THE CAUSE OF DEATH IN THE INFLUENZA PANDEMIC OF 1918-1919

An Hypothesis

Lieutenant-Colonel P. D. MEERS, M.D., M.C.Path., Dip.Bact., R.A.M.C.

*The Queen Alexandra Military Hospital, Millbank**

SUMMARY: An hypothesis is presented linking many of the deaths in the influenza pandemic of 1918-1919 with the occurrence of a pulmonary Arthus reaction. This it is suggested followed the appearance of two new serotypes of the influenza A virus in quick succession in 1918, leading to the immunisation of some against an antigen reintroduced in quantity at the time of a second attack. Arguments are advanced to suggest that this hypothesis provides a more credible and complete basis for the recorded events of the pandemic than do other suggestions current in the literature.

The waves of influenza which swept over the world in 1918 and 1919 were characterised at the time as one of the greatest scourges ever to have been visited on mankind. In a few months millions died; 150,000 deaths certified as due to influenza were registered in England and Wales alone. Despite wide ranging theories no completely satisfactory explanation has emerged to account for the so far unique virulence of the disease during this outbreak. None of the newer virological knowledge indicates that a repetition of the event is impossible or even unlikely. For this reason a re-examination of the events of 1918-1919 in the light of recent advances might prove of value.

As it affected any given population the pandemic of 1918-1919 was usually separated into three quite distinct waves. These may be seen in Fig. 1, where the mortality from influenza in London during the period is plotted by week. As influenza is not notifiable there are no figures for the incidence of the disease. Consequently it is necessary to depend on the impressions of those who kept records at the time for an idea of the incidence, as well as for the clinical manifestations in each of the waves. One such record which forms part of the official history of the epidemic is that of French (1920). From his account a very clear picture emerges. The first wave in the summer of 1918 was an explosive outbreak of mild three-day fever with high morbidity and low mortality. The second and third waves in late 1918 and early 1919 were of the same disease for the majority attacked, though for those who developed pulmonary complications there was a very high mortality. This high mortality was particularly noticeable in the second wave, during which the death of so many young otherwise healthy adults attracted particular attention. This effect is seen in Fig. 2, where deaths from influenza in London are related to the total of persons in each of five age groups in each of the three waves. (In preparing this set of histograms it was not possible to allow for those of military age who were away from home at the time. In consequence the death rates in the age groups 5-45 are underestimates, possibly by as much as 20 per cent). Despite the highly significant variation in mortality between waves French is emphatic that the average case of influenza in the second or third wave was little if any more severe than in the first. In the second wave, of each 100 cases of the disease 80 fell into the category of mild illness. The remaining 20 developed lower respiratory symptoms and were more ill. Of these 10 had the now famous heliotrope cyanosis, and 8 died. The pneumonic symptoms

* Now Director, Public Health Laboratory, Greenbank Road, Plymouth.

Fig 1. Influenza deaths, total by week for London, 1918-19.

(Constructed from figures given in *Reports on Public Health and Medical Subjects*, No. 4. (French, 1920).

developed at any stage of what had been up to then a normal attack of influenza. The change for the worse was sudden and the effect so fulminant that it was not uncommon for a patient to die within twenty four hours. Other patients lived for several days after developing severe cyanosis, but most of those who did develop it died. French described the post-mortem appearances: "the lung lesions, . . . struck one as being quite different in character to anything one had met with at all commonly in the thousands of autopsies one has performed during the past 20 years". The principal picture was of acute congestion with diffuse haemorrhage and haemorrhagic infarction. Sometimes purulent bronchitis was also found with lung abscesses of varying size. Microscopically the alveoli were crowded with white and red blood cells and desquamated epithelial cells, often with haemorrhages into the alveolar walls. A conspicuous feature was the development of the so-called hyaline membrane, thought to be the result of an outpouring of a "coagulable albuminous material". This was found both in alveoli and in the alveolar walls.

A theory which is widely held to account for these changes is that they were caused by a virus of unusual virulence for the lower respiratory tract. Such a virus by itself or with the addition of secondary infection due to staphylococci, streptococci, pneumococci or *Haemophilus influenzae*, is thought to have been the cause of the pulmonary complications. The fact that pneumonia can be produced in experimental animals by sequential passage of influenza virus through the lungs is used to support this theory. The similarity

Fig. 2. Influenza death rate, by age and wave, London, 1918-19.

