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THE INFINITELY SMALL IN BIOLOGY[1]

By THOMAS M. RIVERS, M.D.

DIRECTOR OF THE HOSPITAL OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH

INFECTIOUS diseases and contagion were recognized many centuries before the causes of these phenomena were known or understood. Bacteria, which are considered to have been discovered by Leeuwenhoek in 1675, were known and had been studied for nearly two centuries before they were definitely associated with disease. The names of Dujardin, Davaine, Ferdinand Cohn, Koch and Pasteur stand out in the consciousness of every one as being associated with the proof that microorganisms are the cause of infectious maladies. Indeed, the labors of bacteriologists between the years 1840 and 1890 so clearly established the fact that microscopic animals and plants are the cause of infectious diseases that it became heresy to hold that such diseases might be produced in any other way.

In 1872, Ferdinand Cohn reported that Chaveau and Klebs had passed pus through compact filters consisting either of clay cylinders or membranes and that the material passing through the filters was not capable of producing disease. In other words, the contagious elements in the pus which were considered to be bacteria were retained by the filters. Later, Pasteur, because of his inability to see anything of causative or etiological significance in material capable of producing hydrophobia, suggested that there might be infectious agents smaller than visible bacteria. In 1892, Iwanowski, working with tobacco mosaic, passed juice from an infected plant through a filter and noticed that the filtrate was capable of producing disease in healthy plants. At the time little attention was paid to this observation, but in 1898 Beijerinck made a similar observation. He was impressed by its importance because he could see nothing in the filtrate

[1] Address presenting Dr. Wendell M. Stanley to receive the 1941 Gold Medal of the American Institute of the City of New York, February 6.

and could cultivate no bacteria from it. In spite of the absence of visible bodies, the filtrate was highly infectious and the disease caused by it could be passed in series through a large number of plants. He spoke of the infectious agent in the filtrates as a "living fluid contagium" in order to indicate that he thought it to be different from ordinary bacteria. In the same year Loeffler and Frosch showed that foot-and-mouth disease of cattle is caused by a filterable agent and Sanarelli demonstrated that infectious myxomatosis, a tumor-like malady of rabbits, likewise is induced in a similar manner. Shortly after this a number of diseases were found to be caused by agents so small that they could not be held back by filters capable of retaining ordinary bacteria. Thus, very quickly there was brought together late in the history of infectious diseases a group of maladies now known as "filterable virus diseases." In other words, the story of viruses and virus diseases as a group is a relatively recent one extending over a period of about 42 years.

The early observations on the filterability of tobacco mosaic virus were readily confirmed, but promptly differences in opinion arose regarding the nature of this incitant of disease. A number of bacteria and even some protozoa have been considered the causative agent, but in due course most workers arrived at the conclusion that an organism capable of cultivation on an artificial medium is not responsible and that infectious units of the active agent are too small for resolution by means of ordinary light. In 1935, Dr. Wendell M. Stanley reported the results of work in which he was able to obtain from the juice of plants infected with tobacco mosaic virus large amounts of a crystalline protein possessing all of the characteristics of the incitant of the disease. This protein has been shown to be a nucleoprotein. In addition, it has been demonstrated that a number of other plant viruses are of a similar nature and some of them have been crystallized.

While a few investigators previously had stated that a chemical agent instead of a microorganism is responsible for tobacco mosaic, Stanley was the first to bring a respectable amount of proof that infectious diseases are not of necessity caused only by microorganisms. Stanley's findings, which have been confirmed, are extremely important because they have induced a number of investigators in the field of infectious diseases to forsake old ruts and seek new roads to adventure. As much as many bacteriologists hate to admit it, Stanley's proof that tobacco mosaic virus is a chemical agent instead of a microorganism is certainly very impressive. Moreover, every one admits that the agent of tobacco mosaic is transmissible indefinitely in series from plant to plant, a fact beyond dispute, indicating abundant multiplication or reproduction of the virus. Inasmuch as reproduction is usually considered an attribute of life, great confusion and consternation have been caused. In fact, the results of Stanley's work had the effect of demolishing bombshells on the fortress which Koch and his followers so carefully built to protect the idea that all infectious maladies are caused by living microorganisms or their toxins. In addition, his findings exasperate biologists who hold that multiplication or reproduction is an attribute only of life. In the midst of the wreckage and confusion, Stanley, as well as others, finds himself unable at the present time to decide whether the crystalline tobacco mosaic virus is composed of inanimate material or living molecules. In fun it has been said that we do not know whether to speak of the unit of this infectious agent as an "organule" or a "molechism."

Dr. Wendell M. Stanley, who has wrought this upheaval in the world of infectious diseases, was born on August 16, 1904, in Ridgeville, Indiana. He received his B.S. degree from Earlham College, Richmond, Indiana, in 1926, his M.S. from the University of Illinois in 1927 and his Ph.D. from the same institution in 1929. He was a national research fellow in Munich, Germany, in 1930–31. In 1931 he received an appointment on the staff of The Rockefeller Institute, becoming a member in 1940. Dr. Stanley was awarded the American Association for the Advancement of Science prize in 1936, the Isaac Adler prize by the Medical School of Harvard in 1938, the Rosenberger Medal by the University of Chicago in 1938, the John Scott Medal, certificate and premium of the City of Philadelphia in 1938, for studies on the biochemistry of viruses. He received the honorary degree of doctor of science in 1938 from Earlham College, Harvard University and Yale University.

