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PROGRESS IN THE CONQUEST OF VIRUS DISEASES[1]

By Dr. W. M. STANLEY

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

VIRUSES are small infectious agents that can cause disease in man, other animals, plants and bacteria. They range in size from about 10 mμ, or a size slightly smaller than that of certain protein molecules, in an almost continuous spectrum of sizes up to about 300 mμ, or a size slightly larger than that of certain accepted living organisms. A given virus can multiply and cause disease only when within the cells of certain specific living organisms. No virus has been found to reproduce in the absence of living cells. During multiplication viruses occasionally change or mutate to form a new strain which in turn causes a new disease. Viruses were not discovered until 1892, when Iwanowski demonstrated that the causative agent of the mosaic disease of tobacco would pass through a filter that retained all known living organisms. Six years later Beijerinck proved that this agent was not an ordinary living organism and recognized it as a new type of infectious disease-producing agent—namely, a virus. The same year Loeffler and Frosch demonstrated that foot-and-mouth disease of cattle was caused by a virus. The discovery of the first virus disease of man, that of yellow fever, was made in 1901 by Reed and coworkers. Since then over two hundred diseases of man, other animals and plants have been found to be due to viruses. Among such diseases are smallpox, measles, poliomyelitis, St. Louis encephalitis, influenza, virus pneumonia, fever blisters, equine encephalomyelitis, rabies, hog cholera, dog distemper, fowl pox, jaundice of silkworms, tumorous growths in fowls and in other animals, various yellows and mosaic diseases of plants and the transmissible lysin of bacteria.

The agents responsible for these and other virus diseases are characterized by their small size, by their

[1] Address at the Scientific Award Ceremony of the American Pharmaceutical Manufacturers' Association, at the Waldorf-Astoria in New York, December 11, 1944.

ability to multiply only within the cells of specific living hosts and by their tendency to mutate or change. Because properties such as reproduction and mutation have long been regarded to be characteristic of living entities, viruses were, for many years, regarded as living organisms somewhat smaller than ordinary bacteria. However, the isolation in 1935 of tobacco mosaic virus in the form of a crystalline nucleoprotein of unusually high molecular weight and the subsequent isolation of still other viruses in the form of high molecular weight proteins, some of which were also crystallizable, cast doubt upon the validity of classifying all viruses as organisms. With the exception of virus activity, the properties of some of the smaller viruses are quite similar to the properties of ordinary protein molecules, whereas at the other extreme, with respect to size, the properties of the viruses are more nearly like those of accepted living organisms. The viruses, therefore, serve as a bridge between the molecules of the chemist and the organisms of the bacteriologist, and provide us with new reasons for considering that life, as we know it, owes its existence to structure, to a specific state of matter and that the vital phenomenon does not occur spontaneously, but is possessed in varying degrees by all matter. This phase of viruses can not be developed at this time, for to-day we must be interested in viruses as disease-producing agents.

The almost miraculous results that have been obtained during the past few years with the sulfa drugs and with penicillin in the treatment of infectious diseases caused by bacteria bring into bold relief the fact that these same wonder materials are almost without effect in the treatment of diseases caused by viruses. This fact can be regarded as an indication that the mode of action of viruses differs fundamentally from that of bacteria. Since practically nothing is known of the mechanism of virus reproduction, an attack, at the present time, on virus diseases from the standpoint of chemotherapy, will have to be more or less empirical in nature. Fortunately, however, progress has been made in the conquest of virus diseases, although made, not as a counterpart of modern advances in the conquest of bacterial diseases, but rather as a result of the application of two basic procedures, one of which became established empirically at least three thousand years ago and the other of which was probably used by Pasteur in 1884. It is paradoxical that these two basic procedures were known long before the discovery of viruses as such and that, with the possible exception of the use of virus antibody for the prevention or modification of a disease, as in the case of measles, no fundamental improvement has been made during the intervening years.

About three thousand years ago, at a time when disease was generally regarded as being due to evil spirits or to the will of the gods, it was known that the application of the dried scabs or the contents of pocks and pustules from a person suffering from smallpox, to the lightly scarified skin of persons who had never had the disease, resulted many times in only a mild reaction. These persons were then protected against the more severe disease, smallpox. Scabs or material from the sites of the mild reactions could be applied to still other persons, usually with good results. It seems likely that the smallpox virus was modified by the repeated skin passage in man and that here we have the first example of the modification or mutation of a virus and the use of the new virus strain for purposes of immunization. During the ensuing years occasional references were made to artificial variolation as a means of protection against smallpox, for the method was used from time to time for the immunization of royal personages, yet it was not until 1798 that a definite method of immunization against smallpox was formally advocated. In that year Jenner reported that lymph tissue from cows suffering from cowpox could be used to vaccinate or protect man against smallpox. Although the method was still purely empirical, Jennerian vaccination came into general use throughout the civilized world and is used to this day. The first basic procedure consists, therefore, in the inoculation of a vaccine containing active virus, the virus usually first having been modified by passage in an unnatural host. Although variations of this procedure have been introduced, such as, for example, the inoculation of unmodified virus by an unnatural route or the inoculation of unmodified virus simultaneously with immune serum, the essential immunity which results is due in all cases to the active virus that is produced in the host. Because of the tendency of viruses to change or mutate during reproduction, the possibility always exists that an unwanted strain of virus may arise during the production of the virus; hence, it is obvious that such active vaccines must be tested continuously to be certain that they do not contain undesirable viruses or virus strains.

