EPIDEMIOLOGY OF INFLUENZA

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The behaviour of influenza has seemed so erratic as regards its occurrence in both time and space that it has fascinated epidemiologists for many years. Recent work seems to show that the influenza virus is more variable and plastic than are most disease agents, and it may well be that this variability can be held largely accountable for its vagaries. The history of modern research on influenza dates from the discovery in 1933 of the susceptibility of ferrets to the virus. Since then we have been able to say whether or not in any " influenza " outbreak we are dealing with a particular disease agent. As to the influenzas of the 19th century and earlier, and the 1918-19 pandemic, we can guess that we have to do with diseases caused by influenza viruses A or B, but we cannot be sure. In the forthcoming discussion, the assumption is made, for convenience, that most of the influenza of the last century has been due to viruses A or B, or to variants of them.

History of Influenza Epidemics, 1850-1950

The earlier influenzas, of which there were several pandemics between 1820 and 1850, will not be discussed here. We may divide the last century into four periods :

(1) Up to 1889 influenza was at a low ebb and was becoming an almost extinct disease.

(2) A period was ushered in by the pandemic of 1889-90; influenza then became, and has since remained, an important cause of mortality and morbidity in most temperate climates.

(3) In 1918 influenza reached pandemic proportions and is believed to have killed 15-20 million people within a couple of years. Its special character was a tendency towards bronchopneumonic complications fatal to previously healthy young adults. In the years following it gradually became less virulent.

(4) Since about 1933 influenza A has come to many countries in outbreaks every two or three years, with a tendency as time has passed for

the peaks to come less frequently and to attain lesser heights. It is, we may hope, again a waning disease; but we cannot be sure that another lethal pandemic may not be immediately ahead.

The period of abeyance of influenza

Apart from a minor outbreak in 1855, influenza seems to have caused few deaths in Britain in the 40 years preceding the 1889-90 epidemic. Much the same seems to be true of Australia, though some epidemic respiratory infection occurred there in 1860 and 1885. In Britain at the present time deaths from influenza are recorded by practitioners as occurring in years when, in the laboratory, no virus is isolated; very probably wrong diagnosis is to be blamed, for no one can infallibly diagnose influenza on purely clinical grounds. It is not at all unlikely that between 1855 and 1899 influenza was almost or quite absent from Britain. Alternatively, it is possible that it was so infrequent that doctors got out of the habit of using the name in their diagnoses. According to the review by Burnet & Clark [6] influenza, though absent from western Europe, caused outbreaks in Russia in 1886 and 1887. They suggest that it had remained endemic somewhere in central Asia, and that its virulence became exalted in Bukhara and elsewhere in May and June of 1889. Other parts of Russia (Tomsk in Siberia, and St. Petersburg [Leningrad]) were affected in October 1889, and western Europe generally in November and December. The particular months may be significant in view of more recent events to be discussed presently.

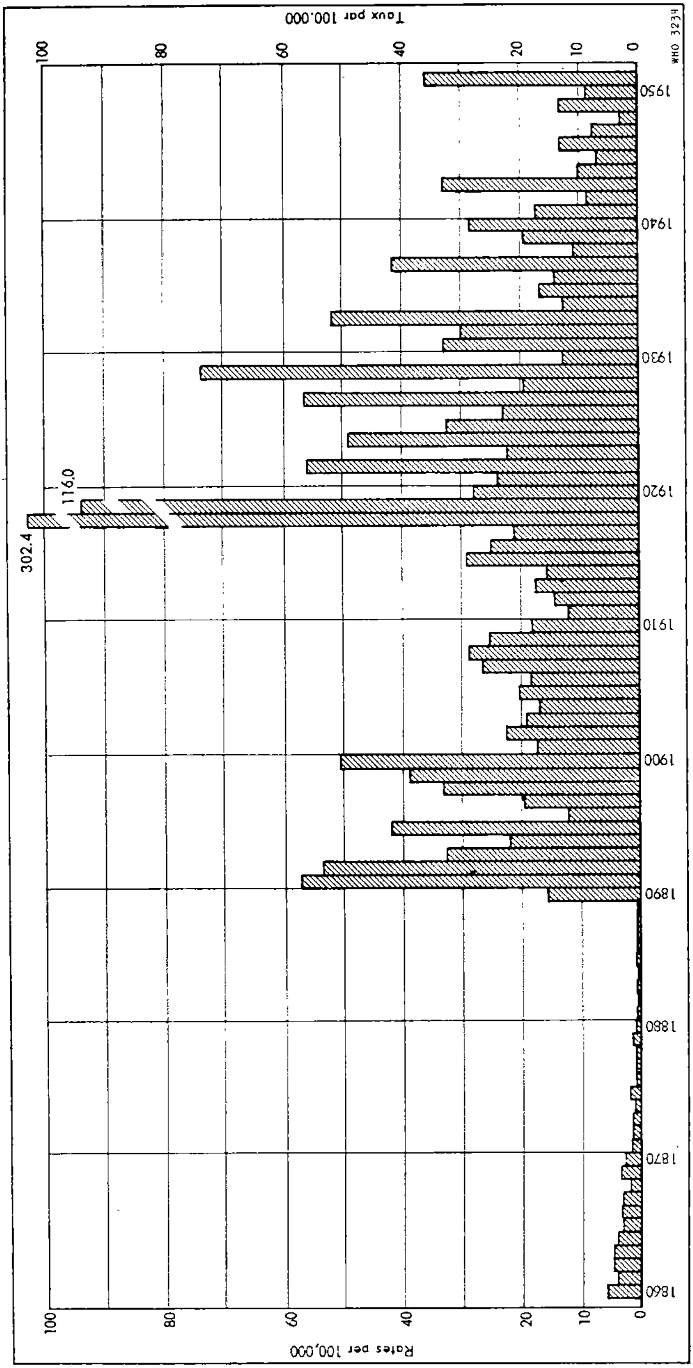
The 1889-90 epidemic and after

The 1889-90 pandemic affected a large part of the world but was not associated with particularly high mortality for young adults. Its chief interest lies in the fact that never subsequently has influenza fallen to the pre-1889 low level. The first wave, in January 1890, was succeeded by others in May 1891 and January 1892, causing progressively higher mortality. There was yet another in December 1893, but, as Burnet & Clark state,

> " it would be preferable to consider the third wave as the last portion of the 1889-93 pandemic, otherwise there seems to be no reason whatever to regard it as finished until its continuing reverberations were lost in the vast new disturbance of 1918 ".

As Greenwood [12] has put it, " the position lost in 1890 has never been regained ". He discounts the idea that the higher level of influenza since 1890 can be accounted for by changing fashions in nomenclature. The striking nature of the change is well shown by fig. 1, depicting the annual death-rate per 100,000 from " influenza " in England and Wales. What underlies this dramatic change is at present a mystery. It is not simply that a " new " disease has now become endemic. As already mentioned, laboratory tests fail to reveal the presence of influenza virus infection

FIG. 1. THE HISTORY OF INFLUENZA IN ENGLAND AND WALES, 1860-1948, AS INDICATED BY THE ANNUAL DEATH-RATE FROM "INFLUENZA" PER 100,000 POPULATION *



* Data based partly on the League of Nations Health Organization's *Annual Epidemiological Reports*

in non-epidemic years—or they show it very rarely. Yet there is some respiratory infection which kills people every year and which was not widely prevalent before 1890. The writer [1] has discussed whether, between epidemics, influenza virus may not persist as a "basic virus" which cannot be recognized as influenza by current laboratory tests. Such a virus could perhaps be held accountable for the "influenza" deaths of "non-influenza" years. Otherwise we must believe either that the statistics are meaningless, or that influenza virus is present but is overlooked in some years, or that some quite different respiratory infection has enjoyed increased prevalence, alongside influenza, since 1890.

The 1918-19 pandemic and after

This, the most lethal pandemic known in history, will not be discussed except in relation to the general theme. According to Frost,[11] there had been a steady increase in the mortality from influenza and pneumonia in New York between 1914 and 1918. In view of recent experiences, it is very questionable whether this progressive rise can be ascribed to the activity of influenza A or of any other single virus. We do not, in fact, know at all what led to the catastrophic events of 1918-19. In the early months of 1918 the influenza had no unusual properties, but in June, in Britain, there was some indication that it was beginning to kill young adults. The really virulent form of the disease appeared at about the same time in the United States of America, around Boston, and in France, in Brest —i.e., at ports of embarkation and debarkation of American troops coming to Europe. In the ports of western Europe, too, there were people of many other races. In view of recent work on gene-recombination among influenza viruses it might be argued that a vicious new hybrid virus had been born in that very mixed culture. (Burnet & Lind,[7] it will be recalled, found evidence that, experimentally, the properties of two influenza viruses could be exchanged, producing a stable variant having mixed attributes.)

The rapid spread of the lethal kind of influenza all over the world is a familiar story. It is estimated that at least 15 million people died as a result. The island of St. Helena in mid-Atlantic is one of the very few places known to have definitely escaped. It seems likely that during the pandemic several different mutants may have arisen, having differing antigenic properties but all still sharing the ability to kill young adults. In such a way we can perhaps account for the fact that, in some English schools and other communities, later waves of influenza might or might not spare the victims of earlier waves.[12] A partial but incomplete protection by one strain against the effects of another could be invoked to explain the varying number of waves which hit different cities in the USA (Pearl [26]). We may picture a number of virus outbreaks moving around, being deflected from their courses when they met with foci of greater resistance.

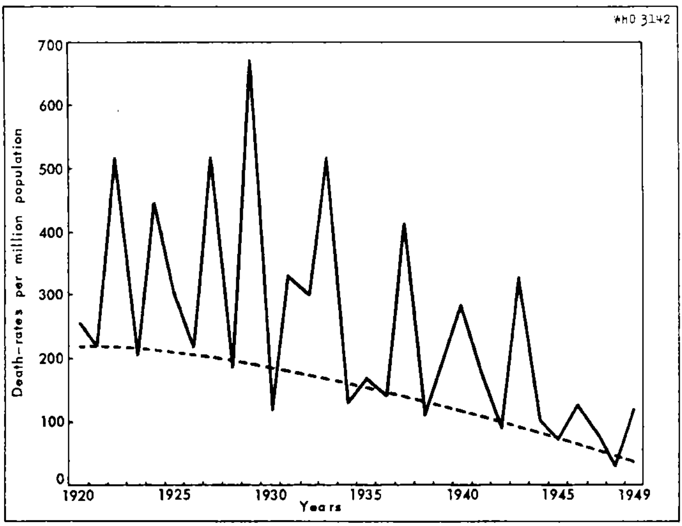
An interesting question of some practical importance is raised by the considerable postponement of the entry of pandemic influenza into Australia : this is claimed to have been due to the imposition of quarantine (cf. Burnet & Clark [6]). The quarantine was, however, far from complete, and experience with the influenza of these times tells us that many carriers and subclinical cases occur. It is quite likely, therefore, that Australia's immunity up to the beginning of 1919 can be attributed rather to the prevalence there of what we may call a routine outbreak of ordinary influenza in September-October 1918.

After the pandemic years influenza returned gradually to its former habits of killing the old and weak rather than the young and vigorous. This reversion took at least three years in the USA and perhaps a decade in Britain. We may suppose that the 1918-19 influenza, aggressive as it was, lacked some property enabling it to persist between epidemics, so that a less spectacular derivative, or perhaps the resurrected pre-pandemic strain, gradually replaced it.

Recent history

There has, perhaps, been a steady change in the epidemiology of influenza even since the pandemic, but it is convenient to treat " recent history " as being from 1933 when the influenza virus was first transmitted to ferrets. The changing death-rate in England and Wales has been discussed by Martin.[24] It seems that, especially since 1933, the mortality

FIG. 2. DEATH-RATES FROM INFLUENZA IN ENGLAND AND WALES, 1920-1949, PER MILLION POPULATION *



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from influenza has been falling and the peaks have been tending to be smaller and more widely spaced. It is true that there was a big peak in 1951 in Britain and in much of Europe, but we cannot yet assess whether that was just a " flash in the pan ". Fig. 2 reproduces a chart from Martin's paper, to show this tendency; it has been modified by inserting a line joining the " troughs ". Such a line indicates deaths from " influenza " in the years when no influenza virus is recovered. Something has apparently been declining just as remarkably as the influenza which produces sharp outbreaks. As discussed earlier, this " something " could be a " basic influenza " not recognizable by laboratory tests, or some other disease which became important when influenza did in 1890 and is now declining pari passu with it. Martin thinks that the " decline in mortality is certainly not due wholly to the use of antibiotics, although it may have been accelerated by it ".