Dr. Stanley is a chemist and has achieved fame early in life. He announced the discovery for which he is receiving the medal to-night five years ago, when he was thirty-two years of age. Not only has he developed rapidly, but he carried out the early part of his work on the crystallization of the virus in the face of opposition. Five or six years ago very few biologists or chemists thought it worth while to spend much time in attempting to crystallize infectious agents. This story reminds one somewhat of the record of another pioneer in the field of infectious diseases, Louis Pasteur, who as a chemist made outstanding contributions in the field of infectious diseases, often in the face of opposition. In still another respect, Dr. Stanley is like Pasteur; he is a master of exposition and knows well how to defend his work.

I have already mentioned several virus diseases. This group of maladies is large and includes many more than those mentioned, for example, infantile paralysis, St. Louis type of encephalitis, Japanese type B encephalitis, equine encephalomyelitis, small-

pox, vaccinia, yellow fever, human influenza, swine influenza, measles, chickenpox, shingles, lymphogranuloma inguinale, pseudo-rabies, cattle plague, leucosis of fowls, Rous's sarcoma of chickens, peach yellows, curly top of beets, aster yellows and bacteriophagy. This partial list leaves no doubt in the mind of any one that the virus group of maladies is an extremely important factor in the physical and economic well-being of man.

In addition to the immediate importance of virus diseases, there is a more remote one of a philosophical trend which has to do with the nature and origin of their causative agents. A consideration of this phase of the problem eventually leads to a discussion of the nature and origin of life. As every one knows, this discussion was started many years ago. In 1872, it was already well under way in relation to bacteria which at that time were considered the smallest of living things or as Pouchet expressed it "the infinitely small in biology." Indeed, Cohn in an article of that year made the following statement: "Through these facts we surely have a right to hope that in the development of bacteria the key will be found to the origin of life in the world in general."

Scientists of seventy years ago were hoping to find in a study of bacteria an answer to questions about the origin and nature of life. After a time it was realized that these small entities are not simple but quite complex and that it would be unlikely to find in a study of them all the secrets of the origin and nature of life. When a group of infectious agents, the viruses, was found, members of which are smaller than ordinary bacteria, when it was realized that some of them are much smaller than ordinary bacteria even approaching in size that of certain protein molecules, and when a few of these infectious agents were shown to be crystalline proteins, the old discussions regarding the origin and nature of life and what constitutes "the infinitely small in biology" were resurrected and clothed in new garments. Dr. Stanley has played a leading rôle in these discussions and has said and done many things to arouse the curiosity of numerous investigators in many and diverse fields of science.

In these times when the world is greatly disturbed by wars and rumors of wars, it is nice to take a recess from anxiety about what is going to happen to us and our cherished institutions and pay tribute to a man who seeks to make life on this earth more profitable and pleasant. In this connection there comes to mind a statement made by Louis Pasteur in 1888:

> Two contrary laws seem to be wrestling with each other nowadays; the one, a law of blood and of death, ever imagining new means of destruction and forcing nations to be constantly ready for the battlefield—the other a law of peace, work, and health, ever evolving new means of delivering man from the scourges which beset him.
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> The one seeks violent conquests, the other the relief of humanity. The latter places one human life above any victory; while the former would sacrifice hundreds and thousands of lives. . . .

Mr. President, I have the privilege of presenting to you for the high honor of the Gold Medal of the American Institute of the City of New York, a true pioneer in science, one investigating "the infinitely small in biology," a man respected and honored by his colleagues, my friend, Dr. Wendell M. Stanley.

SOME CHEMICAL, MEDICAL AND PHILOSOPHICAL ASPECTS OF VIRUSES[1]

By Dr. W. M. STANLEY

MEMBER OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH, PRINCETON, N. J.

I DEEPLY appreciate the high honor which is conferred by this presentation of the Gold Medal of The American Institute of the City of New York for crystallizing the virus of tobacco mosaic. However, I should perhaps say that I greatly doubt that the crystallization of tobacco mosaic virus which I accomplished in 1935 was the first time that this material had been crystallized. It has been known for years that crystalline inclusions occur within the cells of certain mosaic-diseased plants. Within the past few years, evidence was obtained that this crystalline material consists almost exclusively of tobacco mosaic virus; hence, credit for first crystallizing this virus must go to nature. It might be expected that I should be able to claim to have been the first person to bring about the crystallization of this material. However, I believe that even this is denied me. In 1904 Iwanowski prepared stained sections of mosaic-diseased leaves and noted that the addition of an acid fixative caused the formation of a "striate material." I think, in view of present-day knowledge, that the striate material was crystalline tobacco mosaic virus which was induced to crystallize by the addition of the acid fixative. Therefore, to Iwanowski, who is already credited with the discovery of viruses in 1892, must also go the credit for the first crystallization of a virus. Now, in order to forestall the beginnings of wonderment in the minds of some of you as to why we should be gathered here

[1] Address accepting the 1941 Gold Medal of the American Institute of the City of New York.