INFLUENZA: ITS SEQUELAE AND TREATMENT*

BY

JAMES TORRENS, M.D., F.R.C.P.,
SENIOR PHYSICIAN, ST. GEORGE'S HOSPITAL

It is obvious that in one evening's discussion only the fringe of so large a subject can be touched upon, and I am faced at the onset with the very real difficulty of deciding not so much what to say as what to leave out in the short time at my disposal. I have therefore thought that it may make for simplicity if I restrict my remarks to some general considerations on what we understand by the term "influenza," and how this disease behaves to the community at large as well as to the individual sufferer from it.

Influenza, then, is an infective disease capable of producing an infinite variety of clinical manifestations and differing in severity within the widest possible limits; it is always present in a sporadic and usually mild form, but it tends to assume epidemic proportions at frequent intervals. Such epidemics may occur in the winter months, when the clinical manifestations are for the most part catarrhal and respiratory, or they may occur in the summer months, when there seems to be a greater tendency to implication of the nervous or alimentary systems. When epidemic proportions are reached—and this happens every year or two—there seems to be a tendency for a similar clinical type to develop in the great majority of cases of that particular epidemic, but this is not invariable, and in every considerable epidemic we find examples of an entire household struck down within a few days, each member of which may exhibit a different clinical picture of disease. In addition, however, to the constant mild sporadic cases (the so-called influenza cold), and the frequent more severe but not too serious epidemics, influenza gathers its forces together every thirty to forty years, exalts its virus, and sweeps a continent, or even the entire globe, like a veritable destroying angel. These pandemic visitations spread with the precise speed of human intercommunication, and their range is only limited by the movements of humanity, so that at the present time, with aeroplane and other transport facilities, no part of the earth is likely to escape the malign "influence." When once a populated area has been exposed to infection the spread throughout that area is extremely rapid, till within three or four months every susceptible person has been laid low and the pestilence has moved on. Unfortunately, influenza—in marked contrast to measles and poliomyelitis—does not seem to provide any lasting degree of immunity to its victims, though there seems to be enough immunity persisting to prevent a second attack during the same epidemic; but countless individuals have undoubted influenza, though often of widely differing clinical type, every year throughout twenty or thirty years or longer.

HISTORICAL

Records show that there have been some fifteen major epidemic visitations of pestilence to Europe in the last 500 years, and that, although the clinical types have varied greatly, each of these would, or should, now be recognized as influenza. There is no reason to suppose that such epidemics have only been manifest for some 500 years. Indeed, there is every reason to believe that they have occurred throughout the ages, but have been limited in extent by the relative lack of intercommunication between one populated area and another which obtained in bygone centuries. Thus the epidemic agues

and the sweating sicknesses of the Middle Ages, as well as certain so-called epidemic dengues, can fairly be regarded as influenzal, while the "trousse-galant" which swept through France in 1529 appears to have been a form of encephalomyelitis developing a few months after all Europe, except France and Italy, had been subjected to the fourth epidemic of "sweating sickness." This name was translated into English as "stup-gallant," and used later for the fifth epidemic of "English sweat." The malady known as "coqueluche" was widespread throughout France during the months of February and March, 1510, and again several times during the sixteenth century, and seems to have been a form of epidemic influenza, which we still see, characterized by an absence of catarrhal symptoms but an intolerable pain in the head, back, and shoulders. The actual name "influenza," as also "la grippe," seems first to have been used about 1745. It was used by the Italians much in the same sense that it was used by Job in the Old Testament—"Canst thou bind the sweet influences of Pleiades, or loose the bands of Orion?"—save that the "influence" was far from sweet.

EPIDEMIOLOGY

An important point in connexion with the major epidemics of influenza is the fact that they are preceded and followed by lesser outbursts of epidemic disease for several years, and that such lesser outbursts are not of the same clinical type as the pandemic visitation when it does arrive. Further, it would seem that before and after a major influenzal epidemic there are seen in epidemic form various diseases of the nervous system, of which the most consistent seem to be poliomyelitis, cerebro-spinal meningitis, and encephalomyelitis (lethargic or spasmodic). It is stated that cerebro-spinal meningitis and encephalitis follow the influenza after an interval of a year or more, while poliomyelitis is more often seen a year or two before the influenza, but this is by no means invariable. In this connexion it is interesting to note that Hippocrates described a serious epidemic of paraplegia occurring one year at Thasus in the winter months, and followed with the commencement of spring by an epidemic of "burning fever" or influenza. This suggests that influenza was behaving in very much the same manner 2,500 years ago as it is to-day. I wonder if Hippocrates failed to observe and note accurately any single manifestation of disease that came within his purview!

