus. (2) Once established the new synthetic machinery goes into action and produces virus which is identical with the molecules which served as the original stimulus for the cell.

Biochemical Mystery

The greatest mystery in this process is how the entering virus actually determines that the biochemical machinery of the cell shall produce a nucleoprotein which is the replica of the virus.

This question is the fundamental problem of all biological reduplications. Dr. Commoner pointed out that, to accomplish this basic effect on the infected cell, the entering virus must somehow leave an impression of its own specific chemical composition on the chemistry of the tobacco leaf. He stated that he and his colleagues had kept a sharp lookout in all their experimental work for any chemical change in the infected cell which seemed to imitate the composition of the invading virus. Until recently no such effect was noted.

However, in recent studies of the changes in the nucleic acid composition of the leaf during the infection process, the first break in this problem occurred—it was found that the infected cell synthesized new nucleic acid which, while not identical to the nucleic acid of the virus, bore a simple numerical relationship to it.

This discovery indicates that the invading virus imprints the structure of its own nucleic acid on the nucleic acid-synthesizing machinery of the host. It suggests that this event is the key to the question of how the virus is able to redirect the chemical machinery of the host cell toward the making of virus instead of normal protein.

This new information opens the way for new studies which should in time spell out in specific chemical terms the exact way in which the virus exerts this influence over the nucleic acid metabolism of the tobacco leaf. Dr. Commoner stated that this information ought to shed a good deal of light on the general question of virus reduplication, and on the more general problems associated with the growth and reduplication of cells.

Incomplete TMV Fragment

The two electron micrographs—one on the cover of this week's SCIENCE NEWS LETTER and one on page 42—show, at approximate magnification of 55,000 times, the molecules of tobacco mosaic virus, or TMV, (opposite page) and of the new non-virus protein B8 (front cover).

Protein B8 is produced by polymerization of a small protein which is found in TMV-infected tobacco leaves, but which is absent from normal tobacco. Results suggest that this non-virus protein may represent an incomplete fragment of the TMV protein.

The fact that the non-virus protein may be polymerized to form protein B8 which resembles TMV closely in size and shape is support, *but not proof*, of this idea. Other non-virus proteins have also been found associated with TMV infection but electron micrographs of these have not yet been obtained.

Protein B8 is a close immunochemical relative of TMV in that it will react with anti-sera prepared by injecting rabbits with purified virus. Conversely, TMV will react with anti-sera prepared by injecting protein B8 into rabbits.

Dr. Commoner's work has already lead to the discovery that a drug, thiouracil, which imitates the structure of a key component of virus nucleic acid is an infection suppressor of tobacco mosaic virus reduplication. Such information serves to stimulate the search for drugs which may be effective against other viruses.

Dr. Commoner placed special emphasis on his conviction that the importance of the investigations carried out by his group was that they were directed toward finding the answers to broad, general questions of how living things reproduce. He pointed out that this type of investigation is the essential requirement for progress on all fronts of science.

The investigations were supported by research grants from the National Foundation for Infantile Paralysis, and the American Cancer Society and the Lederle Laboratories.

For earlier reports on the work of Dr. Commoner and his associates, see SCIENCE NEWS LETTER, Jan. 10, 1953, p. 25.

Science News Letter, January 16, 1954