EPIDEMIC INFLUENZA.[1]

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Those of us who have had the opportunity of working upon the subject of influenza during recent years have speculated from time to time upon the possibility of a renewed pandemic of the disease. Now that war has again involved a large proportion of the world's population this possibility has become a matter of great practical importance if it is true, as many believe, that the disastrous pandemic of 1918–19 was in some way related to the world war of 1914–18. Divergent views upon this latter theory exist, but a statement of the present knowledge of the causation of epidemic influenza and of the possibilities of the control of the disease by specific means may be opportune.

Relation between Influenza Virus and Epidemics of Respiratory Disease.

Since the first isolation of influenza virus in 1933 by Smith, Andrewes and Laidlaw, the findings of these workers have been confirmed by investigators in all parts of the world. The use of the ferret as a test animal for the presence of virus in the throat and nasal secretions during the early stages of the disease has led to the demonstration of the virus in many of the epidemics of influenza which have affected the populations of whole countries since 1933. The virus was not found by Francis (1937) in an epidemic diagnosed as influenza in California in 1935 and it has not been demonstrated in Britain in those localized outbreaks frequently diagnosed as influenza which occur often in public schools and Service establishments chiefly during the winter and spring. At one time it seemed possible that major clinical or epidemiological differences might be discerned between those localized outbreaks which were not associated with influenza virus and those epidemics where the virus was present. This hope appeared brightest in 1937 when many cases of influenza virus infection were seen, and a composite picture of the typical attack was drawn which contrasted with the picture seen in 1936 in the non-virus outbreaks then designated "febrile catarrhs" (Stuart-Harris, Andrewes and Smith, 1938). The acuteness of the onset of illness, the emphasis upon general or constitutional symptoms, and the absence of catarrhal symptoms or signs were held to be characteristic of influenza virus infection. The explosive onset and spread of the outbreak, and the uniformity of clinical picture in those attacked

[1] Read before the British Medical Society of the Dieppe area on January 13, 1940.

were also thought to be characteristic features of the virus infection. Our recent experience in the early spring of 1939 has discouraged us in that at Hampstead we were unable to detect clinical differences between cases or outbreaks where influenza virus infection was proved and those where the virus seemed to be absent (Stuart-Harris, Smith and Andrewes, 1940). In this year the outbreaks seemed indeed to be a mixture of different infections, the virus being isolated from certain outbreaks but not from others. Furthermore, cases were seen which possessed the same clinical features as the virus-positive cases of 1937. The failure to isolate virus from some of these 1939 cases and the absence in them of serological changes specific for influenza virus infection has made the task of clinical differentiation infinitely more difficult.

However, in 1937 influenza caused an epidemic which spread rapidly from one end of Great Britain to the other and which was associated with a sharp rise to a peak in the figures for pneumonia incidence and death-rate. In 1939 there were many localized outbreaks of respiratory disease but no spreading epidemic. There was also a slow rise in the pneumonia incidence and death-rate, which was sustained without a characteristic peak of any considerable magnitude. This epidemiological difference between the years must be considered side by side with the fact that influenza virus was isolated from the majority of human garglings tested in 1937 but from a minority only in 1939. The year 1933, which was a year with a big influenza epidemic and peak in pneumonia mortality in Great Britain, was also the year when influenza virus was first isolated, and the epidemiological and laboratory findings in 1935 in Britain were closely similar to those of 1939. We may argue from this that although influenza virus infection is not a recognizable disease in the individual case or perhaps in a localized outbreak, yet when it occurs as a spreading epidemic of the type seen in 1937, it partakes of the characters recognized historically as significant of influenza and the epidemic is associated with an abrupt rise in the incidence and mortality rate from pneumonia.