Antigenic Studies of Influenza Viruses

In recent years it has been possible to isolate viruses from each epidemic and thus to discover much more than is possible by the mere study of vital statistics. Since 1940 we have known that there are two influenza viruses, A and B, having nothing in common antigenically, and therefore likely to behave epidemiologically as separate entities. It has been suggested that in the USA visitations of influenza B have tended to come every four or six years, and those of A every two or three. In some outbreaks, serological evidence of double infections with A and B has been rather frequent and it is difficult to be sure that epidemiologically the two agents act quite independently. There is no evidence as yet that influenza C (Taylor; [32] Francis, Quilligan & Minuse [10]) is of much epidemiological importance.

What seems very clear is that major influenza outbreaks can mostly be ascribed to influenza virus A. Great interest therefore attaches to the antigenic variations which have been occurring among the A viruses since 1933. Antigenically, the original (1933) A virus, WS, stands somewhat alone. It had been passed many times in ferrets and mice before antigenic comparisons with later strains were made, and it may have become modified during that time. In the few years following 1933 a few other strains antigenically similar to WS were recovered, but at that time the danger of picking up strains as laboratory contaminants was not appreciated, and we must beware of accepting unreservedly the view that all early isolations of A were of strains closely related to WS; it may well be, however, that 1933-5 was the end of a period when WS-like strains were prevalent.

During the decade 1936-46 the influenza strains isolated from all parts of the world were more or less closely related serologically to the PR8 strain recovered from Puerto Rico by Francis in 1934, and to the

Melbourne virus isolated by Burnet in Australia in 1935. Within this group there were minor variations such as those detected in southern England in 1936-7 (Stuart-Harris et al.[30]). Also, in 1943, the Weiss strain was sufficiently different from PR8 for homologous (Weiss) vaccines to give particularly good results in a vaccination trial in the USA (Commission on Influenza [33]). Still, all the strains from this decade were fairly closely related.

In 1946 in Australia, a strain (Cam) was isolated, and proved to be somewhat removed antigenically from those previously prevalent. Its significance was not at first appreciated, but in 1947 similar viruses were recovered in numbers in North America and also from Europe (Sweden, the Netherlands, and Great Britain). In the USA, these strains were called A-prime (A′) strains, to indicate a major divergence from the classical A viruses; strain FM1 from the USA is regarded as a typical representative. Since 1947, strains related to FM1 have been recovered from A outbreaks in every continent, and seem, quite suddenly, to have completely replaced those related to PR8. It is true that a few workers have reported isolation of viruses closely related to PR8. From their first isolation, however, all these strains have been virulent for mice—a thing which did not happen in the era when PR8-like viruses were of widespread occurrence. Andrewes et al.[2] have made clear the dangers of an accidental " pick-up " of a contaminating virus in the laboratory; and Isaacs & Andrewes [19] have adduced arguments for believing that such pick-ups may be responsible for all or most of the isolations of PR8-like viruses in recent years.

There is a general belief among those studying the antigenic characters of viruses that a succession of antigenic changes is occurring. Viruses resembling WS have not appeared since 1935 or thereabouts, having been replaced by those related to PR8. Since 1947 these too have gone, and the A-primes hold the stage. In the PR8 decade there were variations on the main antigenic theme; and nowadays variations are played from year to year on the theme of FM1. Isaacs, Gledhill & Andrewes [21] felt that, by refined serological methods, they could distinguish in most instances between the A-primes of 1947, of 1949, and of 1951. While almost all workers are agreed as to the existence of progressive antigenic changes among A viruses, there is considerable divergence of views as to detail, depending on the techniques used. Thus, British workers take the view just expressed—that there was a decade of prevalence of strains related to PR8 and that the A-primes which have held the stage since 1947 differ from each other in minor respects and can all be considered members of one group. These opinions are based on studies with immune sera prepared in ferrets. The ferret sera have shown up an epidemiologically important difference between two strains occurring in 1950-1—" Scandinavian " and " Liverpool " substrains, to be referred to later. Magill & Jotz,[22] like other American workers, have made antisera in rabbits, which, unlike ferrets, are insusceptible to actual infection and have to be immunized intravenously or intraperitoneally rather than by intranasal infection. These workers concur in finding that PR8-like strains replaced the WS type about 1934, and that these in turn gave way to different viruses in 1946-7. They encountered two strains, one from 1936, one from 1940-1, with properties of somewhat intermediate nature. They, too, find changes in prevalent viruses from 1947 to 1948-9 and from then to 1950-1, but do not, as do Isaacs, Gledhill & Andrewes,[21] sharply differentiate between a major change from the PR8 era to the A-prime era, and relatively minor changes occurring since.

Hilleman,[14] using roosters to make antisera, has reached conclusions broadly similar to those of Magill. In studying a series of strains isolated in 1933, 1943, 1947, 1948, 1949, and 1950 he finds evidence of gradual loss of " earlier " antigens and an emergence of new ones.

Hirst [16] has used rabbit sera and by absorption tests with large quantities of virus has studied individual antigens; he has distinguished between group antigens and those specific to certain strains. He identifies a specific WS antigen from 1933 but considers that at least four different specific types can be recognized in the PR8 era—one prevalent in 1934, one in 1935-7, another in 1937, and one in 1941-3; then there have been the A-primes since 1947. Unlike Magill, who studied few pre-1947 strains and many recent ones, Hirst's viruses were more regularly spaced in time, but he used only one post-1947 antiserum in his studies. He suggests that

" prior to 1940, a wide variety of strains were prevalent at one time, even in the same epidemic, while since 1940 the existence of a single variety of strain throughout the world has been the dominant characteristic ".

In the writer's opinion, Hirst's tables do not very convincingly support this conclusion. Differences of view among workers are closely related to the use of different animal species for making antisera. Sampaio [28] has made comparisons between antisera made in susceptible species (ferret and hamster) and in insusceptible ones (rabbit and rooster), and has shown that the latter wholly fail to differentiate between the 1951 Liverpool and Scandinavian strains, which behaved quite differently epidemiologically. It seems likely that such inconsistencies as exist would be resolved if all workers used the same techniques. Possibly the use of ferret or hamster sera, combined with an absorption technique, would give the maximum information.

One may perhaps sum up the antigenic changes which virus A seems to have undergone by an elaboration of the metaphor used earlier. Over a period of years, variations may be played upon one antigenic theme, but after some time the possibilities will be exhausted (the herd will be generally resistant to closely related variants), and the introduction of a new motif will be necessary to keep things alive. New variations again upon this will be possible.

Some writers think that the virus has unlimited capacity for variation, others that this is not infinite and that one day we shall inevitably be brought back, as in so many musical compositions, to the original theme. Francis [9] thinks such a circular course would afford " a splendid basis for the classical notions of the periodicity of influenza ".

Studies of Epidemic Spread in Recent Years

In 1945-6 influenza B showed very widespread activity. It was active in the Pacific (Guam, Hawaii) about June 1945 and thence seemed to spread south to Australia, east to the Caribbean, to South and North America, and later to Europe (1945-6). This worldwide activity drew attention to the desirability of some concerted attempt to study the global epidemiology of influenza. After discussions at the Fourth International Congress on Microbiology held in Copenhagen in 1947, the World Influenza Centre (WIC) in London and its network of associated laboratories came into being as one of the activities of WHO. In the winter of 1948-9 came the first opportunity to test the value of the arrangements for observing the spread of an epidemic in correlation with antigenic studies of the viruses concerned (Chu, Andrewes & Gledhill [8]). News came first of an outbreak in Sardinia in September 1948. Magrassi [23] noted that this was apparently multicentric in origin, starting almost simultaneously in ten inhabited localities. Very soon after, influenza was reported in Sicily and Calabria (November 1948) and then along the length of Italy (December 1948 to January 1949) and in Switzerland, Austria, France, the Netherlands, western Germany, and northern Spain. About the New Year of 1949 virus was isolated in southern England, but the morbidity was less than in most of continental Europe and the evolution of the outbreak was slow. It spread also to Iceland and Denmark, but the force of the wave was spent. In Ireland and Sweden the existence of A infection was determined serologically, but there was no epidemic.

Two interesting things emerged from the study of this outbreak. Strains were sent to the WIC laboratory from Italy, Switzerland, France, the Netherlands, Britain, and Iceland. All were A-prime and were serologically quite homogeneous, differing slightly but recognizably from A-primes of previous years. It thus seems clear that a single type of virus was concerned in the outbreak which covered all western Europe. Belief in actual spread of a virus seems inescapable, although the spread may, of course, have occurred some time before, rather than immediately before, the appearance of a visible epidemic.

Magrassi [23] writes that " migration of an individual carrier of infection into new groups of population is insufficient to give rise to influenza ".[a]

[a] " ... non è sufficiente la migrazione dell'individuo portatore dell'infezione in nuovi gruppi di popolazione, per diffondervi l'influenza... "

It is noteworthy that it took some months for the September influenza in Sardinia to involve the rest of Italy; but from Rome to Iceland the passage was very swift. It is also remarkable that the 1948-9 influenza did not apparently spread to eastern Europe. At any rate, influenza A was not very active in Czechoslovakia or Hungary : as to Poland, we are less certain. Possibly a comparatively limited interference with freedom of travel hampers spread of the infection.

The other point of interest is that influenza first arose in Sardinia, Sicily, and Calabria—provinces in which there had been a small outbreak in the early summer of 1948. Some of this infection was apparently due to influenza B, but the circumstances recall events of 1943 when, in Britain, Canada, and the USA, an autumn epidemic was preceded by a small outbreak in the same areas in the early summer. In Britain the spring outbreak had been of influenza A following B. It seems possible that virus which fails to start an epidemic in the, for it, unfavourable season of early summer, may " go underground " and become seeded in a widespread manner, to be activated by unknown factors and appear " multicentrically " in the autumn.

In the winter of 1949-50 there was virtually no influenza in Europe, but in June 1950 the A-prime virus became locally active in Sweden. This virus was serologically a little different from that of 1949; and it was with much interest that one learned of the beginning of influenza in Denmark in October 1950, and soon after in Sweden. Again a local summer outbreak had appeared, died down to vanishing point, and reappeared in the same area in the autumn (Isaacs & Andrewes [19]). Epidemic influenza was reported before long in Norway, Finland, Iceland, western Germany, and the Low Countries, and about Christmas-time on the eastern coast of England and Scotland. Viruses from most of these places were obtained and proved to be A-primes similar to that isolated in June 1950; they were called the Scandinavian subtype. A similar virus apparently became active in southern Ireland about December 1950 and spread north (Meenan & Clarke [25]). There did not occur, however, a regular spread over western Europe from Scandinavia similar to the northward march of 1948-9. In Britain, a week or two after influenza had appeared in Aberdeen and Newcastle, very possibly from across the North Sea, a much more vicious type became active around Liverpool, killing many old and infirm people and causing considerable disquiet. Virus from here was also an A-prime but, with ferret and hamster sera, was readily distinguishable from the Scandinavian strains. This Liverpool subtype became prevalent soon afterwards in Belfast and was recognized in other parts of England, although there it did not show the same killing powers as in Liverpool. It soon appeared that viruses sent in from influenza then present in France, Spain, Italy, Greece, Turkey, and Palestine were of the Liverpool type. Further, these viruses were identical with some which had been received from epidemics that had occurred in Melbourne, Johannesburg, and Cape Town six months or so earlier. Viruses subsequently occurring in Canada, and at least one from the USA, were also Liverpool type. A tentative explanation of these findings is that the influenza in north-west Europe had a double origin—partly from the activation of a dormant virus in Scandinavia, partly from a strain coming up from the southern hemisphere. A line drawn from Dublin to northern England, and so to the Netherlands and Italy, leaves most of the isolations of Scandinavian virus to the north and east and of the Liverpool variety to the south and west.

Influenza in 1952-3

In December 1952 influenza A appeared almost simultaneously in several parts of the northern hemisphere—Japan, the central USA—and, at least by early January, in France and southern England. In France it appeared simultaneously in widely separated parts of the country. By the middle and end of January it was prevalent in southern Germany, Switzerland, and Iceland, and was also widespread in the USA and Canada. Denmark was having a double epidemic, caused mainly by A, although the role of B was far from negligible. Sweden had a good deal of influenza; laboratory tests revealed B only but A may have been present also. By the beginning of February influenza had reached the Netherlands, Finland, Yugoslavia, Italy, and Portugal. In Britain its attack was for long concentrated mainly in the south, especially in and around London; only rather slowly did it spread to northern England and Scotland, and even then its attack was less severe than in the south. This is of interest since, two years before, the north was hit severely while southern England escaped quite lightly. Up to mid-March Ireland was unaffected, having only a little influenza B. Whereas in 1948-9 influenza apparently began in Sardinia and in 1950-1 first news was definitely from Scandinavia, the 1952-3 outbreak seems to have started almost simultaneously over a considerable area of western Europe. Not only that, but the European outbreak came very little later than those in Japan and North America.