The conquest of yellow fever is the outstanding modern example of the application of this basic method for the control of a human virus disease. The earlier history of the United States is replete with harrowing descriptions of the ravages caused by this virus disease, and until recently there was no means of immunization against yellow fever. Fortunately, in 1930 Theiler reported that yellow fever virus could be altered by passage in mouse brains. Later the virus was further modified by passage in tissue culture so that a strain, known as 17 D, was evolved, which was found useful for human vaccination. The use of this vaccine plus adequate mosquito control measures have resulted in the elimination of yellow fever as a major public health problem in the Americas and in Africa. During the year ending in June, 1943, The Rockefeller Foundation distributed approximately seven and one-half million doses of this vaccine. The experience of The Foundation has also demonstrated the great benefits that can be derived by measures to eliminate the arthropod vectors that assist in the dissemination of certain viruses. A development of the war becomes of importance in this connection. The Army found a material, known as DDT, to be of great value in the control of an outbreak of typhus in Naples last year because of its lethal effect on the body louse, the arthropod vector of epidemic typhus. This or similar materials will probably be used in the future to control other arthropod vectors of disease agents. However, as was found to be the case with yellow fever, such measures will probably have to be supplemented with the use of adequate vaccines.

Outstanding successes have also been achieved in the control of certain virus diseases of animals by the use of vaccines containing active virus. The most important of these include hog cholera, fowl pox, laryngotracheitis of chickens and ovine ecthyma of sheep and goats. In the immunization of swine against hog cholera, active virus is administered to the animal at one spot and immune serum is administered simultaneously at another spot. In the cases of the virus diseases of fowls and ovine ecthyma of sheep, immunization is achieved by the administration of the active viruses by unnatural routes. The tremendous annual losses which used to occur in the swine, poultry and sheep industries have largely been eliminated because of the development of these effective vaccines. They are used on a scale little appreciated by the general public and have contributed greatly to the economy of the nation. I should perhaps mention that vaccines are not used in the control of virus diseases of plants. Such diseases are controlled by destroying the virus diseased plants as soon as possible and by the development of plant varieties that are resistant to virus diseases. In addition, heat treatment has effected cures in the case of certain plant virus diseases. Rigid quarantine measures established by the State and Federal Governments have proved of benefit in the control of many plant virus diseases. Quarantine measures have also proved useful in the control of certain animal virus diseases, for example, foot-and-mouth disease of cattle in this country and rabies in England.

The fact that mutant strains of viruses are useful for purposes of immunization provides fascinating possibilities for the chemist, for as more and more is learned of the chemical structure peculiar to viruses, the better becomes the chance of altering a virus structure by means of definite chemical reactions with the formation of a new virus strain. The possibility exists, therefore, that at some time in the future the chemist may be able to produce by known chemical reactions definite virus strains for use in vaccines.

The second basic procedure which has proved useful in the conquest of virus diseases consists of vaccination with inactivated virus. This method has been exploited only recently, chiefly because of the general acceptance, for a great many years, of the idea that inactive virus fails to produce immunity. Nevertheless, the first example of the utilization of this method is probably furnished by Pasteur's experiments on rabies. Pasteur noted that the passage of rabies virus in rabbit brains caused a modification of the virus. However, in his classical immunization experiments, he vaccinated a given individual on the first day with a preparation obtained from a diseased rabbit cord that had been subjected to desiccation for 14 days, the next day with a preparation of a cord desiccated for 13 days, then with a 12-day cord and so on until the final vaccination was made with a preparation obtained from a freshly removed cord. He proved that the rabies virus in cords dried between 1 and 6 days was active. Although the cords dried for periods of time longer than about 6 to 8 days failed to produce the disease, it was thought, until recently, that they still contained a small amount of active virus. Now it seems possible that the initial immunity that was established and permitted the subsequent introduction of virus known to be active, arose from the introduction of the inactive virus present in the 9- to 14-day cords. In recent years the idea that inactive virus can produce immunity has been accepted and it appears likely that the use of inactivated virus vaccines will be greatly increased in the future. Attempts to use this method for certain virus diseases have resulted in failures, but it has been used successfully in the cases of dog distemper and equine encephalomyelitis. It seems likely that the failures were due largely to the use of inadequate amounts of inactivated virus or to destruction of the antigenicity of the virus during inactivation.