Little can be said regarding the ætiology of the localized outbreaks of " febrile catarrhs " which occur seasonally in schools and Service establishments. In certain years, as in 1939, some of the outbreaks or perhaps a proportion of the cases in one outbreak appear to be cases of influenza-virus infection. The majority are not infected with influenza virus and although most of the cases comprise colds, pharyngitis, tonsillitis, or pharyngo-laryngo-tracheitis, cases will at times be encountered with a syndrome indistinguishable from influenza-virus infection. We do not know the cause of these types of respiratory disease or even if they represent one or a group of diseases. It is clear that we are still only on the fringe of knowledge of the causation of epidemic diseases of the respiratory tract in man. Nevertheless, the ferret-pathogenic virus which we can identify in the laboratory seems to have been associated with nearly all the major epidemics of influenza experienced in various countries since 1933.

The causation of the pandemic type of influenza such as that experienced in 1918–19 remains for the time obscure. The occurrence of three distinct waves of infection, the high incidence of pneumonia in the last two waves, and the shift in mortality towards the younger age-groups were features of the 1918 pandemic, which contrast sharply with the experience during recent epidemics. Because such definite epidemiological differences exist between pandemic and inter-pandemic influenza, differences probably exist between the ætiological agents responsible for the outbreaks. It is possible that in 1918 a strain of virus of exceptional virulence with the power to attack the lung arose spontaneously as the result of exceptional world conditions at the time. On this theory the first wave in June, 1918, was due to the type of virus with which we are now familiar, and the succeeding waves were due to the mutant pneumotropic virus which was aided in its attack in certain localities by a variety of secondary bacteria. Such virus mutations can occur in the laboratory and strains of virus of widely differing pathogenicity have been produced by simple passage from one animal to another. Thus strains of the W.S. virus which was first isolated in 1933 have now been produced which differ from the original virus in that they are highly virulent for the ferret and mouse and cause death from pneumonia. Two mouse strains of the W.S. virus have been produced, one of which is highly lethal when introduced intranasally and the other of which (Stuart-Harris, 1939) kills when introduced directly into the brain without the induction of lung lesions. It is interesting to note that these changes in the pathogenicity of the virus are not accompanied by antigenic variations. It is obvious that changes which occur in the laboratory may be exceptional, but they indicate that this particular virus is not fixed in its behaviour. The fact that the virus can be induced to attack the lung in the laboratory indicates the possibility that it will under natural conditions attack the human lung and the isolation of virus from the lung of rapidly fatal cases of pneumonia was recorded by us in 1938 (Stuart-Harris, Andrewes and Smith, 1938). It has been suggested (Laidlaw, 1935) that swine influenza, which made its first appearance in 1918 in the Middle West of the U.S.A. represents the survival in swine of the causative organism of the human pandemic. The virus of swine influenza is certainly a close cousin of the human virus but differs from it serologically. The natural disease of pigs is due to the combined action of a *Bacterium hæmophilus influenzæ suis* and of the virus (Shope, 1931). Shope has suggested (1936) that this bacterial association of swine influenza virus, which is not a property of human influenza virus isolated of recent years, might explain the common occurrence of bacterial invasion in the cases of influenza in 1918, if we assume that swine influenza virus was then a human pathogen. At any rate, nothing is truer than the fact that it is impossible to do more than speculate about influenza epidemics of the past and the causation of pandemic influenza must remain a mystery for the present.

Immunization with Influenza Virus.

It is not the purpose of this paper to detail the mass of observations which have been made in the laboratory upon the immunization of laboratory animals with preparations of influenza virus. The recent reviews of Andrewes (1938, 1939) should be consulted by those interested in the problem. The studies in this country of Wilson Smith, Andrewes and Laidlaw, and of Fairbrother and Hoyle, of Francis and his associates in the U.S.A., and of Burnet in Australia, have laid a solid foundation of knowledge concerning the behaviour of human influenza virus in the laboratory. The less well-known studies of Shope upon the natural disease of swine—swine influenza—have been hardly less important in their bearing upon the human problem. Thus Shope showed at an early stage of his investigations that the pig disease had a dual ætiology and he then demonstrated (1932) that immunization of pigs with virus alone would protect against subsequent infection with both virus and bacterium. The importance of this finding with regard to the human problem is obvious inasmuch as secondary bacterial invasion was probably responsible for the deaths from influenzal pneumonia in recent epidemics.