A viruses from all the countries mentioned above were examined; all were A-prime and all but a very few were like the 1951 Scandinavian subtype. They differed, however, considerably among themselves as regards their P-Q behaviour (see page 22). Table I shows the behaviour of strains examined in London in 1950-1 and 1952-3 respectively.

Nine strains resembled the Liverpool 1951 subtype. They were found as follows: 2/2 from Paris, 1/3 from southern France (Toulon), 2/2 from Switzerland, 3/3 from Portugal, and 1/10 from Finland. No important differences were found between the Scandinavian subtype strains from Japan, the USA, and Britain. It would appear that for one reason or another the Liverpool subtype had a poorer ability to survive than the Scandinavian.

TABLE I. A-PRIME VIRUSES EXAMINED IN LONDON

Date	Number of strains	S (Scandinavian)	L (Liverpool)	Intermediate
		all strains		
1950-1	96	46	47	3
1952-3	93	84	9	0
		United Kingdom strains		
1950-1	13	4	8	1
1952-3	52	52	0	0

The facts of this epidemic suggest that " hidden " Scandinavian virus persisting from the 1950-1 outbreak may have become activated simultaneously in widely separate centres—Japan, the mid-west of the USA, France, and Britain. Later occurrence in more distant areas such as Iceland, Finland, Yugoslavia, Italy, and Portugal may well have been due to epidemic spread. The 1952-3 outbreak was not preceded by any recognized warning sign in the affected areas in early summer, as had happened previously; it was also unusual in that there was no local prevalence in the autumn before the major epidemic.

The origins of influenza A epidemics

These studies have an important and obvious bearing on the vexed question of the origins of influenza epidemics. Some maintain that influenza never arises from within a country but always comes from abroad. It is so hard for any worker to find influenza virus in his own country between epidemics that this view is only natural. One might, on superficial examination, think it easy to imagine that the virus could flit from country to country whenever it found the inhabitants susceptible, till it came back to its starting point and set off another epidemic, two years or so later. It is, however, very difficult to find influenza anywhere for long periods. Even if one imagines an annual swing between northern and southern hemispheres, one has to remember that influenza A does not break out in Europe every winter.

The alternative view is that influenza, between outbreaks, can go " underground ", possibly in chronic lung lesions in man, possibly in a form unrecognizable by conventional tests (" basic virus "). Shope [29] has in fact shown that the related virus of swine influenza can survive for months or years in pig lung-worms which pass stages of their life-cycle within earthworms. The virus cannot be revealed within these worms either directly or by any immunological or microscopical test, but only by infecting pigs orally and then " provoking " infection by various non-specific stimuli. If such is the state of affairs with swine influenza virus, it is not difficult to believe in the existence of similarly " masked " human influenza virus. We have, of course, no reason for suspecting a helminth intermediate host or carrier for the human virus; nor do we know what non-specific stimuli could activate the human disease.

It appears that when influenza virus is introduced into a country one of two things may happen. It may be imported in its fully-fledged and active state, and set off an epidemic forthwith. This apparently happened when influenza was introduced into Fort Barrow in Alaska in 1935 (Pettit, Mudd & Pepper [27]); also when coolies from China brought the infection to Ocean Island in the Pacific in 1948 (Isaacs et al.[20]). More often, however, events are less dramatic : the virus introduced takes hold less readily and some time has to pass, something else has to happen, before the epidemic begins. When a vessel touched at Angmagssalik in Greenland in 1935, influenza was apparently introduced, but an epidemic did not start until two months later (Høygaard [17]). Many similar instances could be given. The idea that virus may be introduced and widely seeded, and only later produce an outbreak, is one which would help to explain many apparent anomalies in the spread of the disease.

Reasons for believing in the existence of hidden virus are several. There is our inability to find overt virus over long periods. There are the early summer " flurries " which on several occasions have preceded a widespread autumn epidemic caused by an antigenically similar strain. There are the multicentric origins of outbreaks, and the appearance of influenza simultaneously over large areas, the spread being almost too quick for any explanation based on human communications. On the other hand, the events of 1948-9 and many other years leave no doubt that country-to-country spread can occur. One concludes, therefore, that both theories of the origins of epidemics are probably true: that latent virus can probably become activated and start an outbreak, and that in favourable circumstances this may gather momentum and spread across national frontiers. Such happenings form one of the main objects of study of the WHO influenza programme; they will need to be watched for many years yet before the pattern becomes clear and we are able to foretell what will be the next move of the influenza virus.

Antigenic variation and epidemics

No doubt one of the factors determining the occurrence of an influenza epidemic is the immunity-level of the population. It is doubtless a rise in this which determines the end of an outbreak. There is good evidence that subclinical infection is very common and that the antibody level of the community as a whole rises during an outbreak.

It would seem that, when conditions are unfavourable for it, influenza disappears—either overseas or underground—and that it does not readily and automatically arise again, at least for several years. In remote places, such as St. Helena and the Arctic, it probably dies out altogether. Perhaps it did so over much of the world between 1850 and 1890. When it does return, variants of somewhat novel antigenic make-up would seem to have a greater chance of survival than old strains, for which most people will have the appropriate antibody ready and waiting.

P-Q variation

Apart from its comparatively infrequent major antigenic changes, influenza A would seem to be capable of a less drastic type of variation. Van der Veen & Mulder [34] described P, Q, and R " phases " of A viruses. P viruses reacted to high titre in haemagglutination-inhibition tests with homologous sera, and to a much lower titre with heterologous ones; Q viruses reacted very poorly with all, even homologous, sera; the much less frequent R viruses were inhibited very well by all sera. It has been suggested (Isaacs & Andrewes [19]) that Q viruses, in a phase less readily suppressed by specific antibody, might be better able to survive in an immune population. Evidence was adduced that by laboratory manipulations a P-Q change in either direction might be induced. P viruses were made to become Q by passage in eggs in the presence of gradually increasing doses of homologous immune serum. Conceivably a Q virus is half-way to an undifferentiated " basic " virus. It was of interest in 1950-1 that all the Scandinavian strains isolated early in the outbreak were in the Q phase; only later did P-phase strains appear. The Liverpool virus, which seemed a more successful " spreader ", was probably all P-phase. Recently, Isaacs [18] has reported on two viruses isolated in the Persian Gulf in October 1952, 18 months after the 1950-1 outbreak was over and done with. These consisted of a mixture of P- and Q-phase viruses related to Liverpool. He raises the question of whether they may have been on the way " down " from P to Q; or whether, after a period " underground ", they were " coming up " and just acquiring P characteristics. A particularly interesting point is that the Q viruses concerned very closely resembled Q-variants of the Liverpool substrain, artificially produced in the laboratory in 1951 but not found occurring naturally at that time.

Outbreaks of influenza B

So far only passing mention has been made of influenza B. It tends to be more of an endemic disease than A, rarely initiating very large epidemics, and much more apt to cause merely local outbreaks in schools and other closed communities. Some B type seems to occur almost every year, but it is hard to say how much its incidence varies from year to year.

In years when A is not about, small B outbreaks are likely to be better studied and their causative virus determined. When virus A is attacking in strength, a similar number of small B outbreaks might well be overlooked. Influenza B epidemics seem rarely to spread across frontiers; a possible exception is afforded by the worldwide activity of the disease in 1945-6.[5]

Virus B seems to be a better antigen than A: to this has been attributed the apparent wider spacing of its more extensive visitations. Also, vaccines made with it are possibly more effective than A vaccines, even if not made with the current strain of virus.

There are some differences of opinion as to the importance of antigenic variations among B viruses. All workers agree that the original (Lee) strain of Francis stands antigenically as apart from other strains as the original WS does from subsequent A viruses. Some American workers (Tamm et al.;[31] Hilleman et al.[15]) suggest that there have subsequently been antigenic changes in B viruses somewhat similar to those shown by A. On the other hand, Bozzo,[3] Brans,[4] and Hennessen [13] have found that almost all recent B viruses are much alike, even though isolated from different countries in different years. There is at present no suggestion of simultaneous worldwide changes in virus B such as occur with A; and this agrees with the notion that the activities of virus B are more apt to be parochial than international.

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INFLUENZA ANTIBODIES IN THE POPULATION OF THE USA *

An Epidemiological Investigation

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Early in the study of viral influenza it was noted that the immunology of this disease conformed to the basic principles established for other infectious agents. Thus, infection is followed by specific antibody production and there is a rough but not absolute correlation between the amount of specific antibody in the circulating blood and the susceptibility or resistance of the host (Francis et al.; [14] Rickard et al.; [40] Salk et al.[41]). Moreover, the kind and amount of specific antibody may be used as an index of previous infection with the virus, and information regarding the past occurrence of these agents may be obtained by determining the antibody level against the various types of virus in representative samples of the population.

In the early investigations of this sort, the antibody levels were usually measured by the serum-neutralization test (Francis et al.; [14] Horsfall et al.; [28] Rickard et al.[40]). This method was reliable, but costly in time and material, and has largely given way to the simpler haemagglutination-inhibition test of Hirst.[25] Unfortunately, the value of the latter technique has been qualified because of the presence in animal and human sera of heat-stable mucoprotein substances (Hirst; [26] McCrea [33]) which inhibit haemagglutination by the influenza A and B viruses. This inhibition is non-specific, and inhibitors are often present in such quantities that they

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prevent agglutination at higher dilutions than do the specific antibodies. This results in false positive antibody readings.

It was found that the inhibitory activity of this non-specific factor in serum is destroyed by treatment with the filtrate of cultures of *Vibrio cholerae* rich in a substance called receptor-destroying enzyme (RDE) (Anderson [2]). Moreover, the recent studies by Mulder and associates [36] and by Tyrrell & Horsfall,[47] as well as unpublished investigations in this laboratory, have shown that this cholera-filtrate treatment will remove the non-specific inhibitor of influenza A and B viruses from serum without destroying significant amounts of antibody. Hence, it is now possible to measure accurately the antibody in human serum against these two viruses by the haemagglutination-inhibition method. Recent investigations in this laboratory (Hilleman & Werner [24]) showed that the 1233 strain of influenza C virus was not inhibited by the non-specific factors in human serum. For this reason it is not necessary to treat the sera with cholera filtrate in order to measure the antibody against this agent.

This article describes the findings of a study made on human serum to determine the relation between the distribution of specific influenza antibody in the population of the United States of America and the prevalence of the various types of influenza in recent years. The population was sampled in two ways. The first method employed sera collected during 1951 from persons of various ages, while the second employed sera collected from representative groups of adults during each calendar year from 1943 to 1951, inclusive. Although the samples were small, the findings obtained by each of these methods were in good agreement and, moreover, were consistent with those of virus isolation studies made during the same period.

Materials and Methods

Serum

The sera tested in this study were selected as representative of the population of the USA with respect to influenza antibody. Most of the specimens had been obtained for other purposes and had been stored for years. The sampling of the population was therefore by no means random, but, within the limits of the availability of serum, the selection could be considered reasonably representative.

All sera were obtained from military personnel or their dependants free from active respiratory disease at the time of collection. Specimens used in the tests for influenza A and B were from groups of persons different from those tested for influenza C. The children's sera [a] were from patients hospitalized for non-respiratory causes in the summer and autumn months

[a] We are indebted to Colonel O. C. Bruton, M.C., Chief, Pediatrics Section, Walter Reed Army Hospital, Washington, D.C., USA, for these sera.

of 1951. The adult sera dated prior to 1951 were from persons ill with non-respiratory disease during the summer and autumn months of the indicated year. The adult sera for 1951 were from soldiers in good health; those tested against influenza A and B were collected in August, and those used in the tests for influenza C antibody were drawn in February. All specimens were stored at —20°C in this laboratory from the time of their collection.