If we consider the epidemic happenings in the few years before and after the pandemic of 1918-19, it is possible to see how accurately the events of those years conform to the epidemic concept briefly described above. For example, there was a considerable epidemic of grippe through the United States in 1915. This was closely followed by a notable epidemic of poliomyelitis in and about New York. In 1915-16 there was a considerable incidence of purulent bronchitis with heliotrope cyanosis in the Army at home and abroad. In the spring of 1918 there was a widespread, but not severe, epidemic of febrile disease associated with a rash, and generally thought to be influenza, in Europe, while in the autumn and winter of 1918-19 the pandemic visitation occurred. A year later there was a considerable amount of much less severe influenza, and the first cases of encephalitis lethargica were described. These persisted till 1924-5, and then gradually died away. There was then a period of relative rest from influenza and kindred manifestations until 1929. It is interesting to note here that just as the influenzal encephalitis in the early 'nineties was thought to be due to botulism, so were the earliest cases of lethargic encephalitis in 1919 given the same name. Similar mistakes have very often occurred before. If we accept as correct this picture of influenza and its habits in relation to the community as a whole, it is easy to

* A paper read before the Westminster and Holborn Division of the British Medical Association, December 14th, 1933.

forecast that somewhere between 1945 and 1955, if not before, there will be another pandemic visitation, which will afflict the entire world. And unfortunately, in view of our present ignorance concerning the causation of influenza, there is very little we can do to prevent this catastrophe.

INFLUENZA AND THE INDIVIDUAL

I have tried to sketch briefly the epidemic course of influenza and to show that, if you consider it in sufficiently large a pattern, it repeats its programme with considerable uniformity at approximately regular intervals. I will now turn for a moment to the way in which influenza affects its individual victims; there is no disease so protean in its manifestations, and it is only because these different manifestations have been so clearly connected with epidemic waves of disease that it has been possible to recognize them all as manifestations of the same fundamental malady. At the same time three main types can be distinguished—respiratory, gastrointestinal, and nervous. These may merge the one into the other, or they may be utterly distinct. A great majority of all cases show catarrhal affections to a greater or less extent; but such are by no means necessary, and the symptoms of influenza may be strictly confined to the nervous system, with no vestige of catarrh from start to finish. In the absence of an epidemic the difficulties of diagnosis of the less common variants of influenza are very great, and it is not uncommon to suspect such widely different conditions as cerebral tumour, tuberculous or other forms of meningitis, enteric fever, food poisoning, and acute or subacute rheumatism when the cause is really one of influenza; conversely, in the presence of an epidemic, these various diseases may quite well be labelled influenza, and their real nature overlooked until it is too late. I do not think that detailed consideration of the clinical course of an influenzal attack comes within the scope of this discussion, but I think it is important to try and arrive at some idea as to the nature of the infection which is such a scourge to industrial humanity—an infection which can vary in intensity from that of an innocuous cold in the head to that of a pestilence which kills in a few hours, which confers so transient an immunity, and which can present so diverse a clinical picture.

It has been suggested, if I understand rightly the views of the late Dr. Crookshank, that no single bacillus or no single virus can be found or postulated to fulfil the requirements of this disease, and that influenzal pandemics may depend on telluric or cosmic happenings, the nature of which we cannot even guess at, whereby from time to time humanity as a whole is rendered liable to invasion by various secondary infections, streptococcus, pneumococcus, Pfeiffer's bacillus, etc., against which there is for the time being a greatly lessened power of resistance; but it does not seem necessary to invoke witchcraft or celestial influences to explain influenza. It is, of course, true that the actual and ultimate cause of death in influenza is usually one or other of these secondary organisms, but the spread of an epidemic, and its posting character—limited in scope and rapidity only by the facilities of human travel—and its extraordinary power of case-to-case infective transmission when once it has reached a new area, strongly suggest to me the existence of a basic communicable specific infective agent. I shall never forget watching influenza spread from bed to bed round two wards full of cases of gunshot wounds of the chest in 1918 in France, immediately following the admission of a new patient who had influenza as well as a trifling wound of the thorax; no man escaped in these wards, and half the total number perished. Within a fortnight the entire hospital of 2,000 beds was ravaged, and from twenty to thirty deaths were occurring daily.