Three methods of vaccinating ferrets and mice with human influenza virus have been found to be effective in producing immunity and have been applied on a limited scale in man. Firstly, the inoculation of ferrets and mice with living virus subcutaneously or intraperitoneally will not cause infection unless the virus is given in massive doses, and it will protect the lung from subsequent deliberate infection. It will not, however, protect ferrets against direct intranasal infection although some resistance to contact infection is obtained. The method will reinforce a waning immunity in ferrets who have suffered a previous infection with virus but have become susceptible again owing to the passage of time. Francis and Magill (1936, 1937) showed that living virus cultivated in chick embryo tissue cultures was harmless to man when injected subcutaneously, and that so given it produced an increase in neutralizing antibodies against the virus present in the blood. Stokes *et al.* (1937) have claimed that vaccination of children with living virus cultures caused a reduction in the incidence of febrile respiratory infections during an influenza epidemic subsequent to inoculation. The method has not yet been tried in this country.

Secondly, the intranasal use of virus attenuated by passage upon the chorio-allantoic membranes of developing hens' eggs has been tried. This strain of virus (Burnet, 1937*a*) produces only an inapparent infection in the ferret and has been given to man without harm. It is claimed that a rise of antibodies in the blood follows the intranasal inoculation, but no test of the prophylactic value of the method has yet been obtained. It is clear that the method might be dangerous in that if the attenuated virus was given on a large scale it might regain its virulence and be responsible for the outbreak of an epidemic. On the other hand, this risk would not be

present if the virus was only given during an actual epidemic and it is possible that thus administered it might exert a blocking or interference effect upon natural virus acquired by contact infection, even prior to the development of a true immunity response.

Thirdly, virus which has been inactivated by heat (Fairbrother, 1938), or by formaldehyde (Andrewes and Smith, 1937) will immunize ferrets and mice although less effectively than living virus. When administered subcutaneously in the form of a formolized filtrate of infected mouse-lungs it will produce a substantial rise in circulating antibodies to the virus (Stuart-Harris, Andrewes and Smith, 1938). Two field trials of this method of vaccination have been carried out by us, but a conclusive answer has not been obtained as to its value. The trials have, however, demonstrated to us the extraordinary difficulties which exist in assessing the value of any prophylactic in this disease. The first difficulty is that of judging the time when an epidemic is to be expected. In 1937 the epidemic broke out while vaccinations were actually in progress, but in 1939 the Naval Institution, where inoculation was carried out, did not suffer an outbreak of influenza until four months after the completion of inoculation. The importance of judging the best time to carry out inoculation is due to the fact that serological studies suggest that immunity following subcutaneous vaccination does not reach its peak for at least ten days after the injection and will probably have begun to decline six weeks later. The second difficulty is that of assessing the nature of the infections which develop in the inoculated persons subsequent to vaccination because of the existence of the "febrile catarrhs," streptococcal and other infections which cause influenza-like diseases. In the field trial of 1939 this difficulty was considerable because of the existence of outbreaks of "influenza" which were not due to influenza virus. We did isolate influenza virus during the outbreak at the establishment where vaccination had been carried out, but were unable to arrive at any conclusion as to the proportion of cases infected with influenza virus at the time. In view of the other outbreaks which did not yield influenza virus it seemed probable that only a proportion of the cases in both vaccinated and control subjects were due to influenza virus infection. The third difficulty is that of the manufacture of the virus vaccine and the selection of the strains of virus most likely to produce a good immunological response. Formolized mouse vaccine is certainly more difficult to prepare than living culture vaccine, and it requires a large stock of healthy mice. The need for selection of strains of virus has arisen from the discovery that antigenic differences exist between the various human strains so far isolated (Magill and Francis, 1936; Burnet, 1937*b*; Smith and Andrewes, 1938). A polyvalent vaccine composed of several different strains of virus may therefore be more effective than a vaccine composed of a single strain. On the other hand, strains of high virulence for the animals used in preparing the vaccine are needed in order that the maximum yield of virus be obtained.