In many cases it has proved very difficult to secure large amounts of highly infectious diseased tissues for use in the preparation of vaccines. However, in 1931 there occurred a very important development which was destined to alter this picture considerably. In that year Woodruff and Goodpasture found that fowlpox virus would multiply within embryonated chicken eggs, and since that time over 20 different viruses have been grown in chick embryos. Because of the ready availability of fertile chicken eggs, an almost inexhaustible source of these viruses thus became available. To-day several active as well as inactive virus vaccines are prepared from viruses produced in chick embryos. Unfortunately even this rich source of virus appears to be inadequate in certain instances when the material is used directly. It is obvious that when vaccines consisting of inactive virus are used, they must contain a sufficient amount of immunizing antigen if they are to be successful. Fortunately, viruses can be concentrated and it is possible that the concentration of viruses for use in the preparation of vaccines containing inactive virus will provide a new epoch in the conquest of certain virus diseases. One of these is influenza, a virus disease that was responsible for one of the three most destructive outbreaks of disease within the knowledge of man. During the influenza epidemic of 1918–19, approximately five hundred million people suffered from this disease, and of these approximately fifteen million died. At the height of the epidemic, one out of every fifty people in the world died each month, a death rate that is unsurpassed in history. During World War I no means of protection against influenza existed. Even the cause of the disease was unknown. Since then the virus of influenza has been discovered, and it has been grown in chick embryos.

Events of major significance appear to be taking place in connection with the control of influenza, for an Army Commission reported in a recent number of the *Journal* of the American Medical Association that through the use of a concentrated vaccine prepared from the allantoic fluid of infected chick embryos the attack rate during an influenza epidemic was drastically reduced. It seems likely that progress will continue and that the concentration and purification of viruses by modern methods, such as differential centrifugation, will provide vaccines that will result in the elimination of influenza and certain other virus diseases as major health problems. Thus, this type of biological engineering and vigorous, aggressive research on the viruses themselves should provide the means for the future conquest of virus diseases. The American pharmaceutical manufacturers can contribute greatly to this conquest by sponsoring research work on viruses in their own laboratories and in the laboratories of our universities. There is also a need for an awakening, on the part of the public, to the possibilities of medical research. Mankind's complacent and resigned acceptance of a world-wide catastrophe, such as the 1918 influenza epidemic, has been a source of wonderment to me. Here is a disease that in four months killed a half a million people in the United States alone, yet even the nature of the responsible infectious agent was unknown. Despite the tremendous destruction of human life by influenza, a destruction which in four months was far greater than that which resulted in years of combat activities in World War I, the annual monetary expenditure for searches for the true cause of the disease has probably been far less than the cost of a single bomber. The public should insist that the attack on these invisible agents of disease be pursued with the same vigor with which the attack on our visible enemies is now being made. Research is the foundation of this attack and with increased emphasis on research we will eventually realize the true conquest of virus diseases.

THE MARINE ALGAE OF CALIFORNIA[1]

By Professor GILBERT M. SMITH
STANFORD UNIVERSITY

INSTEAD of speaking to you about the marine algae of California I would prefer to substitute a field trip where we could actually pull the algae from the rocks and talk them over one by one as we found them. This being impossible, I propose to take you on a hypothetical field trip and discuss some of the marine algae found along the coast of California. Since this is a hypothetical excursion we could ignore distances and cover a thousand miles of the coast in a single field trip. However, to make it more realistic, this discussion will be restricted to what one could see during a single favorable low tide at a suitable locality.

Before deciding upon the particular locality we intend to visit it might be pointed out that the algal flora is much the same throughout the entire 1,200-mile stretch between Puget Sound and Santa Barbara, California. This is in marked contrast with the algal flora along the corresponding portion of the east coast of North America: the stretch from Newfoundland to North Carolina. There one would find marked differences when comparisons were made between collections made in Maine, at Woods Hole and at Beaufort, North Carolina. The uniformity of the algal flora along the western shore of this continent is in large part due to the California current flowing south along the coast. This current has two marked effects upon the temperature of shore waters. Firstly, there is only a slight gradient in water temperatures from northern Washington to central California. Secondly, the annual variation of water temperature from winter minimum to summer maximum is usually less than five degrees Centigrade. It might even be said that the uniformity of the western flora is due to the thermostatic control exerted by the California current.

On the Pacific coast, as elsewhere throughout the world, there are marked differences between the algae

[1] Address of the retiring vice-president of Section G—Botanical Sciences, American Association for the Advancement of Science, Cleveland, Ohio, September, 1944.