BIOLOGY-MEDICINE-CHEMISTRY

Dr. Stanley's Prize Research Described in His Own Words

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SOME of the most devastating diseases affecting man, animals, and plants are caused by invisible infectious agents called viruses. In the past viruses have been generally characterized by their invisibility, by their ability to pass filters capable of holding back ordinary bacteria, and by their inability to multiply in the absence of living cells. However, even these general characteristics have not been completely acceptable, for there have been reports that some viruses have been seen, others held back by filters, and still others cultivated on lifeless media. The confused state of our knowledge concerning even simple basic properties of viruses has led to an even greater confusion regarding the nature of these agents. They have been regarded variously as protozoa, as invisible forms of ordinary bacteria, as a new kind of invisible living organism, as unusual products of cellular metabolism, as enzymes, and as different kinds of inanimate chemical substances. Because of the general confusion regarding the very nature of these agents, because of the increasing importance of certain virus diseases, and because of improvements in the technique of handling and titrating certain viruses, the time seemed propitious for a concentrated, definitive attack on the nature of viruses. It seemed obvious that this attack should be centered on tobacco-mosaic virus, the first virus to be discovered, because of its high infectivity, its stability, and its availability.

Accordingly, four years ago a study of tobacco-mosaic virus was started in this laboratory. Since knowledge concerning this plant virus was as confused and contradictory as that concerning viruses in general, it was deemed advisable to confine the preliminary work to a study of the basic properties of this virus. Perhaps the most important finding resulting from this preliminary work was the indication that this virus was protein in nature. This information plus improved methods for working with proteins, recently made available through studies on crystalline enzyme proteins, soon led to the isolation from mosaic-diseased plants of a crystalline protein possessing the properties of the virus.

This protein proved to be quite unusual, for it was found to have a molecular weight of about 17,000,000, a value considerably larger than that of any other known protein. This high molecular weight has made it possible to centrifuge the molecules from solution and to crystallize the protein by means of an ultracentrifuge. Chemical studies on this unusual crystalline protein indicate that it is tobacco-mosaic virus. The virus activity, chemical composition, and optical rotation of protein obtained from many different batches of starting material are the same. These properties remain constant during ten recrystallizations of the protein, or when the protein is fractionally crystallized, or fractionated by means of adsorption on and elution from celite. Denaturation or hydrolysis of the protein by enzymes, by acids, by alkalis, or by heat is accompanied by loss of virus activity. It has been impossible to separate the activity from the protein by filtration through collodion membranes, by centrifugation of protein at the isoelectric point, by centrifugation of negatively or positively charged protein from solution, or by centrifugation of the protein from solutions containing other proteins such as tobacco plant proteins, egg albumin, trypsin, or pepsin. The results indicate that the protein and the virus are identical. The fact that the absorption spectrum of the protein agrees essentially with the destruction spectrum of the virus activity is a further indication that they are identical. Chemical analyses, ultracentrifugal analyses, and absorption spectrum measurements have demonstrated that this high molecular weight protein does not exist in normal plants and that it is characteristic of mosaic-diseased plants. Furthermore, the same or a closely related active, high molecular weight, crystallizable protein has been isolated from mosaic-diseased tomato, spinach, and phlox plants. The isolation of the protein from the two latter plants is of especial interest and significance, since there is no serological relationship between the protein from normal tobacco plants and that from normal spinach or phlox plants. Two additional crystalline proteins have been isolated from extracts of Turkish tobacco plants infected with a masked and a yellow strain of tobacco-mosaic virus, respectively. These two proteins are related to each other and to ordinary tobacco-mosaic virus protein, yet they possess chemical and physical properties that distinguish them from each other and from the latter protein. Thus, when tobacco-mosaic virus becomes changed or mutates, it gives rise to a new protein. There is, therefore, abundant evidence indicating that the virus activity is a specific property of these unusual high molecular weight proteins. It seems reasonable to conclude, for the present at least, that the unusual high molecular weight protein isolated from mosaic-diseased plants is actually tobacco-mosaic virus.

Since this is a typical virus, it seems likely that other viruses will be found to be similar entities. Thus, considerable information is now available concerning the nature and mode of action of certain viruses. Infection may be regarded as the introduction of a few molecules of a virus protein into a susceptible host. These few molecules have the ability to direct the metabolism of the host so that it produces not normal protein but more of the virus protein. Disease may be regarded as the disruption of normal metabolism caused by the production of virus protein. Occasionally during the production of virus protein by the host new strains arise, possibly through the chance production of one or more molecules of a slightly different protein. The mutation of tobacco-mosaic virus and the rate of inactivation by X-rays indicate that certain of its properties are similar to those which have been regarded as characteristic of genes.

It is obvious that the protein possesses certain properties which have been regarded as characteristic of living things, yet it itself is non-living. This fact may be of fundamental importance in biology. From the standpoint of chemistry, the net result of virus activity may be regarded as that of an autocatalytic reaction, yet the protein is not a simple autocatalyst. It may be regarded as a super-catalyst, possessing not only catalytic properties, but properties characteristic of genes and other properties similar to those of mammalian organizers. In view of the properties which the crystalline tobacco-mosaic virus protein possesses, the borderline between the living and non-living tends to become non-existent.