Cholera-filtrate preparation

V. cholerae strain 4-Z was used for the preparation of cholera filtrate. This agent was obtained from Dr. B. Briody, who had received it from Sir Macfarlane Burnet. The filtrate was prepared by growing the organism for 24 hours at 35°-37°C in fresh beef-heart infusion broth containing 1% neopeptone and 0.5% sodium chloride. The pH of the medium was adjusted to 7.6 and the material sterilized in the Arnold sterilizer. This represented a modification of the original method of preparation described by Burnet & Stone.[5] The Seitz filtrate was adjusted to a pH of 7.0 and usually had an RDE titre of 1/256 when tested with egg-line FW-1-50 virus by the assay method of Burnet & Stone.[5] It was highly effective in removing the non-specific inhibitor from serum but did not destroy any significant amount of specific antibody.

Cholera-filtrate treatment of serum

All the sera to be tested against influenza A and B viruses were treated with cholera filtrate to remove non-specific inhibitor by the method of Mulder, de Nooijer & Brans.[36] In this procedure, each volume of serum was incubated for 14-15 hours at 37°C with four volumes of the filtrate. Residual filtrate activity was removed by heating the mixture at 56°C for 50 minutes. Under the test conditions employed, influenza C virus (strain 1233) was found to be unaffected by non-specific inhibitor in human serum and, hence, the sera tested with this virus were not given cholera-filtrate treatment.

Viral antigens

Antigens were prepared from strains of virus selected as representative of the various known types and subgroups of the agents of human influenza (van der Veen & Mulder;[50] Burnet;[4] Isaacs;[29] Hilleman;[19, 20] WHO [51]). These were as shown in table I.

These viruses have been discussed previously (Hilleman et al. [19, 22]) and have been used as prototypes for earlier strain-analysis studies (Hilleman [19]). The antigens were prepared by methods already described (Hilleman et al.[21]) and were preserved in the dried state until used.

TABLE I. STRAINS OF VIRUS USED FOR PREPARING VIRAL ANTIGENS

Virus type	Subgroup name	Test viruses employed	
		strain	year isolated
A	WS	WS	1933
A	PR8	PR8	1934
A	A-prime	FM1	1947
A	A-prime (contemporary)	FW-1-50	1950
B	Lee	Lee	1940
B	Warner (synonym Bon)	IB1	1950
C	1233	1233	1947

Test procedure

The haemagglutination-inhibition titrations conformed to the technique of the Standard Reference Test in Influenza Diagnostic Studies (Committee on Standard Serological Procedures [8]). Type " O " human red blood-cells were employed in all tests. With influenza A and B viruses, the tests were read after the sera had stood for 55-60 minutes at room temperature. In the tests with influenza C, the sera were incubated in the refrigerator at 4°C for 60-65 minutes. Care must be taken in the reading of tests with low dilutions of treated serum because the characteristic shield pattern of haemagglutination is not always present. In such sera which are free of antibody, floccules of agglutinated cells may be formed which slide towards the bottom of the tube. Unless the tests are carefully observed, they may be interpreted erroneously as negative agglutination.

The titre of each serum was read as the highest initial dilution of serum which gave definite inhibition of haemagglutination. The antibody level of each group of sera tested was expressed as the geometric mean of the titres of the individual sera in the group. Differences in antibody level were considered significant if they were more than twice their standard error.

Findings

As might be expected, the antibody levels of the individual sera against any particular virus showed a considerable variation, and it was not until the mean levels of the groups were calculated and compared that the epidemiological pattern became clear. In the body of the report only the mean antibody levels for the various groups will be considered. However, illustrative examples of the amount of individual variation found are given in Annexes 1 and 2 (see pages 38 and 39). The mean antibody levels against the influenza A, B, and C viruses in sera collected in 1951 from persons of

TABLE II. MEAN ANTIBODY TITRES * OF SERA OBTAINED IN 1951 FROM PERSONS OF VARIOUS AGES

Age (years)	Number of sera	A		A-prime		B		C	
		WS	PR8	FM1	FW-1-50	Lee	IB1	number of sera	1233
		geometric mean of titres							
< 1/2	7	2	13	1	6	9	2	0	—
1-2	16	0	2	2	9	2	2	6	4
3-5	31	2	7	15	41	7	2	27	63
6-8	30	2	7	44	64	6	3	24	89
9-11	25	2	10	68	52	10	8	10	121
adult	74	32	118	43	46	56	44	33	204

* Titres expressed as denominator of serum dilution

various ages are summarized in table II. The results of similar tests with the sera collected in the years 1943-51 from adults are given in table III. These data are presented graphically and discussed in the subsequent sections of the paper.

TABLE III. MEAN ANTIBODY TITRES* OF GROUPS OF ADULTS, FREE FROM ACTIVE RESPIRATORY DISEASE, OBTAINED EACH YEAR : 1943-51

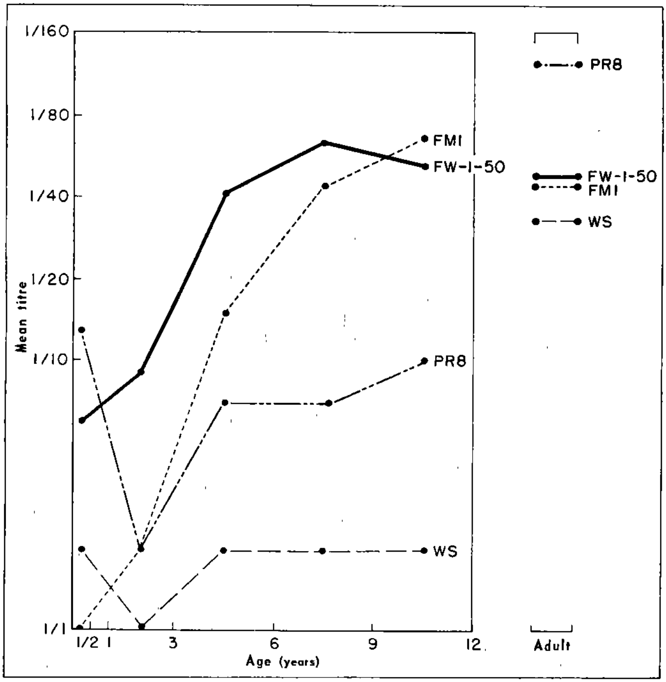
Year	Number of sera	A		A-prime		B		C	
		WS	PR8	FM1	FW-1-50	Lee	IB1	number of sera	1233
		geometric mean of titres							
1943	35	9	18	3	5	10	7	32	263
1944	33	21	78	6	8	9	11	33	182
1945	33	14	65	13	8	24	20	33	129
1946	35	21	96	14	8	71	62	33	191
1947	32	28	91	18	20	65	49	33	159
1948	33	35	96	25	21	47	41	33	162
1949	35	23	83	18	21	59	39	33	219
1950	34	28	60	18	30	38	35	33	200
1951	75	32	118	43	46	56	44	33	204

* Titres expressed as denominator of serum dilution

Influenza A

Age-specific antibody levels. The mean antibody levels against the various subgroups of influenza A of those persons bled in 1951 are shown by age in graphic form in fig. 1. The differences in the antibody patterns of the A and A-prime viruses are quite striking. Antibody levels against the A-type PR8 virus were very low in children under 12 years of age, in contrast with a high level in the adult population. Only one group of children showed a mean antibody titre of over 1/10. This was the group of infants under six months of age who had a mean titre of 1/13 against the virus.

FIG. 1. AGE-SPECIFIC MEAN ANTIBODY LEVELS AGAINST INFLUENZA A VIRUSES FOUND IN SERA OF PERSONS BLED IN 1951

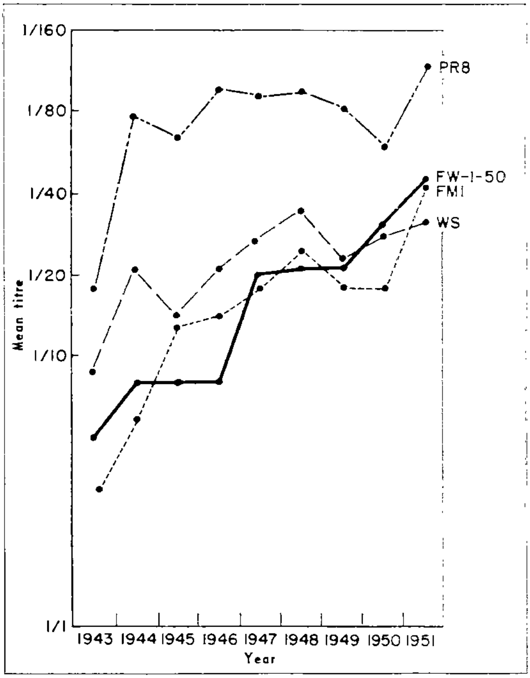


This antibody was, in all probability, acquired from the mother since it was not found in children between one and three years of age. The pattern of the WS antibody was similar to that for PR8, but the mean titres were much lower. There was almost no antibody against this virus in any of the children's sera, but a mean titre of 1/32 was obtained in adults.

In contrast with this, the antibody for both the A-prime strains FM1 and FW-1-50 rose from almost zero at under six months of age to a peak at 6-11 years. The adult levels of both FM1 and FW-1-50 were no higher than those found in children over six years of age. All children had more antibody against the A-prime than against the A strains.

Annual sampling of adult sera, 1943-51. The changes from year to year in the antibody level of adults against the A-type viruses are shown in fig. 2. As with the age-specific levels, marked differences are noted in the antibody pattern against the A and A-prime viruses. Antibody against PR8 virus increased significantly between the times when the 1943 and the 1944 sera were drawn, and thereafter remained relatively constant at a high level without significant variation for the remaining eight years. The curve for the WS antibody paralleled, and roughly maintained half the

FIG. 2. MEAN ANTIBODY LEVELS OF ADULTS AGAINST INFLUENZA A VIRUSES FOUND BY ANNUAL SAMPLING, 1943-51



height of, that for the PR8 strain. The only notable divergence from this general trend was the fact that, in addition to the 1944 increase in antibody, there was a significant increase in the WS level between 1945 and 1947.

Antibody against both the A-prime strains increased steadily from inconsequential levels in 1943 to mean titres of 1/43 and 1/46 in 1951. These rises were characterized by significant increases against FW-1-50 in 1947 and in 1950-1. A similar rise was found in the FM1 antibody in 1944-5 and in 1951. It may be noted that, despite progressive annual increases in antibody levels against the A-prime viruses, it was not until 1951 that values approaching those for PR8, or surpassing those for WS, were reached.

Discussion. The findings described above are consistent with, and tend to confirm, our knowledge of the prevalence of the different types of A virus among the population of the USA. Thus, PR8 virus was isolated in 1934 (Francis [11]) and is representative of the A-type viruses commonly recovered over the ensuing ten years (Hilleman;[19] Magill & Jotz;[35] van der Veen & Mulder [49]). The latest epidemic attributed to this type virus occurred in the winter of 1943-4 (Collins & Lehmann;[7] Commission on Acute Respiratory Diseases;[48] Francis [13]) and the strain has seldom been recovered since that date (Lépine et al.;[32] Nagler et al.;[37] van Rooyen et al.[39]). This distribution in time has resulted in an adult population with considerable past exposure to PR8 and a childhood population with little or no evidence of contact with this virus. Consequently, we find high antibody levels in adults and almost no antibody in children born since 1944. It is noted also that the latest significant augmentation of PR8 antibody in adults occurred after the epidemic in 1943-4. There are several possible explanations for the steady high PR8 antibody level maintained in adults since 1944 despite the apparent infrequency of the virus in the community. Perhaps homologous influenza antibody levels persist in persons for long periods of time. However, a more likely explanation would seem to be one involving an anamnestic response to antigenic components which are common to PR8 and A-prime viruses but which represent only a minor portion of the mosaic of the latter.

The A-prime viruses, on the other hand, have been predominant at least since 1946 (Anderson;[1] Chu et al.;[6] Hilleman;[19] Isaacs et al.;[30] Magill & Jotz;[35] van der Veen & Mulder [50]) but were not prevalent before that time. The FMl strain was isolated in 1947 (Rasmussen et al.[38]), while FW-1-50 was recovered in 1950 (Hilleman et al.[23]) and represents the contemporary A-prime virus. Epidemics of influenza ascribed to A-prime strains have occurred in the USA in the late winters of 1947 (Collins & Lehmann;[7] Francis et al.;[17] Rasmussen et al.;[38] Sartwell & Long;[42] Sigel et al.[43]), 1950 (Collins et al.;[7] United States, Influenza Information Center [49]), and 1951 (Collins et al.;[7] Davis [9]). Such a known distribution of A-prime viruses can be readily correlated with the data illustrated in fig. 1, which indicate that children over six years of age and adults have similar antibody levels against these agents.