The relative immunity of the medical and nursing staffs was striking, as showing the influence of general hygiene and ample fresh air in limiting case-to-case infection.

THE CAUSAL AGENT

A vast amount of work has been done on the bacteriology of influenza, though for many years the work of Pfeiffer and the discovery of his bacillus in 1892 was accepted as indicating the true cause of influenza; but Pfeiffer's bacillus is not the cause of influenza, despite the dictum of Wassermann, "Wo Influenzen da Influenzen bazillin"—a remark which only serves to show the danger of dogmatic utterance in the realm of medicine. If Pfeiffer's bacillus were the cause of influenza, it would be found in a very high percentage of epidemic influenza cases either before or after death, just as *B. typhosus* can be demonstrated post mortem in every case of fatal typhoid fever. Neither in life nor after death can Pfeiffer's bacillus be found in as many as 40 per cent. of any large number of cases of influenza, while in many series of cases it is not found at all. Further, Pfeiffer's bacillus is known to exist in saprophytic form in many tuberculous cavities and other lesions, or in perfectly healthy persons, though undoubtedly it can at times assume a state of high pathogenicity. Neither has any other single organism been found present with sufficient constancy in different influenza epidemics to justify it being labelled as the cause of influenza. It is hard to believe that, if influenza is due to any microscopically visible bacillus or coccus, it would not have been identified with reasonable certainty by now, considering the numerous investigations into this question during the last forty years.

In view of the frequency with which the haemolytic streptococcus is found in the blood stream, or in the lesions of fatal cases of influenza in certain major epidemics, it might be thought that influenza is merely a variant manifestation of the streptococcus; but again many fatal cases do not show any streptococcus infection—in some it is a pneumococcus, in others, a mixed infection with Pfeiffer's bacillus in predominance, while simple uncomplicated influenza does not seem to show any special tendency to streptococcal associations. One is thus forced to conclude that the occurrence of these demonstrable bacteria, although causing the death or serious symptoms of the individual, is really only a secondary and complicating infection, the way for which is paved by the incidence of an unidentified primary influenzal infective agent. That death in influenza epidemics is not due to the influenza itself but rather to a secondary and complicating infection has been believed for many years, and Broussais in 1837 wrote in the *Paris Lancette*: "What have necropsies shown? With regard to the entity of la grippe they have shown nothing. When the sick man dies of it, it is no longer la grippe, it is a complication! But how can you say that this man would have had this affection of which he has died, if he had not had la grippe?" Broussais was tilting at the morbid anatomist Andral, who, because post mortem he could find nothing characteristic *per se* of influenza, declared that the disease only existed in the imagination of the physician. Nevertheless, Broussais' view expresses very much what is thought to-day: "You do not often die of influenza itself; you die very often in times of epidemic influenza of complicating infections that you would not have acquired but for the fact that you were first afflicted with influenza."

If, then, the cause of influenza is not to be found among the microscopically visible bacteria, we must proceed to search for it among the ultra-microscopic filter-passing viruses, which would bring it into line with measles, poliomyelitis, and probably many other diseases.

Recent work by Smith, Andrewes, and Laidlaw is highly suggestive that this may be the true solution of the problem. These workers have succeeded in producing influenza in ferrets and from ferrets to ferrets thereafter by the nasal route, using bacteria-free filtrate from nasal washings from influenza patients. Ferrets were not infected by similar material from non-influenzal persons or from persons who had a cold in the head. Serum from convalescent humans protected other ferrets from infection for several months.

A PLEOMORPHIC VIRUS ?

If influenza is a virus disease, is it not possible to assume that the virus may be of several types, just as the pneumococcus and the meningococcus are of several "types," and that the different clinical forms of disease may depend on which type of virus is the predominant infecting agent, or even that the virus may exhibit mutation from one type to another, or again that there may be several allied viruses in the sense that typhoid and the various paratyphoid bacilli are allied but yet sufficiently different, in that they do not confer cross-immunity the one to the other? This might help to explain the rather anomalous questions of post-influenzal immunity as, for example, the apparent clinical fact that people who had suffered from influenza in 1890 and who were alive in 1918 for the most part escaped infection in that year. In contrast with this we find that annual influenzal attacks are a commonplace. May it not be that this hypothetical virus attacks by preference the mucous membranes or the nervous system, and that at times of epidemics the virus is more deadly, and so damages the mucosae, or so impairs the balance between the sympathetic and parasympathetic nervous systems, or other parts of the central nervous system, that invasion by secondary pathogenic organisms is made easy, and resistance to these invaders is made difficult or impossible by reason of upset and damage to the nervous and metabolic processes which regulate the healthy protective mechanism against bacterial invasion?