Since at least certain virus diseases are really protein diseases, the pathological aspects of virus disease acquire a new significance. Certain basic facts concerning one virus disease may prove to be useful in the study of other virus diseases. For example, in the case of most virus diseases it has been difficult to induce immunity without the use of active virus. Inactive virus has given poor results, yet in most cases it is dangerous to use active virus. In the case of crystalline tobacco-mosaic virus, methods have been evolved for inactivating the virus so that the inactive virus gives practically the same immunological response as that given by active virus. These methods involve careful treatment of the active protein so that the groups responsible for the virus activity are blocked or removed without disrupting the molecule as a whole. It is possible that this and similar studies on crystalline tobacco-mosaic virus may prove useful in the study of other viruses. Whether this unusual, high molecular weight, crystalline protein is regarded as living, as non-living, as a gene, as a super-catalyst, as an organizer, or as a pathological protein, a complete study of its basic properties should prove of importance. It is now possible to list protein molecules, along with living organisms such as bacteria, fungi, and protozoa, as infectious disease-producing agents.

Science News Letter, January 9, 1937

MATHEMATICS

Harvard Mathematician Made President of A. A. A. S.

Dean of Graduate School of Arts and Sciences, Author of Mathematical Theory of Beauty Is Honored

OFFHAND you might not expect a great mathematician to be interested in why it is that men throughout countless ages have taken joy in looking on the moon, a shapely tree, a pearl or the rhythmical curves of a woman's form.

Yet Dr. George D. Birkhoff, Harvard mathematician, who was elected president of the American Association for the Advancement of Science for the coming year, has made the mathematical measure of art one of his main branches of research.

He has devised formulae that enable you to analyze the source of delight in the creations of painters and poets. The esthetic value of a shape or form as determined by the Birkhoff formula conforms to the emotional judgment of those who look upon it. Not that you need to be a mathematician to delight in art. Esthetic pleasure is due to an unconscious appreciation of the mathematical proportions of the object.

In a detailed treatment of esthetic measure which he published not long ago, Dr. Birkhoff has told how painters, architects and others can use consciously some rules that he has discovered. Take forms made with straight lines. The square is rated as the straight line form having the highest esthetic appeal, being rated as 1.50 compared with the diamond at 1.00 and the triangle at 0.63. Take a famous painting. Dr. Birkhoff finds that its composition involves geometric forms which are pleasing to the eye.

The pretty girl is pretty because all her measurements are in correct relation to each other—if her arms were longer or her nose shorter or her height just a little different in relation to her weight, the effect would not be at all the same.

Dr. Birkhoff's formulae for esthetic values can also be applied to music and poetry. The scale used for poetry, for example, is not the same as the one applied to pictures, but it involves such artistic qualities as rhyme, rhythm and alliteration. Dr. Birkhoff has even tried building experimental poems and musical compositions by deliberately placing in them the elements indicated by the formula.

Just a short time ago Dr. Birkhoff, who is only 52, was made dean of Harvard's Graduate School of Arts and Sciences, where he has been professor of mathematics since 1919.

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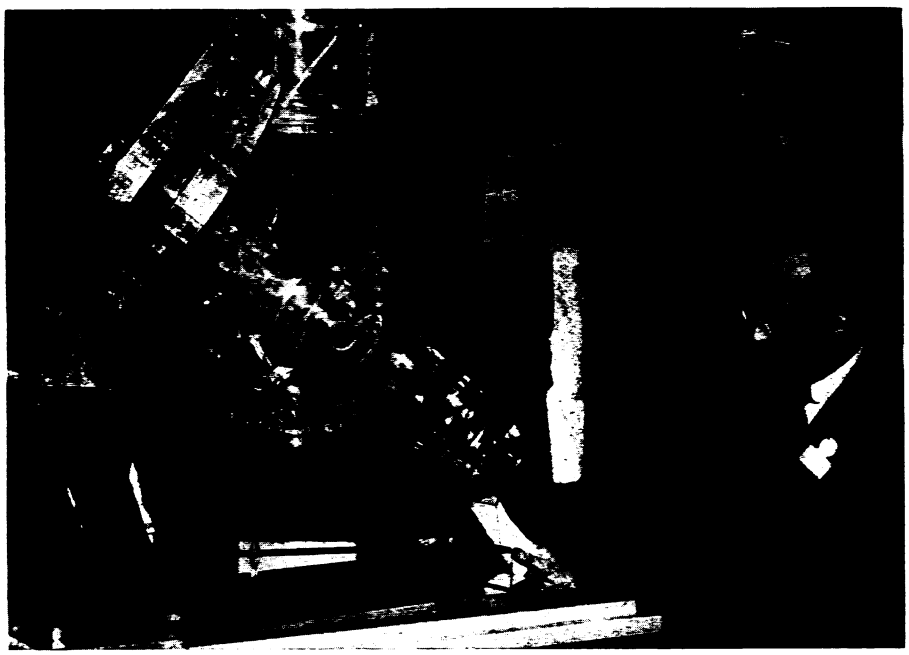

200-INCH TELESCOPE MODEL

Dr. Harlan T. Stetson, Massachusetts Institute of Technology, with a celluloid model of the great instrument on exhibit at the Atlantic City science meeting. Notice the scale figure of the man on base of instrument.

PHYSICS

New Theory of Atom by New A.A.A.S. President

A NEW theory of atomic structure that may allow physicists to understand better the composition of matter was presented to the American Association for the Advancement of Science by Prof. George D. Birkhoff, of Harvard, one of America's leading mathematicians. It is called "a conceptual theory of atomic structure" and may recall to modern approval fundamental ideas that were first presented by the famous James Clerk Maxwell.