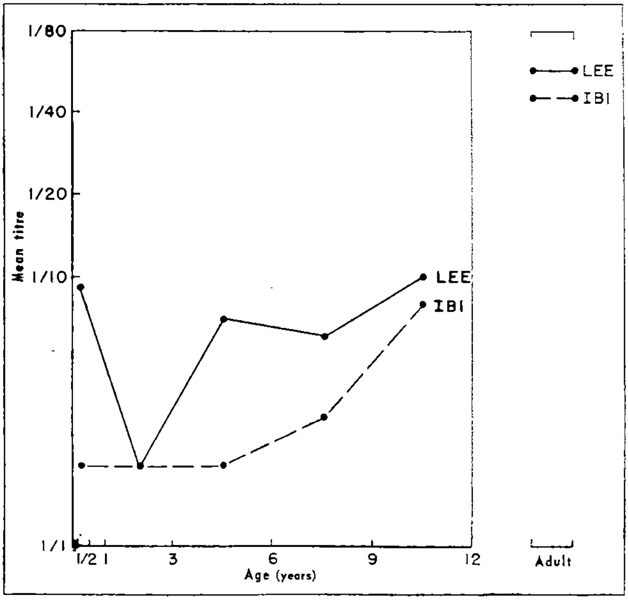
The occurrence of the A-prime epidemics in 1947, 1950, and 1951 is reflected in the levels of the adult sera. This is particularly true of the antibody against FW-1-50. It may be noted in fig. 2 that the antibody rise against FM1 began as early as 1945, and this may indicate the presence of this type virus at least one year before the strain was isolated.

The WS strain was isolated in England in 1933 (Smith et al.[44]) but has not been known to be prevalent since that time. Because this was the first strain of human influenza virus to be isolated, nothing is known of when it first appeared or how long it had been present. The almost complete absence of antibody against this strain in children and the comparatively low levels in adults may be ascribed to the long interval that has elapsed since this virus has been known to be prevalent.

Influenza B

Age-specific antibody levels. The antibody levels against the Lee and IB1 types of influenza B of persons bled in 1951 are shown, by age, in fig. 3. The mean titre of the children's sera against either of these viruses

FIG. 3. AGE-SPECIFIC MEAN ANTIBODY LEVELS AGAINST INFLUENZA B VIRUSES FOUND IN SERA OF PERSONS BLED IN 1951



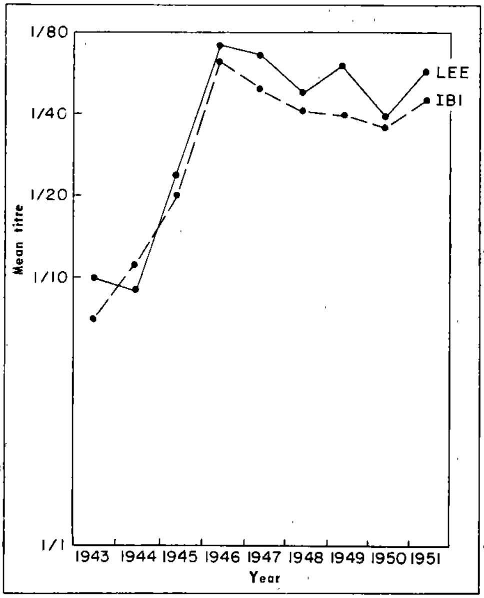
never exceeded 1/10, indicating little exposure of the population under 12 years of age to these strains. In adults the antibody reached titres of 1/44 and 1/56.

Annual sampling of adult sera, 1943-51. The yearly fluctuation in the antibody level of adults against influenza B is illustrated in fig. 4. These sera showed low levels in 1943 and 1944, and significant increases in 1945 and 1946; thereafter, the mean titres were maintained at levels between 1/35 and 1/65.

Discussion. The Lee virus was isolated in 1940 (Francis[12]) and is not known to have been prevalent since that time, whereas the IB1 virus (Tamm et al.[45]) was isolated in 1950 and is representative of the subgroup of B viruses which have been isolated since 1943 (Brans;[3] Burnet;[4] Hilleman et al.;[19, 20, 22] Magill et al.;[35] Tamm et al.[45]).

The serological patterns for B viruses, summarized in fig. 3 and 4, appear to be less closely related to the known epidemic prevalence of influenza B than are the periods and incidences of influenza A and A-prime, discussed earlier. The significant rise in B antibodies in 1946 and the subsequent maintenance of a high level in adults correlates with the 1945-6 epidemic (Collins & Lehmann;[7] Francis et al.;[16] Hirst et al.;[27] Kalter & Chapman[31]) and the intermittent prevalence of the virus since that time.

FIG. 4. MEAN ANTIBODY LEVELS OF ADULTS AGAINST INFLUENZA B VIRUSES FOUND BY ANNUAL SAMPLING, 1943-51



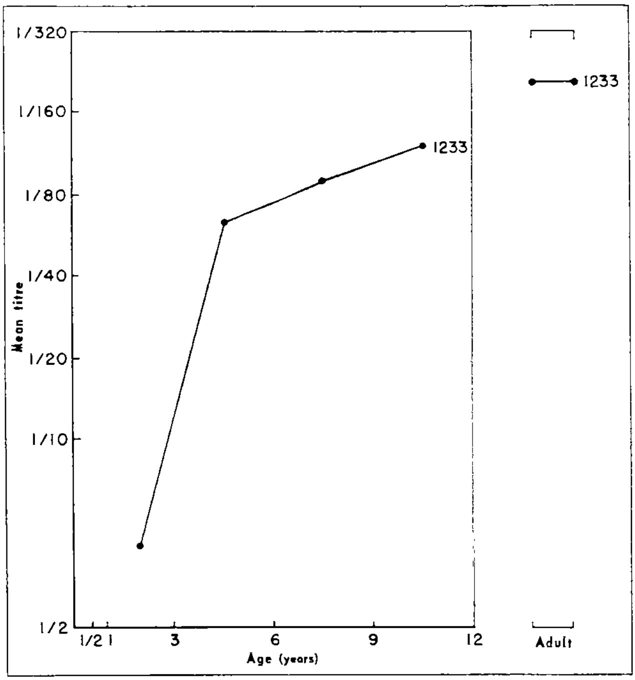
However, one wonders why the level remained in the neighbourhood of 1/10 during 1943 and 1944, only a few years after the 1940 epidemic of influenza B (Collins & Lehmann;[7] Eaton & Beck;[10] Francis;[12] Magill[34]), and why the antibody level increased significantly in 1945, one year before the 1945-6 epidemic. Moreover, the B antibody levels are relatively low in children of from 9 to 12 years of age who lived through the 1945-6 period. Certain observations may be considered in attempting to understand these aberrancies. These are concerned with the rather sporadic distribution of the disease, even during periods of prevalence of B virus and the relatively long periods between such episodes.

It is of interest that the antibody levels in human sera summarized in fig. 3 and 4 are similar for both strains. However, the two agents can be distinguished antigenically without difficulty in tests with animal sera (Hilleman et al.;[19, 22] Magill & Jotz;[35] Tamm et al.[45]). The findings of this investigation seem to indicate that in human serum the tests measured the same antibody in spite of the antigenic differences demonstrable by other methods.

Influenza C

Age-specific antibody levels. The antibody levels against influenza C are shown by age in fig. 5. No sera were available from children of less

FIG. 5. AGE-SPECIFIC MEAN ANTIBODY LEVELS AGAINST INFLUENZA C VIRUS FOUND IN SERA OF PERSONS BLED IN 1951

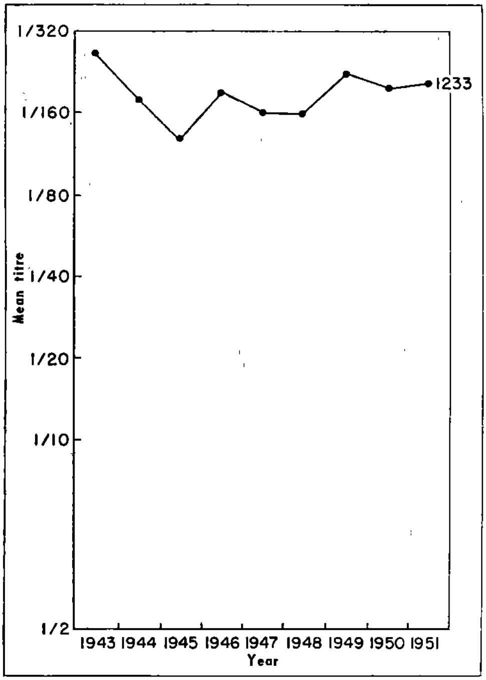


than six months of age at the time when the investigation referred to in fig. 5 was carried out. Subsequent tests performed on the sera of three infants aged between six weeks and three months gave titres of 1/20, 1/40, and 1/320; this antibody was probably of maternal origin. The antibody was at insignificant levels at from one to two years of age and then rose sharply to high levels at from three to five years. This high level was maintained throughout all the older age-groups.

Annual sampling of adult sera, 1943-51. The annual sampling of the adult sera shown in fig. 6 indicates a consistently high level of antibody throughout the nine years.

Discussion. Strain 1233, recovered from a case of respiratory disease in 1947 (Taylor[46]) was the first influenza C virus to be isolated. Its relation to clinical influenza was not clearly established until 1950 (Francis et al. [15]). Relatively few cases of this type of influenza have been reported to date, and few outbreaks have been described (Francis et al.;[15] Gerber et al.[18]).

FIG. 6. MEAN ANTIBODY LEVELS OF ADULTS AGAINST INFLUENZA C VIRUS FOUND BY ANNUAL SAMPLING, 1943-51



In spite of this, the antibody level for influenza C in sera of children over three years of age is high and indicates that infection occurs at an early age. Furthermore, the presence of large amounts of antibody in sera collected from adults in 1943 indicates that the virus was widespread in the population before that time. These findings are in agreement with those reported by Francis et al.[15] and support the concept that infection with this agent has been widespread in the population of this country for many years.

General Discussion

These studies utilized the diagnostic haemagglutination-inhibition method for the survey of influenzal antibody in the population. The results of the tests with the influenza A and B viruses would not have been valid had not the sera been treated to remove non-specific inhibitor. Unpublished studies from this laboratory have shown that the PR8 virus employed in the tests was especially affected by the non-specific substance. Thus, it was observed that untreated sera from 16 children of from one to two years of age had a mean titre value of 1/160 with PR8; these same sera failed to give significant inhibition of haemagglutination after cholera-filtrate treatment. The WS, FM1, Lee, and IB1 strains were also markedly affected by the non-specific substance, but to a somewhat less extent; the FW-1-50 agent was relatively unaffected, and the 1233 strain of influenza C virus was not influenced by the inhibitor.

In this study, the measurement of influenzal antibody in population groups was applied to the retrospective determination of influenza virus occurrence. It is not unreasonable to expect that the same approach may be useful in predicting the susceptibility of a population to a particular virus. This method might have been utilized at the time the first A-prime virus, Cam, was isolated in Australia in 1946 (Anderson[1]). Cam virus is essentially identical, antigenically, with the A-prime FM1 virus recovered in the USA the following year. As shown in table III, the mean titre in adults for the FM1 virus in 1946 was only 1/14. This level was considerably below that for the A strains occurring previously, and studies of this type would have suggested the susceptibility of the population to this kind of virus. Findings of this kind, if confirmed by a larger sampling of a representative group of persons, together with the results of the strain analysis studies, would suggest a need to include a newly isolated virus in the vaccine before the occurrence of an epidemic.

While the measurement of influenzal antibodies may provide a valuable yard-stick for estimating susceptibility of a given population to a given virus, it should be noted that the relationship between antibody titre and immunity is not always consistent. Thus, it has been shown in studies of naturally and experimentally induced influenza that the disease sometimes occurs in persons with high antibody levels, and that persons with low titres may escape infection (Francis et al.;[14] Rickard et al.;[40] Salk et al.[41]). It would appear, then, that other factors in addition to circulating antibody may be of importance in the immunology of this disease.

