Editorials

FILTERABLE AGENTS

THE Latin word *virus*, literally a slimy liquid, venom or poison, was first introduced into English usage in 1599,[1] and even today it occupies a position which is difficult to define, although in a general sense the limitations of its application are understood and taken for granted. It is usually associated with the words "filterable" or "ultramicroscopic", but this is no longer strictly tenable since many spirochætes, some bacteria, and Rickettsia are filterable and even with the highest powers of the ordinary microscope some of the larger accepted viruses, such as those of vaccinia and psittacosis, are visible. Present-day usage limits the use of the term *virus* to agents which vary in size from the largest protein molecules to that of the smallest bacteria and are obligatory intracellular parasites. Their distribution in nature is widespread since man is subject to thirty-five virus diseases; many hundreds are known to affect plants, insects, birds and other living things,[2] and these may represent but a small percentage of the sum total as only rarely are other than the disease-producing viruses recognizable.

There are two current theories as to the nature of viruses. The first of these is that they are living entities which propagate from one generation to another. Evidence for this is based on the observation that minute particles or elementary bodies have been described in the infected tissues by staining or fluorescent microscopy; that these elementary bodies may be separated by differential centrifugalization and the disease produced by them in susceptible animals; that they apparently grow in tissue culture, may be neutralized by immune sera, and some are even known to go through a developmental cycle. Such elementary bodies have been demonstrated in many of the virus infections of man including influenza, trachoma, herpes, and varicella. Among the animal viruses it is interesting that the Rous sarcoma of chickens and the Shope rabbit fibroma agents are included as showing the presence of elementary bodies.

The second theory is that viruses are autocatalytic heavy proteins produced by the infected cell after such a heavy protein has entered it or possibly even under the influence of some other stimulus. Such a state of affairs would amount practically to spontaneous generation, and additional evidence in favour of the autocatalytic theory has been adduced by Stanley and more recently by others. Stanley isolated a crystalline, chemically pure, protein from tobacco mosaic disease which even after repeated recrystallization was infective. Further, to refute the criticism that a virus was adsorbed to his protein and that this would cause its activity, he showed that when the protein was denatured by any means the activity was likewise lost. No direct evidence is available at present to show that similar heavy proteins are solely responsible for virus activity in animals, but it is particularly pertinent to mention that in polyhedral disease of silkworms minute granules exist as well as crystals in the blood and some of the body cells, and that a serum which agglutinates the granules also agglutinates the crystals, suggesting a near relationship. These virus nucleo-proteins with molecular weights around fifteen to twenty million possess some of the properties of life, *i.e.*, they are able to assimilate, reproduce, and undergo variation, activities which are possessed by the genes.

The portal of entry is important in virus diseases, since a virus which is pathogenic when introduced by one route is without effect when introduced by another. Also lesions are not necessarily produced at the site of entry but at some distant point. Entrance may be by the skin, either directly or by the bite of an animal or insect, through the conjunctiva, the oral, nasal or genital mucosa, but rarely through the alimentary tract. Transplacental passage has also been

1. FINDLAY, G. M.: *Liverpool Med. Chir. J.*, 1937, **45**: 195.
2. *Idem*: *Brit. M. J.*, 1939, **1**: 257.

recorded. The infected cells respond in two ways, either undergoing hyperplasia (warts) or becoming necrotic, apparently on account of a disturbed metabolism. This two-fold tissue response is well illustrated in the reaction of the simple-structured chorioallantoic membrane of developing chick embryos which has proved a highly satisfactory method of culturing many of the viruses. In a single disease both the above reactions may occur together in varying degrees of intensity. The incubation period of virus diseases varies greatly, being as short as two days in the case of the common cold and as long as eight months in rabies and infective warts. Much longer incubation periods have been reported in some of the virus diseases of animals.

Viruses exhibit a considerable degree of specificity, some infecting only the skin, others the nervous system (neurotropic), and still others all the germinal layers, as in the case of herpes (pantropic). They are spread not only by the bites of insects but also from the skin lesions, by the secretions of the upper respiratory tract, by the saliva and the fæces. It is likely too that subclinical cases occur and these may be of considerable importance in the spread of viruses. Carriers also convey these infections the agents being recoverable in some instances months after convalescence (poliomyelitis—four months; lymphogranuloma inguinale—eighteen months). A considerable degree of immunity develops after some virus diseases while in others it is transitory, a good example being the common cold. The exact mechanism of the immunity is not known. It is not wholely dependent on circulating antibodies but residual in the cells themselves. The best prophylaxis at the present time is the active immunity produced by inoculation of a variant strain. In measles a satisfactory passive immunity is obtained with convalescent serum. The fact that two virus diseases, *i.e.*, lymphogranuloma inguinale and trachoma, are susceptible to specific drug therapy suggests that further work along these lines may be fruitful.

Are new virus diseases occurring? Many of the so-called new diseases are not in reality new except in the sense that a heretofore unknown etiological agent has been unearthed, or in other cases are new in location due to the introduction of a disease from its customary endemic centre to a region where it has not been previously recognized. However in the case of St. Louis encephalitis a distinct new disease seems to have arisen. Do saprophytic viruses acquire pathogenicity by mutation, or is there a transference of a virus from one species to another for which it has different pathogenic properties?

Finally, the pleuropneumonia-like organisms must be considered briefly which were first discovered in 1898 and which are now undergoing intensive investigation. In one stage of their developmental cycle they are filterable, but they are not classified with the filterable viruses, as in other developmental forms they are quite large. They are also capable of being grown in cell-free media. Within the last few months Swift and Brown[3] have isolated these organisms from rheumatic fever lesions, and Sabin[4] has produced experimentally in mice arthritis, using mouse strains isolated by himself. He has also found that *Toxoplasma*, a protozoan infecting mice, is a carrier for these pleuropneumonia organisms. Kleineberger[5] had previously discovered a pleuropneumonia-like organism living in symbiosis with a streptobacillus which causes pulmonary lesions in rats.

Can it be that we shall have to add protozoa and bacteria to the already known vectors of viruses in like manner as they are carriers of pleuropneumonia-like organisms?

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3. SWIFT, H. F. AND BROWN, T. M.: *Science*, 1939, **89**: 271.
4. SABIN, A.: *Science*, 1938, **88**: 271, and 1939, **89**: 228.
5. KLEINEBERGER, E.: *J. Path. Bact.*, 1935, **40**: 93.