In this particular example, the Capetown strain of virus is poorly neutralized, even by its own antiserum, although that antiserum can be shown to contain antibody by its moderately high titre with the Johannesburg strain. In fact, one important characteristic of the Scandinavian group of viruses is that they combine poorly with antibody in this test (and incidentally in other tests which we have carried out) whereas the Liverpool viruses have a high avidity for antibody.

So far as is known at present, the main defence of human beings against influenza virus infection is the production of specific antibody. It is quite clear, therefore, that a virus which is not readily neutralized by specific antibody has an advantage in nature over one which is readily neutralized. One might expect, therefore, that the Scandinavian type of virus could survive longer than the Liverpool virus in a population with some basic immunity to infection with influenza A. Is it possible that the two groups of viruses represent alternate phases of the one sub-type of virus, the one phase being better adapted to survival in a relatively immune population? It was with these ideas in mind that we attempted experiments to see whether it was possible to transform one virus into the other in the laboratory. Our results so far indicate that it has been possible to transform a Liverpool type virus into a Scandinavian type virus. The principle of the method used is to passage the Liverpool virus in eggs in the presence of homologous antiserum. These conditions favour the multiplication of any variant virus particles which are not readily neutralized by anti-serum, and after three or four egg passages it was found that virus with the properties of the Scandinavian type was obtained. In the absence of antiserum, all the strains which we have tested have retained their serological identity on passage in eggs.

The question which remains unanswered is whether a similar transformation can occur in nature; and if so, at what stage from the point at which the seeds of the epidemic are first sown until the harvest of virus strains is gathered does the mutation occur? Now there is no evidence that mutations of this particular type occur during the manipulations carried out when these viruses are isolated in different laboratories. Also, there is strong evidence from the 1949 epidemic that a virus can maintain its serological integrity as it passes from one country to another. Our own results with the 1951 Liverpool viruses strongly support this; strains isolated thousands of miles apart have been strikingly similar serologically. One is led to wonder, therefore, whether the mutation to the Scandinavian type occurred at an earlier stage. In other words the Scandinavian type may be the form in which the seeds from the previous epidemic maintained themselves during the interepidemic period when the soil was unfavourable. There are three small pieces of evidence to support this idea. First, the Scandinavian viruses were responsible for a small summer outbreak of influenza in Sweden in June 1950; this outbreak is believed to have been the forerunner of the northern European influenza of 1950–51. The second piece of evidence is that Scandinavian type strains isolated from different places are much less similar to one another than are Liverpool type strains; this is what one would expect if they had arisen in separate foci. Thirdly, some of the 1949 viruses show a low avidity for antibody; in this property they are intermediate in character between the 1947 A-prime strains and the 1950–51 Scandinavian viruses. It will be important to watch for summer outbreaks of influenza in the future and to study carefully the characteristics of any strains isolated.

Epidemiology of Influenza in the Light of the 1951 Outbreak

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Several writers have felt that between epidemics influenza must somehow go "underground" (metaphorically speaking). It is not easy to explain survival of virus for months or years in terms of infrequent and sporadic 'flu cases occurring all the time. Shope (1941) has shown that the virus of swine influenza can "go to earth"—in this case, literally—in the earthworm and in the pig lung worms which the earthworms harbour. But no similar mechanism has been demonstrated for human 'flu. I have previously suggested that between epidemics 'flu virus may exist in a modified phase, a basic virus, devoid of the antigenic and other characters which enable us to recognize it (1942).

Antigenically, 'flu seems to be always changing. The A-viruses which caused outbreaks everywhere between 1936 and 1946 seem to have vanished. Related viruses known as A-prime have caused the major epidemics all over the world since then. Even here, minor variations in antigenic make-up seem to occur between the virus of one year's epidemic and its successor.