ANNEX 1. ANTIBODY TITRES * AGAINST INFLUENZA VIRUSES IN SERA COLLECTED IN 1951 FROM CHILDREN BETWEEN THREE AND FIVE YEARS OF AGE

Serum no.	Type A		Type A-prime		Type B		Serum no.	Type C (1233)
	WS	PR8	FM1	FW-1-50	Lee	IB1		
38	0	10	0	10	0	0	6	10
80	10	20	80	160	10	10	10	320
122	0	10	40	40	0	0	14	320
123	20	40	160	160	40	0	16	40
126	0	0	0	0	0	0	23	320
141	20	80	160	160	20	0	25	320
147	—	—	—	20	10	0	26	320
155	0	0	0	10	0	0	31	80
167	0	0	0	10	0	0	32	10
171	0	10	10	20	20	0	33	160
178	0	0	80	160	0	0	34	320
179	0	0	320	640	10	0	36	0
180	0	10	320	640	20	0	37	20
185	0	0	0	0	0	0	38	40
186	0	40	0	40	40	0	39	80
192	0	10	160	320	0	0	41	40
194	20	40	640	320	40	10	44	20
195	0	0	160	80	10	40	53	160
196	0	20	320	320	20	20	55	320
197	0	20	0	20	20	0	62	160
198	0	0	0	10	20	0	63	80
199	0	20	160	160	20	0	66	20
210	0	0	80	80	0	0	72	10
215	0	0	0	20	20	0	77	10
216	0	0	0	20	10	0	78	160
219	20	40	0	20	40	10	81	10
220	10	20	40	40	20	10	86	640
222	0	20	40	40	0	0		
228	10	20	0	0	20	0		
232	20	40	320	320	20	0		
249	0	20	0	20	20	0		

* Titres expressed as denominator of serum dilution

ANNEX 2. ANTIBODY TITRES * AGAINST INFLUENZA VIRUSES IN SERA COLLECTED FROM ADULTS IN 1950

Serum no.	Type A		Type A-prime		Type B		Serum no.	Type C (1233)
	WS	PR8	FM1	FW-1-50	Lee	IB1		
253	0	0	0	20	20	40	22	40
254	80	160	40	40	80	80	23	40
351	160	320	80	80	20	20	24	160
352	80	320	40	40	160	80	49	320
355	40	160	20	20	320	160	50	320
356	40	160	40	10	20	20	51	320
357	10	40	20	20	40	40	76	160
358	160	160	80	20	160	160	77	80
359	40	80	10	40	40	80	78	40
360	40	40	10	10	20	40	103	640
361	40	80	20	20	0	20	104	160
362	20	160	320	80	80	160	105	320
363	40	160	80	20	20	40	130	320
364	20	20	0	20	80	80	131	640
365	20	80	80	80	20	20	132	640
366	10	20	20	20	40	10	157	640
367	20	40	40	20	80	40	158	80
368	40	80	40	40	40	40	159	320
369	160	160	40	20	160	80	184	320
370	160	320	20	160	80	80	185	320
371	10	20	10	10	40	40	186	80
372	0	0	0	20	0	0	211	640
373	160	320	40	20	320	320	212	640
374	160	160	80	80	80	80	213	640
375	20	40	20	20	320	40	233	160
376	0	0	0	40	10	0	239	320
377	20	320	160	160	80	80	240	320
378	20	80	80	40	20	20	265	20
379	0	0	0	20	0	0	266	40
381	160	80	20	80	80	80	267	40
382	10	80	0	0	10	10	292	320
383	160	320	40	80	160	80	293	160
384	20	40	0	20	40	40	294	640
385	160	320	80	80	20	20		

* Titres expressed as denominator of serum dilution

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TREND OF INFLUENZA MORTALITY DURING THE PERIOD 1920-51

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During the thirty-two years following the great influenza pandemic of 1918-19, some fifteen epidemic waves of varying degrees of importance were recorded in the Northern Hemisphere. During this period, important developments affected the mortality ascribed to the disease. The trends of mortality directly or indirectly attributed to influenza were affected by the wider use, in the treatment of the disease, of sulfonamides and, later, antibiotics.

The gradual adoption of the identification procedures for the virus since it was first isolated in 1933 has added new information on the spread and incidence of the predominant types of the disease. This new knowledge has already helped to clarify some aspects of the epidemiology of the disease hitherto designated " influenza ".

During this important period in the history of influenza, knowledge of the amount of illness caused by the influenza virus has not materially improved; and few contributions have been made towards improving the reporting of influenza morbidity and the evaluation of mortality directly or indirectly connected with influenza epidemics.

It is well known that, in countries where the disease is notifiable, the cases reported to health departments do not constitute any true index of morbidity and can hardly provide a measure of the relative importance of the successive epidemics. The reporting of influenza is both incomplete and irregular, although more incomplete in rural areas than in towns. It is especially defective between two epidemics, but, as a rule, improves at the beginning of an outbreak and during the early part of the epidemic. In spite of their incompleteness, figures of influenza cases notified, if reported promptly by weekly or shorter periods, may serve as an index of the " explosiveness " and of the speed with which an epidemic breaks out and spreads, and are especially useful in its early stages. They are, however, not suitable for the evaluation of the morbidity due to an epidemic.

Household surveys immediately following an epidemic—such as are carried out in the USA—yield valuable information on age-incidence, complications, and case-fatality not obtainable from any ordinary notification system. Such occasional surveys do not, however, provide adequate data for estimating the total morbidity involved in an epidemic.

Data on morbidity among selected population-groups are obtainable, in certain countries, from insurance records. Those collected by the Sickness Insurance Funds in pre-war Germany, for instance, provided a useful source of information on the progress of an epidemic in various industrial centres and on the total morbidity ascribed to influenza among the insured.

In the absence of other data, excess mortality from various causes is the main source of information on the importance of an influenza epidemic. Death figures from influenza and pneumonia in excess of the normal seasonal expectancy are commonly utilized as an index of the size of an epidemic.

Weekly death-rates in excess of seasonal expectancy were used by Collins and Collins & Lehmann [1, 2] in the study of influenza epidemics in the USA. An evaluation of mortality in influenza years in England and Wales by Martin [5] was based on excess deaths recorded in the quarter containing an influenza outbreak.

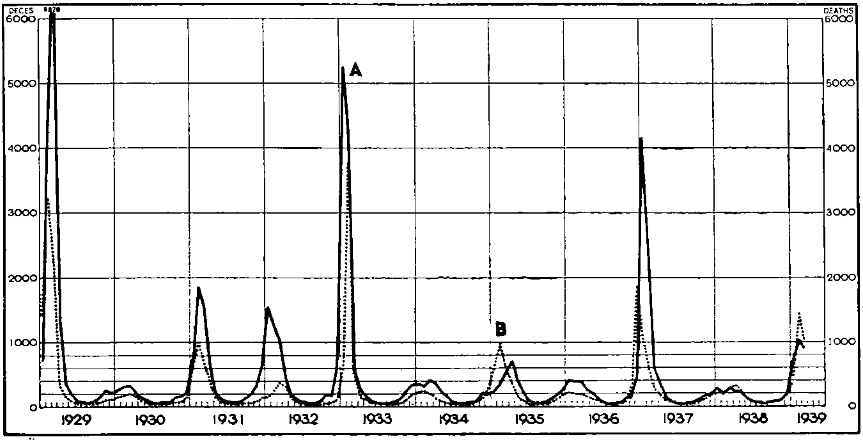
Most influenza epidemics, during the past thirty years, have been accompanied by a significant excess of deaths ascribed to causes other than influenza and pneumonia. During the period of the year corresponding to the influenza epidemic, excess mortality can be observed in most countries, not only from respiratory diseases, but also from heart diseases and other or ill-defined causes, particularly among elderly people.

The close connexion between mortality ascribed to influenza and the higher seasonal peaks of general mortality is well illustrated by curves relating to towns in England and Wales and in Germany in pre-war years (see fig. 1 and 2).

Deaths directly attributed to influenza represent only a fraction of the mortality involved in an influenza epidemic. The comparability of such influenza mortality-rates over a longer period of time is affected by several factors, as the data are influenced by changes in the method of certifying deaths, in reporting procedures, and—in some cases—in the rules applied in the selection of the cause of death, when several are mentioned on the death certificate. Furthermore, the differences in reporting procedures, and in the completeness of data in various countries, do not allow of international comparison of influenza mortality-levels. A varying proportion of deaths, according to the country, is attributed to pneumonia or bronchopneumonia, even when these are mere complications of influenza. In spite of the above-mentioned limitations, the annual influenza mortality-rates in various countries (see table I) show some striking similarities in trends over the period 1920-1951.

Over the period 1920-51, high influenza mortality-rates in most countries of the Northern Hemisphere were reported during six to twelve out of the thirty-two years. Relatively high levels of mortality were recorded in the majority of European countries during the epidemic years : 1922,

FIG. 1. GENERAL AND INFLUENZA MORTALITY IN THE GREAT TOWNS * OF ENGLAND AND WALES AND IN THE GERMAN TOWNS † WITH A POPULATION OF MORE THAN 100,000: INFLUENZA MORTALITY



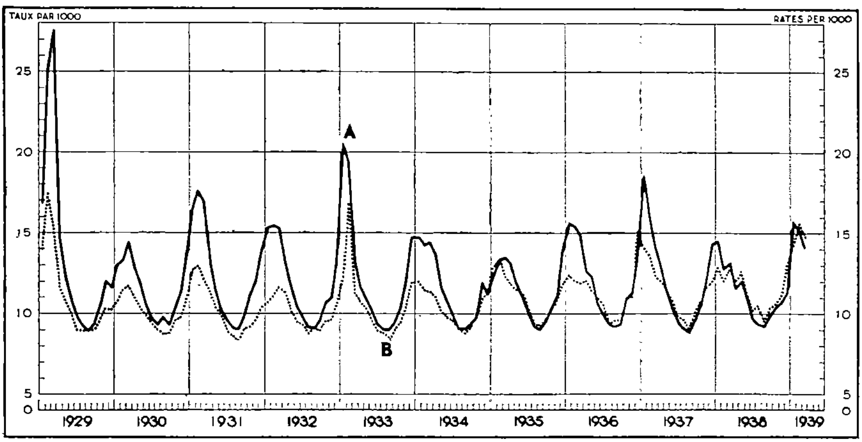
A = English towns B = German towns

* The number of towns has increased gradually from 105 in 1921 to 126 in 1939, and the total population from 19 to 21 million.

† The number of towns has increased gradually from 46 in 1921 to 57 in 1939, and the total population from 16.5 to 21.5 million.

FIG. 2. GENERAL AND INFLUENZA MORTALITY IN THE GREAT TOWNS * OF ENGLAND AND WALES AND IN THE GERMAN TOWNS † WITH A POPULATION OF MORE THAN 100,000: GENERAL MORTALITY

(Rates per 1,000 Population, by Four-Week Periods, on an Annual Basis)



A = English towns B = German towns

* The number of towns has increased gradually from 105 in 1921 to 126 in 1939, and the total population from 19 to 21 million.

† The number of towns has increased gradually from 46 in 1921 to 57 in 1939, and the total population from 16.5 to 21.5 million.