(Constructed from figures derived as in Fig. 1., plus population statistics from the Registrar General's Returns for 1918).

of the histological appearance in the lungs of mice so infected to the lesions in human lung has also been noted (Hers, Mulder, Masurel and Kuip, 1962).

It is believed that this theory has serious flaws. Simple bacterial pneumonia, whether primary or secondary to a virus infection, does not kill as rapidly as has been described in many of the influenzal cases. Also, the onset of an effect dependant on the multiplication of bacterial invaders in an area of damage produced by a virus is most unlikely to be as sudden as has been described. The fact that the uncomplicated form of the disease in the second and third waves did not differ significantly from that seen in the first is a strong point against the theory of increased viral virulence. Had the virus become more pneumotropic in the interval between the first and second waves then all cases of the disease in the later waves would have differed from those in the first. In fact, in the second wave the seriously ill were very sharply divided from those with a mild infection. The most reasonable conclusion is that the difference between the first and the last two waves was caused by an altered or special reactivity of a proportion of the persons affected, rather than to a change in the intrinsic virulence of the infecting organism or organisms. Burnet (1955) concludes: "the simplest interpretation is that it corresponds to those pathological processes in which the reaction of the host rather than any direct damage by the pathogen to vital tissues is the main cause of death".

In considering the nature of the suggested altered or special reactivity, only two

possibilities came to mind. The first is that the population at the time contained a proportion of individuals who were genetically hyper-susceptible to the virus. On development this suggestion proved weak and difficult to sustain. The second of the possibilities lies in a disordered expression of the immune response. The possession of an immune state is commonly thought of as being advantageous to the individual concerned. However, anaphylactic shock, Koch's phenomenon, asthma, hay fever, and auto-immune diseases are examples of disorders produced by the operation of various of the immune mechanisms of the body. Another expression of the immune state which produces damage to its host is the Arthus reaction (Arthus and Breton, 1903). This reaction may be reproduced experimentally by the subcutaneous injection of an antigen into a rabbit which has already a high level of homologous antibody. Over the succeeding hours, the site of injection becomes progressively swollen, the swelling in severe cases going on to necrosis. A brief description of the histological picture of such a reaction is interesting: "polymorphonuclear cell and platelet thrombi develop, producing vascular occlusion, damage to vessel walls, with haemorrhage, oedema, fibrinoid necrosis, and polymorphonuclear and eosinophil exudation" (Boyd, 1956). When this is compared with the description by French of the lungs of those dead of influenza, a similarity is apparent.

In order to hypothecate that a pulmonary Arthus phenomenon was the etiological factor in the exceptional mortality during the 1918-1919 pandemic, it is necessary to make use of facts concerning the Arthus reaction and the influenza virus which have emerged since 1930. It is now generally accepted that relatively large amounts of precipitating antibody must be present in the circulation of the subject for an Arthus reaction to be possible. The reaction then follows the formation of antigen-antibody precipitates in relation to blood vessels (Benacerraf and Kabat, 1950). The influenza virus, the first certain isolation of which was in 1933 (Smith, Andrewes and Laidlaw, 1933), is divided into types A, B, and C. Type A is that which has been constantly and characteristically associated with all pandemics of influenza since its first isolation, and it is assumed that this virus was the cause of the pandemic under consideration. Virus A has two important antigens. The first, the S antigen, is common to all types. The second, the V antigen, is that on which infectivity depends and which has the power of variation from time to time. Since 1933 two major changes in this antigen have taken place, the last in 1957 giving rise to the pandemic of "Asian" influenza.

Using this information, an explanation for the events of 1918-1919 is suggested based on the following hypothesis. The first and second waves of the pandemic in 1918 were due to two distinct antigenic variants of the influenza A virus. Thus there were two influenza viruses active in 1918 which shared the same S antigen, but with different V antigens. Because infectivity is a function of the V antigen, those that suffered an attack of the disease in the first wave would have little or no immunity to the virus of the second wave. An individual who had an attack of influenza during the first wave would have as a result antibody against the S antigen which would be re-formed in quantity during another attack of the disease in the second wave. The conditions needed for an Arthus reaction to occur, the simultaneous presence of large quantities of an antigen and its antibody, might thus have been provided.