Discussion.

It is clear that control of epidemic influenza by specific means of immunization is still far from being within our grasp. Yet the generally acknowledged inefficiency of methods of control by the use of masks, gargles, and of quarantine must stimulate renewed attempts upon the problem by other means. Unless our knowledge of the hygiene of air-borne infection is considerably altered in the near future it seems impossible to prevent a disease-spread by droplet infection from infected cases and healthy carriers except by specific immunization. In the case of influenza a method of vaccination is needed which will produce immunity or blocking of infection in the face of a spreading epidemic. The fact that such a method is still not available should probably not deter us from the use of methods which have been on trial but which are still of unproven value. It is doubtful whether the use of specific methods of immunization would be worth while during the next year or so if we are faced with a repetition of the mild type of epidemic experienced in 1937. If, however, we are unfortunately faced with a reappearance of pandemic influenza of the 1918 type, our attitude should probably be different. It must first be established whether the disease is in fact due to a virus of the ferret-pathogenic type, and attempts to isolate virus must therefore be carried out as an essential preliminary step. In order not to wait until the epidemic is in full sway it will be necessary to test any localized outbreaks of a suspicious nature. It is perhaps true that epidemics usually appear without warning, yet if the events of 1914–18 be re-examined, it becomes apparent that respiratory epidemics of a peculiar nature were seen in the years preceding 1918. The disease described by many workers as " purulent bronchitis " (Abrahams, Hallows, Eyre and French, 1917) may have been in some way a precursor to the pandemic. It is certainly true that although sporadic cases resembling this disorder have been seen of recent years, no outbreak of it, so far as the writer is aware, have been reported since 1918. At any rate, it certainly seems advisable for all of us to be on the look-out for respiratory outbreaks of a peculiar nature at the present time. It is clearly not worth while examining the simple catarrhs and nasopharyngeal infections which are always with us, but arrangements should be made for the proper investigation of any outbreaks with an unusually high proportion of chest complications, for the presence of influenza virus.

Supposing the influenza virus is isolated from some possible pandemic are we justified in hoping that some form of immunization with a virus vaccine may be of value ? In fact, laboratory work suggests that it is easier to protect the lung from infection than the nose, and therefore a virus vaccine might be of considerable value in lessening the incidence of chest complications, although less potent in preventing mild nasopharyngeal infections. As to the type of vaccine to employ, opinions may differ as to the best type of preparation. The method of subcutaneous immunization with living tissue culture virus vaccine seems to me to be the most practical procedure

to adopt. The fact that repeated doses of virus do not seem to produce any greater increase in antibodies than a single dose (Stuart-Harris, Andrewes and Smith, 1938) is also not to be forgotten. A single dose of vaccine subcutaneously might therefore be of use in areas not affected by the epidemic at the time of the first isolation of virus. In an area already affected by the disease, subcutaneous immunization is probably too slow to be of value, but in this case the intranasal use of attenuated virus might be worth while. There is clearly no risk of starting an epidemic once the latter has broken out, and even if the attenuated virus produced a mild infection, if protection was obtained against lung complications, the inoculation would be justified.

In conclusion, the time for plans to deal with a recurrence of pandemic influenza is not when the disease has broken out but during a quiescent period. It has been shown in the course of investigations upon epidemics in mouse colonies (Greenwood, Hill, Topley and Wilson, 1936), that a change of population has a most provocative effect upon epidemic disease. The great changes which are at present occurring in the life and distribution of the populations of entire countries cannot be without effect upon epidemic disease and it is unlikely that influenza will play a minor role in this connexion.

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