TABLE I. ANNUAL INFLUENZA MORTALITY-RATES PER 100,000 POPULATION, 1920-51

Country	1920	1921	1922	1923	1924	1925	1926	1927	1928	1929	1930
Africa											
Union of South Africa [a]	.	82.8	50.6	25.3	30.7	24.4	39.0	24.4	26.9	19.4	23.8
America											
Canada [b]	.	14.7	36.9	54.6	19.7	32.4	54.8	35.9	47.9	71.6	24.2
USA [c, h]	70.9	11.4	31.2	44.3	19.4	29.7	40.8	22.6	45.3	55.5	19.4
Chile	168.–	191.–	125.–	449.–	138.–	204.–	171.–	121.–	138.–	267.–	214.8
Uruguay	2.0	12.2	3.3	14.1	11.5	7.2	7.3	12.8	3.2	9.3	.
Asia											
Japan	194.–	18.2	22.1	11.2	11.0	18.1	7.6	13.2	15.5	13.4	8.1
Australasia											
Australia	8.4	12.0	6.4	21.3	10.0	5.9	12.5	6.9	12.7	15.9	4.3
New Zealand [d]	40.2	8.6	5.3	31.6	6.9	6.5	21.3	9.5	17.4	21.1	9.2
Europe											
Belgium	39.2	30.4	46.4	29.0	27.6	26.5	34.5	32.1	25.0	47.4	15.3
Czechoslovakia	52.4	8.8	16.5	5.3	4.2	8.4	10.5	30.4	7.3	19.1	4.6
Denmark [e]	97.0	4.9	46.1	21.4	18.8	12.1	13.8	55.8	15.0	39.5	9.5
Finland	.	.	.	.	.	.	.	19.6	7.2	39.7	5.2
France	28.7	17.6	.	.	.	14.1	17.1	38.1	15.3	40.2	8.3
Germany [f]	96.0	27.2	64.2	38.8	23.5	22.4	25.8	46.3	19.4	57.5	12.0
Greece	.	72.7	72.9	55.3	76.0	55.7	41.4	87.1	52.8	112.–	52.8
Hungary	71.6	6.0	16.9	5.4	12.4	7.6	5.4	20.0	5.0	15.3	4.1
Iceland	55.5	83.2	25.0	20.6	34.7	7.1	22.8	6.8	16.3	19.9	4.7
Ireland	22.4	20.9	60.0	20.6	69.0	39.2	22.0	71.0	29.1	56.3	21.0
Italy	67.2	11.3	36.1	23.9	22.5	22.5	34.4	22.5	25.3	48.2	17.2
Netherlands	35.8	6.7	52.5	11.0	8.1	8.7	18.8	42.6	18.8	57.1	8.5
Norway	13.8	2.1	20.0	12.6	3.6	2.0	3.5	19.7	5.5	17.2	1.7
Spain	83.7	27.2	36.9	38.3	31.9	28.3	22.5	39.1	14.9	23.4	10.3
Switzerland	90.7	11.8	44.0	13.9	38.2	28.5	20.3	67.1	19.1	44.2	12.7
United Kingdom:											
England and Wales	28.2	23.7	56.3	22.0	49.0	32.7	22.9	56.7	19.6	73.4	12.6
Northern Ireland [g]	44.5	25.1	70.1	33.0	81.6	55.8	38.4	59.6	31.0	107.–	20.6
Scotland [i]	6.0	27.2	75.7	10.9	51.2	25.6	29.2	41.7	19.8	71.1	14.4

Country	1931	1932	1933	1934	1935	1936	1937	1938	1939	1940	1941
Africa											
Union of South Africa [a]	17.4	45.6	17.3	15.2	60.7	17.8	25.1	15.7	13.4	16.3	12.4
America											
Canada [b]	31.0	40.4	37.8	18.7	31.3	28.5	47.7	21.2	35.2	24.5	21.0
USA [c, h]	26.5	30.6	26.4	17.3	22.2	26.4	29.5	12.7	16.4	15.3	15.8
Chile	120.4	134.0	245.5	173.6	185.6	161.8	127.3	156.6	109.2	108.1	85.3
Uruguay	.	.	.	.	12.5	3.6	7.1	8.5	3.4	4.7	2.5
Asia											
Japan	24.0	8.1	7.1	14.8	4.4	12.4	4.2	10.7	8.2	4.4	5.9
Australasia											
Australia	8.7	5.3	13.3	14.1	17.4	7.0	5.8	9.0	12.7	5.0	4.9
New Zealand [d]	15.3	4.6	7.0	12.6	7.4	9.4	7.3	8.8	11.0	7.7	4.9
Europe											
Belgium	31.2	38.0	38.9	19.6	31.7	23.0	24.6	21.3	36.9	24.5	25.0
Czechoslovakia	12.0	7.9	15.9	4.3	13.9	6.5	11.6	6.1	11.9	6.2	14.2
Denmark [e]	34.5	32.7	23.9	6.3	13.6	19.5	20.4	9.8	10.8	15.5	13.9
Finland	8.8	8.7	20.7	5.2	5.8	47.7	15.0	27.0	16.2	24.8	14.3
France	24.8	11.1	21.8	6.3	18.3	10.7	.	.	.	29.7	5.7
Germany [f]	30.0	15.9	41.3	14.2	32.9	28.9	26.0	14.0	28.0	.	.
Greece	87.5	76.3	131.7	43.1	77.2	43.0	100.5	47.9	.	.	.
Hungary	7.7	10.8	9.2	5.6	10.6	5.4	6.3	7.5	.	.	.
Iceland	20.2	0.9	12.4	5.3	19.9	4.3	74.2	0	22.6	1.7	31.2
Ireland	50.2	56.1	60.5	23.2	32.4	23.0	94.0	23.9	37.2	28.0	44.6
Italy	32.2	32.1	28.7	19.6	27.5	24.8	28.0	19.6	21.7	15.7	16.3
Netherlands	39.9	17.4	21.2	10.7	18.9	18.4	36.7	12.7	21.8	17.8	47.9
Norway	9.1	6.4	7.3	1.7	6.4	4.4	5.7	1.8	13.6	4.2	13.8
Spain	31.2	20.6	32.6	22.7	32.9	16.5	18.1	20.0	19.6	16.9	24.4
Switzerland	45.5	46.9	27.6	11.2	45.6	15.2	16.4	28.6	47.5	37.7	7.9
United Kingdom:											
England and Wales	33.0	30.0	52.0	12.7	16.7	14.1	41.8	10.8	19.4	28.6	17.7
Northern Ireland [g]	46.3	36.4	69.3	26.8	32.7	21.4	89.7	20.1	31.0	51.3	34.4
Scotland [i]	26.2	35.3	41.3	12.2	29.5	13.3	54.1	7.9	18.3	37.2	14.6

TABLE I. ANNUAL INFLUENZA MORTALITY-RATES PER 100,000 POPULATION, 1920-51 (continued)

Country	1942	1943	1944	1945	1946	1947	1948	1949	1950	1951
Africa										
Union of South Africa [a]	8.8	11.1	7.1	3.5	2.4	3.5	4.3	3.8	6.6	.
America										
Canada [b]	10.5	20.5	15.6	9.0	13.0	8.8	7.1	8.2	6.9	18.4
USA [c, h]	8.1	12.9	13.1	7.7	6.3	5.3	3.5	3.1	4.4	.
Chile	63.4	49.7	47.0	43.5	32.8	23.0	24.8	25.6	16.1	.
Uruguay	2.6	5.6	.	13.6	6.6	11.2	8.5	7.0	4.2	.
Asia										
Japan	5.4	4.6	.	.	.	2.4	0.6	0.6	1.5	.
Australasia										
Australia	7.7	6.1	2.5	2.2	2.8	2.0	4.9	1.5	4.3	.
New Zealand [d]	16.1	4.2	4.0	3.3	6.7	1.9	3.0	2.6	4.3	.
Europe										
Belgium	19.4	18.7	20.2	22.8	21.5	13.5	12.2	14.6	9.8	17.4
Czechoslovakia	3.7	.	.	.	.	.	.	.	.	.
Denmark [e]	2.9	2.5	5.8	1.7	4.1	3.3	0.7	3.8	6.1	3.4
Finland	9.1	4.9	6.8	2.8	1.4	9.9	2.6	14.0	1.8	8.8
France	4.8	3.9	11.8	5.6	5.9	4.5	3.8	29.3	4.5	19.6
Germany [f]	.	.	.	.	4.5	6.4	7.1	17.2	7.0	10.8
Greece	.	.	.	.	.	.	.	.	.	.
Hungary	.	.	.	.	.	.	.	.	.	.
Iceland	1.6	28.8	3.2	0	5.3	7.4	0.7	7.2	3.5	.
Ireland	13.1	15.7	27.6	10.4	26.0	21.9	6.7	9.4	10.9	77.7
Italy	9.4	9.1	8.7	6.2	7.9	6.9	11.4	12.5	3.7	9.3
Netherlands	10.2	9.4	15.7	5.6	9.4	5.7	3.5	25.4	6.2	15.7
Norway	2.4	3.0	2.7	1.0	2.5	1.8	1.3	2.0	3.4	2.4
Spain	17.7	15.2	19.2	11.6	7.6	13.4	10.0	8.7	6.4	.
Switzerland	7.1	4.6	28.4	13.6	13.0	15.5	5.6	13.2	5.5	24.9
United Kingdom :										
England and Wales	8.8	33.3	10.3	7.0	13.0	7.9	2.9	13.0	8.9	36.1
Northern Ireland [g]	15.0	26.0	16.2	10.5	28.6	20.4	5.6	7.1	11.5	64.4
Scotland [i]	6.5	24.8	7.8	4.4	13.9	6.7	2.7	7.7	7.5	21.8

[a] European population only
[b] Excluding Province of Quebec before 1926
[c] Deaths Registration Area, prior to 1933
[d] Excluding Maoris
[e] Excluding Faroe Islands
[f] Federal Republic from 1946
[g] 1941-49, civilian population only
[h] Since 1940, excluding deaths among armed forces outside the USA
[i] 1940-46, civilian population only

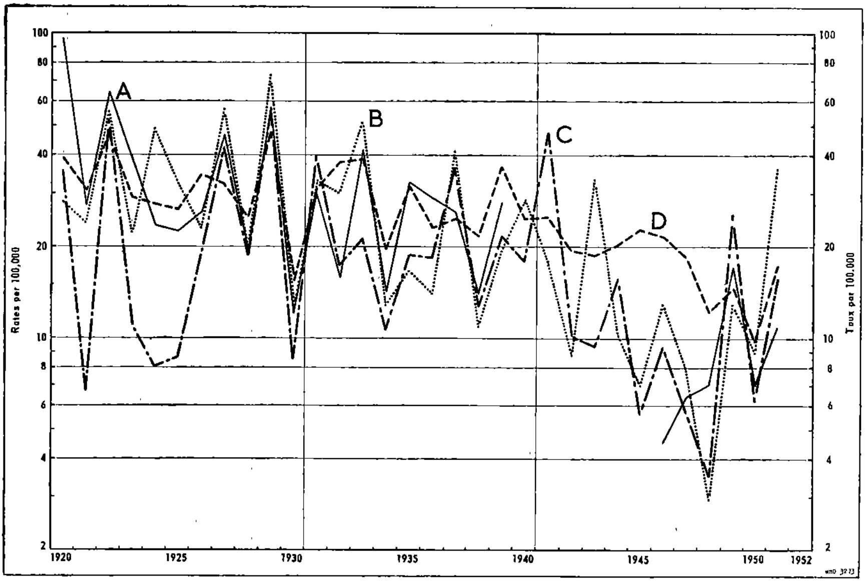
1924, 1927, 1929, 1931, 1933, 1937, and—to a lesser extent—1951, while in the USA and Canada these high levels occurred in 1923, 1926, 1929, 1932, 1937, and 1951. Prior to 1945, low levels of influenza mortality were observed in these countries every two to four years.

Influenza mortality has been falling in all countries for which data are available. This downward trend can be observed both in successive peak years and in the lowest rates of non-epidemic years.

Fig. 3 and 4 represent, on the logarithmic scale, the movement of influenza mortality in various countries. In spite of differences in the range of annual variations, the general trend is apparent.

In England and Wales the downward trend has been observed since 1926 in the non-epidemic years, and since 1929 in the epidemic years. The successive peak-rates during the four epidemic years after 1929—i.e., 1933, 1937, 1940, and 1943—have been decreasing steadily from 73.4 per 100,000 population in 1929 to 33.3 per 100,000 in 1943 (a decrease of about 55% over the fourteen-year period). The fall during the non-epidemic years has been gaining in speed since 1938 : the rates, per 100,000,

FIG. 3. INFLUENZA MORTALITY, 1920-51 (I)
(logarithmic scale)



A = Germany B = England and Wales C = Netherlands D = Belgium

being 10.8 in 1938, 8.8 in 1942, 7.0 in 1945, and 2.9—the lowest on record—in 1948.

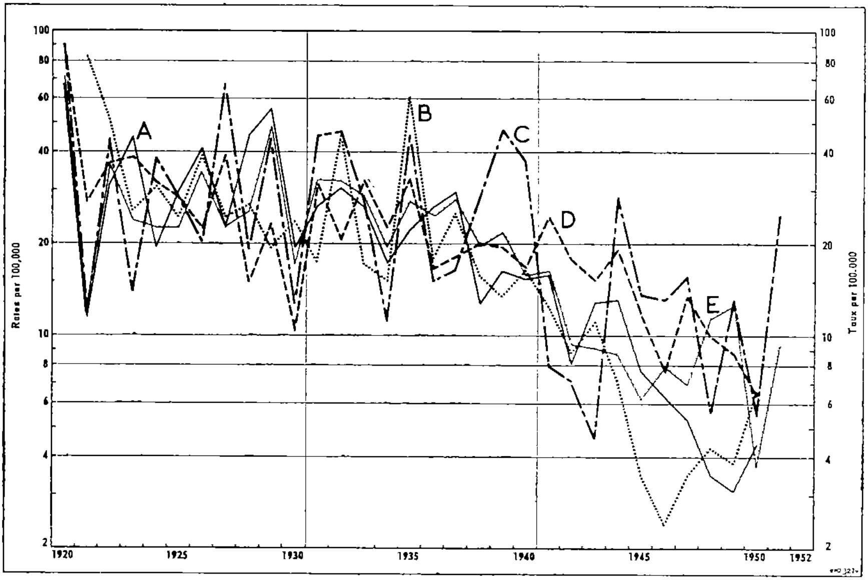
In Germany, the rate of decrease over the period 1920-39 was slower than in England and Wales, the levels during non-epidemic years remaining higher, but the rates in epidemic years being lower.