There is no certainty as to whether influenza really spreads from country to country as

it seems to do; or whether endemic viruses are successively activated in different countries, producing the illusion of an invasion across frontiers. Elucidation of this question was one of the problems before the World Influenza Centre which WHO set up at this Institute in 1948. The epidemic of 1949 gave an apparently clear answer as far as that year's outbreak was concerned. Influenza first appeared in Sardinia in September-October 1948. Apparently it spread from there right across Western Europe. Strains of viruses isolated in Italy, Switzerland, France, Holland, Britain and Iceland were all of the A-prime type: more than that, they were so homogeneous as to be virtually indistinguishable. Occurrence of a true spread from Sardinia to Iceland seems more than probable. We felt at the time, however, that the simplicity of the story was perhaps unnatural and that more complications might turn up next time.

The autumnal outbreak of influenza A in Britain, U.S.A. and Canada in 1943 had been preceded by local outbreaks in all three countries in the early summer, the infection apparently disappearing between June and September. Again, the September 1948 outbreak in Sardinia was preceded by something in the previous May and June, though there is doubt as to whether this precursor was influenza A or B. An area having an early summer outbreak seemed, accordingly, worth keeping an eye on. Such a local outbreak occurred in Sweden in June 1950; virus was isolated and found to be of the A-prime type. Dr. Svedmyr, in Stockholm, kept a special watch on subsequent events.

Our study of the 1950–51 outbreak has not so much solved our problems as dropped a series of fascinating hints for us to follow up in succeeding years.

Again it proved that the early summer precursor outbreak was followed by a major autumnal one in the same part of the world. First news last October came, however, not from Sweden but from Denmark. Sweden itself was involved soon after and viruses isolated thence were of the same antigenic type as the summer strains. Such reappearance of a similar virus in the same area strongly suggests that virus was present there all the time, though over some months it could not be detected.

There may be significance in the emergence of influenza this winter, probably independently, in Scandinavia and Ireland. For the 1948–49 outbreak as it swept over Europe apparently lost momentum in those two areas. It then hit Gothenburg but did not affect Sweden generally; it was just recognized in Ireland, but again failed to establish itself. Emergence of 'flu on the fringe of a previous epidemic is a thing to watch for in future. One can suggest a reason why it might emerge there. It would seem that emergence must be difficult, for it occurs in few places. Unless all our thoughts are wrong it must occur where there is underground virus *to* emerge. It would seem reasonable that its emergence would be hindered by a high level of herd immunity. At the fringe of its earlier exploits, however, herd immunity would be lower (particularly as immune and less-immune populations would mix there) and its reappearance might be more possible. One must imagine that once the difficulty of re-emergence has been overcome, the virus can get under way and spread amongst populations attacked two years earlier and not so susceptible as in the emergence areas. A point to note in relation to beginnings of epidemics is their apparently multifocal origin—in Sardinia in 1948, in Scandinavia and elsewhere last year.

There is still doubt as to the relationship between the Scandinavian and Liverpool types of virus discussed by Isaacs. The facts indicate the possibility that at its origin (Sweden and S. Ireland) the virus had certain generalized or primitive characteristics suggesting a recent origin from the hypothetical basic submerged virus. As the Scandinavian virus passed west it may have acquired other properties. Work is proceeding on the possibility that one virus-type may change into the other.

In complete contrast to the view I have just discussed is the view of transequatorial swing, if I may so call it, recently supported by Burnet (1951). No doubt the 1918 virus travelled across the equator. The first A-prime virus turned up in Australia in 1946 in the southern winter, to appear in N. America and Europe in the next northern winter 1946–47. Some viruses from S. Africa active there last July and August are of the type lately prevalent in Europe, particularly in the Mediterranean and in Belfast and Liverpool. Can it be that 'flu can keep going only in winter months and that to do so it has to follow the winter to and fro across the equator, much as the Arctic tern migrates yearly from the Arctic to the Antarctic and back? I should be reluctant to believe that this was the only mechanism of persistence of influenza and would be more content to imagine that epidemics could have origins of two sorts, one from beyond the equator, another from nearer home. A combination of the two types of origin may sometimes make the picture complex and hard to interpret.

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