With this hypothesis it is possible to explain some of the puzzling features of the pandemic under consideration. The sudden change for the worse in a patient with what had been a normal attack of influenza is readily explained, as the point in time at which

sufficient of the antigen and antibody was present simultaneously would be reached quite suddenly. Once started, an Arthus reaction would develop to its maximum within some six hours. The fact that the sudden worsening might occur at any stage of a patient's illness is accounted for by the necessity for there to have been a sufficient quantity of antibody in his circulation for the reaction to start. If the residue of anti-S antibody from his first attack of the disease was sufficiently high, then his deterioration would take place early. If the level was too low he would have made more (quite rapidly, the response being a secondary one) until the critical level was reached later in the course of the disease. The heliotrope cyanosis is accounted for by the exceptionally acutely developing severe interference with the diffusion of gases between alveolar air and erythrocyte caused by the haemorrhagic infarction and outpouring of oedema fluid. This would have occurred throughout the lungs in a patchy manner dependent on the distribution of antigen and the haemodynamic factors concerned. In those in whom the lung involvement was sufficiently massive death would have followed rapidly due to simple failure of gaseous exchange. In others secondary infection would soon have become established in the infarcted areas and sepsis would then have played its part in causing death at a later stage. The moderately high incidence of lung abscesses of varying size described by French would fit well with this. The wide difference in mortality between the first and later waves follows automatically from the need for the first wave to have sensitised a large proportion of the population to the S antigen of the virus. The fact that only some of the population suffered severe pulmonary complications in the second and third waves is because of the need for an unusually high level of precipitating anti-S antibody in the circulation for an Arthus reaction to start. Experience of serological diagnosis shows the great variability of antibody titres in the sera of patients who have apparently suffered from similar infections. In this case only those who had the misfortune to develop a level of antibody high enough to cause an Arthus reaction when exposed within three or four months to a second attack of the disease would have been at risk. The remainder of the population immunised during the first wave would have suffered no disadvantage from the presence of smaller amounts of this antibody. In consequence if infected in the second or third wave they would have had a repetition of an uncomplicated attack of influenza.

Since 1930, new variants of the type A virus have appeared at intervals of something over ten years. Because recent immunisation is a necessity in the production of very high antibody levels, this time lag has ensured that events on the scale of 1918-1919 have not recurred. However, there is no obvious reason why there should not be an antigenic variation within a period of three months. Indeed the situation in an epidemic should favour the occurrence of such changes by providing both the huge populations of virus and the necessary selective pressure in the form of widespread antibody.

Final proof of the hypothesis suggested may never be possible unless events on the scale of 1918-1919 are repeated, a distinctly unpleasant possibility in the modern world. However in the influenza pandemic of 1957 a few cases of rapidly occurring death in young adults infected with the Asian virus were reported (Ministry of Health, 1960). In this connection it is significant that there were cases of influenza due to the Dutch/56 strain of virus A in the United Kingdom in the early part of 1957. This virus differed from the Asian A strain which reached the country in the summer of the same year in just the way that has been suggested. The possibility therefore exists that these cases were due to the occurrence of Arthus reactions, though on an insignificant scale

compared with 1918. Cases of this type in small numbers have been reported quite regularly associated with epidemics of influenza (Stuart-Harris, 1953).

Experimental evidence in direct support of the hypothesis has proved difficult to produce. However it has been possible to cause subcutaneous Arthus reactions in mice, using the antigen and antibody in question. Mice were immunised passively with anti-S influenza A serum made by hyperimmunising rabbits. This was followed twenty four hours later by the subcutaneous inoculation of S antigen. After six hours the resultant swelling was removed, was sectioned and examined histologically and by immunofluorescence using a fluorescein labelled anti-rabbit gamma globulin. Suitable controls were included in each case. Histologically the components of an Arthus reaction were seen. By immunofluorescence widespread granular deposits were visible which were interpreted as representing antigen-antibody precipitates. This experiment, by no means advancing the hypothesis which has been formulated to the status of a theory, at least demonstrates that the components of the reaction as postulated are capable of interacting in the way suggested.

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