In Italy, influenza mortality decreased slowly from 1922 to 1937, the rates showing little variation between epidemic and non-epidemic years, except for the 1929 peak and the 1930 low rate. In 1950, the rate fell from 12.5 per 100,000 to 3.7, the lowest recorded so far.

In France, the annual rates show considerable fluctuations due, no doubt, to the tendency to return influenza as a cause of death during an epidemic, rather than to truly high levels of influenza mortality. This view is further supported by the fact that mortality attributed to influenza was lower in France than in other western European countries during non-epidemic years such as, for instance, 1921, 1925, 1930, and 1934. During the post-war years, the rate was again unusually high in epidemic years, 1949 and 1951 (29.3 and 19.6 per 100,000), while it was as low as 3.8-5.9 per 100,000 in 1945-48 and 1950.

In Belgium, the curve shows a slow downward trend with very slight annual variations. Except for the 1929 high (47.4) and the 1930 low (15.3) rate, the annual fluctuations of the rate did not exceed 100% over

FIG. 4. INFLUENZA MORTALITY, 1920-51 (II)
(logarithmic scale)



A = USA
B = Union of South Africa (European population only)
C = Switzerland
D = Spain
E = Italy

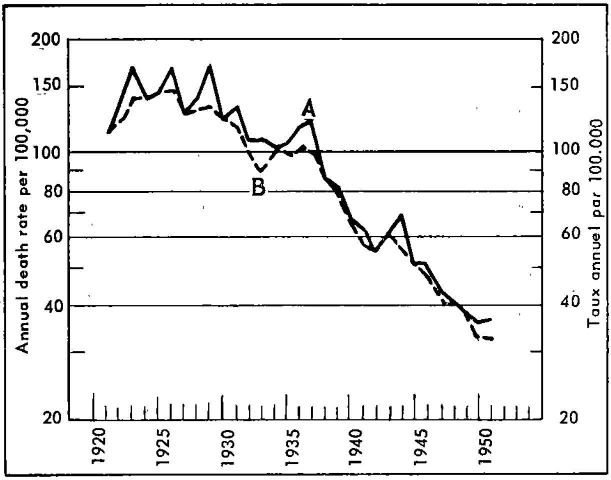
the period 1920-39 and were less than 20% from 1940 to 1947. The recent rapid fall in the influenza mortality-rate observed in most countries is not apparent in Belgium prior to 1948. In contrast to Belgium, the rates show wide annual variations in the Netherlands; the very low rates during known non-epidemic years (1921, 1923-26, 1930, 1945, and 1948) and the high level during peak years suggest that deaths from influenza are reported more frequently during an epidemic.

In Switzerland (as might be expected in a smaller country), considerable fluctuation of the annual rates of influenza mortality was recorded throughout the period 1920-51. A decrease in mortality was apparent only after 1940, when rates under 6 per 100,000 were recorded during three non-epidemic years (1943, 1948, and 1950).

In Spain, the deaths ascribed to influenza remained fairly high during the period 1921-35, and reached 32.9 per 100,000 during the epidemic year of 1935. During the following fifteen years, influenza mortality decreased, showing also less variations between high and low annual rates.

The influenza mortality figures for the USA show the slow downward trend with wide fluctuations from 1920 to 1937, and the more rapid decrease of the annual rates after 1937. This striking characteristic of recent trends in mortality caused by influenza is also apparent from the combined influenza and pneumonia mortality-rates.

FIG. 5. TREND OF MORTALITY FROM INFLUENZA AND PNEUMONIA IN GROUPS OF CITIES IN THE USA, 1920-51



A = total rate B = rate exclusive of epidemics

Note : Logarithmic vertical scale. Rates are for calendar years ; 90 cities 1920-42 ; 56 cities 1943-50. Rate for year ending in mid-August of 1951 estimated on the basis of the change in the rate for the first nine months of that year from the rate for the first nine months of the year ending in mid-August of 1950.

Reproduced from Collins & Lehmann [1] by kind permission of the editors of *Public Health Reports (Washington)*

Collins & Lehmann [1] have shown, with regard to groups of cities in the USA, that the acceleration of the downward movement of influenza and pneumonia mortality since 1937 is the same whether total rates, or rates exclusive of epidemic excess mortality, are considered (see fig. 5).

The same pattern of downward movement of influenza mortality, slow up to the middle 1930's, and accelerated during the subsequent fifteen years, was also observed in the Southern Hemisphere, for instance, among the European population of the Union of South Africa (see fig. 4), in Australia, and in Chile. In the last-mentioned country, where deaths ascribed to influenza were exceptionally high (corresponding to a rate of over 1 per 1,000 from 1920 to 1940), a steady fall in the rate has been recorded since 1933 (from 245.5 in 1933 to 16.1 per 100,000 in 1950).

While the recent fall in mortality ascribed directly to influenza is evident in most countries, the reasons for it cannot be explained fully at this stage. The comparatively short period of time corresponding to the accelerated downward movement, prior to the moderate epidemic year, 1951, does not allow of a conclusion to be drawn as to whether influenza mortality has reached its lowest level in non-epidemic years. It is also likely that virus identification practised on a wider scale has resulted in fewer deaths being returned as due to influenza when the virus is known not to have been identified.

All influenza epidemics invariably result in an increase in general mortality, and in mortality from various causes, and, as stated earlier, the excess mortality during the period of the year corresponding to an epidemic provides an index to the resulting loss in human lives.

The effect of an epidemic on mortality can also be seen from a comparison of annual death-rates during epidemic and non-epidemic years. While such rates for various countries are not directly comparable, it is of interest to note, for instance, the fall in mortality levels in five countries from 1937, the last pre-war epidemic year, to 1938, a non-epidemic year (see table II). The fact that the percentage decrease in death-rates from specified causes (except from bronchitis in Canada and Sweden, and pneumonia and bronchopneumonia in Canada) is higher than that from all causes, shows the effect of an epidemic on the causes of death during 1937. The excess mortality from various causes is, of course, still more apparent in the study of data limited to the epidemic period. Martin,[5] who studied the mortality in England and Wales (in the epidemic years 1922, 1924, 1927, 1929, 1931, 1933, and 1943), found in the quarter corresponding to the epidemic, as compared to the same quarter of the previous year, an excess of deaths from 13.4% to 41.8% for the respiratory diseases, from 13% to 27.2% for the circulatory diseases, and from 1.8% to 3.3% for tuberculosis.

The figures for England and Wales do not indicate any significant shift, in successive epidemic years, in the excess mortality from the above-mentioned causes. In view of the recent fall in mortality ascribed to influenza, an analysis of data for certain countries would be of interest in order to determine whether there has been a true decline in the mortality due to influenza or whether deaths from this disease are now charged to other causes. In their remarkable study relating to groups of cities in the USA, Collins & Lehmann [2] have shown that influenza and pneumonia account for a lesser share in the excess mortality of recent epidemics than was the case previously, while the proportion of deaths attributed to other causes, and particularly to non-respiratory chronic diseases, has correspondingly increased (see table III). Heart disease was the larger non-respiratory contributor to these excess deaths.

An important aspect of the changes in mortality directly charged to influenza during successive epidemic years is the gradual drop in the number of deaths in the lower age-groups, observed in most countries after the 1918-19 epidemic. Logan [3] noted in respect of England and Wales that the proportion of influenza deaths at ages under 55 years was 86% in 1918, 75% in 1919, 37% in 1929, 41% in 1943, and only 11.5% [a] in 1951. A decrease in the influenza mortality-level has, naturally, been

[a] Revised figure

TABLE II. MORTALITY BY SPECIFIED CAUSES IN FIVE COUNTRIES IN 1937 AND 1938 (RATES PER 100,000 AND DECREASE FROM 1937 TO 1938 IN %)

		Canada	USA	England and Wales	Netherlands	Sweden
All causes	1937	1,024.9	1,122.1	1,241.9	878.3	1,201.3
	1938	959.2	1,064.0	1,161.8	852.6	1,154.4
	%	—6.4	—5.4	—6.2	—2.9	—3.9
Influenza	1937	47.4	29.4	45.4	36.7	18.7
	1938	21.2	12.7	11.8	12.7	3.0
	%	—32.8	—56.8	—74.0	—65.4	—84.0
Bronchitis	1937	3.0	3.1	43.6	15.1	8.3
	1938	2.9	2.8	32.2	13.5	8.2
	%	—3.3	—9.7	—26.1	—10.6	—1.2
Pneumonia and broncho-pneumonia	1937	69.6	85.1	72.0	62 5	104.1
	1938	66.7	67.7	63.0	58.3	93.9
	%	—4.2	—20.4	—12.5	—6.7	—9.8
Other disease of the respiratory system	1937	14.7	8.2	11.8	12.5	11.6
	1938	13.7	7.7	10.1	10.2	10.1
	%	—6.8	—6.1	—14.4	—18.4	—12.9
Causes of death unstated or ill-defined	1937	7.0	15.9	3.0	33.9	4.5
	1938	5.5	15.1	2.6	32.6	3.8
	%	—26.7	—5.0	—13.3	—3.8	—15.6

recorded in all age-groups, but this decrease is much slower in the higher age-groups. Martin [4] has shown in respect of England and Wales that the influenza death-rate decreased between the period 1920-24 and that of 1940-44 by 75%-80%, at ages 5-35 years, and by 40%-70%, at ages above 35 years.

The gradual disappearance of influenza as a certified cause of death, and the shift of excess mortality to causes other than influenza and pneumonia, have, no doubt, resulted in various countries in a further shift of mortality due indirectly to influenza epidemics towards the higher age-groups.

* * *

The appraisal of the importance of total morbidity and mortality caused by influenza is difficult owing to the lack of satisfactory statistical data concerning this disease. The mortality caused by its epidemics may, however, be estimated from a computation of the excess of the general mortality during epidemic periods, as compared to similar seasonal periods in non-epidemic years.

TABLE III. EXCESS MORTALITY PER 100,000 FROM ALL CAUSES AND FROM INFLUENZA AND PNEUMONIA DURING THE WHOLE OF EACH EPIDEMIC FROM 1918 TO 1951, IN GROUPS OF CITIES IN THE USA, AND PERCENTAGE OF EXCESS MORTALITY FROM ALL CAUSES CREDITED TO INFLUENZA AND PNEUMONIA *

Epidemic	All causes	Influenza and pneumonia	Percentage
1918–19	598.0	550.5	92
1920	125.5	97.2	77
1928–29	64.9	40.8	64
1930–31	57.1	30.2	63
1922–23	50.4	32.3	61
1943–44	45.8	14.4	58
1926	48.3	28.2	53
1932–33	45.7	22.2	50
1936–37	41.6	20.8	49
1935–36	38.9	15.5	45
1931–32	36.1	13.8	40
Early 1922	34.1	20.7	38
Spring 1928	31.8	14.5	34
1939	26.3	5.5	33
1945–46	24.4	3.7	29
1934–35	18.4	6.3	26
1947	16.6	2.5	21
1940–41	15.7	5.2	19
1951	15.7	4.1	17
1950	14.5	2.7	15
Early 1940	14.5	2.5	15

* After Collins & Lehmann [3]

The curves of mortality directly charged to influenza in most countries for which data are available for the period 1920-51 show a gradual decrease in the range of annual variations and a fall in mortality accelerated after the middle 1930's.

The short period during which this more rapid fall has been apparent does not allow of stating whether influenza, as a certified cause of death, will continue its downward trend in future non-epidemic years, or has already reached its lowest level.

Both influenza and pneumonia, and the associated chronic non-respiratory causes of death, have decreased in the successive epidemic years; however, the latter have done so at a lower pace and their relative proportion has become accordingly higher, which accounts for a slower decline in the mortality recorded for the higher age-groups in recent epidemics.

There seems to be no doubt about the effect of modern therapy in decreasing mortality from infections associated with influenza and particularly pneumonia.

It is likely, however, that part of the impressive decline observed in mortality directly charged to influenza is due to more precise diagnosis of the actual causes of death, and possibly to a change in the rules governing the selection of the underlying cause when several are mentioned on death certificates.

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