It has been suggested by Smith Jelliffe that many of the clinical phenomena of influenza—the headache, the sweats, the pains, the bradycardia, the depression, and the tendency to exudate formation in the lungs and elsewhere—may be explained by a profound disturbance in the balance between the autonomous and sympathetic nervous systems. It seems reasonable. Certainly many cases of post-influenzal bradycardia so marked as to suggest heart-block have been shown by the electrocardiograph to be due merely to vagus over-activity, though in other cases true heart-block and other such disturbances of rhythm as flutter and fibrillation may occur with obvious myocardial damage. May not the apparent connexion between poliomyelitis, cerebro-spinal meningitis and encephalitis, and influenza be explained by the possibility that the one prepares the ground for the invasion by the other, and vice versa; or may not the factor of symbiosis explain some of the secondary invasions and differences in virulence? Hamer has shown that on one occasion when a cerebro-spinal fever epidemic followed closely on an influenzal epidemic the incidence of the cerebro-spinal meningitis was ten times greater among those who had had influenza than the statistical expectation warranted, while Brorström in 1910 emphasized the relation between poliomyelitis and influenza.

TREATMENT AND PROPHYLAXIS

It remains but to say a very few words about treatment. Here I am on difficult ground. The treatment of the attack of influenza is peculiarly the province of the general practitioner; the number of different remedies

that have been extolled shows clearly that there is no specific. All are agreed that early and prolonged rest in bed is all-important, and most of us have our pet prescriptions, usually based on aspirin and caffeine, whereby we hope to relieve the more intolerable of the symptoms; but few of us, I fancy, claim in any way to cure influenza. The prospect of doing good by the use of convalescent serum is attractive but beset with difficulty. We have done a little work in this direction within the hospital, and hope to do more when the opportunity offers. At present it can only be said that research in this direction offers at least a possibility of some day providing a valuable therapeutic agent. The only other question that occurs to me is the possibility of doing good in times of epidemic influenza by wholesale prophylactic vaccination against the secondary invaders. I myself am convinced that therapeutic vaccination when the secondary invasion has occurred is utterly useless, but I feel that the secondary invasion might perhaps be avoided if the individual were protected by a previous course of mixed vaccine against the potential invaders.

THE EPIDEMIOLOGY OF SCARLET FEVER IN A LANDWARD AREA

BY

JOHN RIDDELL, M.B., CH.B., D.P.H.

ASSISTANT MEDICAL OFFICER OF HEALTH, COUNTY OF STIRLING

The recent publication by the Medical Research Council of an *Epidemiological Study of Scarlet Fever in England and Wales since 1900*, by Hilda M. Woods, raises many points of great interest and importance. Perhaps the most striking conclusion to be drawn is that the present low mortality rate is probably only temporary, and that a recurrence of the more malignant type of scarlet fever may be expected. In view of this it would appear wise to concentrate our efforts now on elucidating any factors which might affect the incidence or mortality of the disease, in order that we may be prepared for, and, if possible, prevent, this future source of anxiety. It is hoped that this study, while making no pretension to be exhaustive, may lead to speculation and possibly further investigation into some unexplored aspects of the subject.

The cases dealt with comprise all the notifications of scarlet fever in the landward area of Stirlingshire during the ten years 1921–30. As mentioned in the Medical Research Council's report,¹ notifications do not, of course, form an infallible basis for statistical conclusions, owing, in a landward area especially, to the number of missed cases and other causes, but in a study such as this the effect of these errors can at most only be slight.

PERIODICITY

In the ten years covered no decision can be reached with regard to the periodicity of the disease in this area, but it would appear to conform to the usual five to seven years. In order not to break up the periods of greatest incidence, each year has been taken as commencing on July 1st and ending on June 30th succeeding. Table I shows a minimum incidence in 1922–3, rising to a maximum in 1925–6, and falling to a minimum again in 1927–8—that is, a period of five years between the two minima.

If the cases are now subdivided into age groups—corresponding roughly to pre-school children, school children, and adults—the interesting fact emerges that there is less annual variation in the incidence among adults, and that there is also a tendency for a "lag"