

The role of season in the epidemiology of influenza

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SUMMARY

Four types of observations have been used to illustrate the seasonal characteristics of epidemic influenza: (1) The experience of a small population during 28 consecutive years, 1946–74, (2) world influenza outbreaks 1964–75 reported to the World Health Organization, (3) the experience of two widely separated localities at about the same latitude, 1969–74, and (4) the experience of two places at latitudes $30^{\circ} +$ on opposite sides of the Equator, 1968–74.

The following tendencies are shown. (1) Outbreaks of influenza even in the small community came at approximately the same season almost every year. (2) Outbreaks are globally ubiquitous and epidemic loci move smoothly to and fro across the surface of the earth almost every year in a sinuous curve that runs parallel with the 'midsummer' curve of vertical solar radiation, but lags about six months behind it. Such findings exclude the mediation of seasonal control by any agencies of local distribution, and suggest a direct effect of variations in some component of solar radiation on virus or human host. (3) Antigenic variations in influenza A virus tended to have the same seasonal characteristics as epidemicity. This suggests that epidemicity and virus variation are two facets of one seasonally controlled process.

None of these seasonal characteristics can be explained by the current concept of influenzal epidemiology. A new hypothesis recently proposed and recapitulated in the Appendix offers a possible explanation. The primary agency mediating seasonal control remains unidentified.

INTRODUCTION

A disease is recognized as being subject to some sort of seasonal influence if latitude affects its geographical distribution and if it occurs at a particular time of year. Such temporal and spatial distributions sometimes provide a clue as to the mechanisms through which season is exerting its effect upon the disease as, for example, in the elucidation of the epidemiology of malaria, yellow fever and schistosomiasis.

Epidemic influenza is said to be influenced seasonally (Kilbourne, 1975) but the mechanisms through which the seasonal influence is mediated are not understood. The current epidemiological concept that influenza virus is surviving by endless chains of direct transmissions of which each link is a person suffering from influenza does not explain why the epidemics should be seasonal and leaves other

features of the epidemic behaviour of influenza unexplained even when symptomless infections are taken into consideration. To overcome these difficulties an alternative hypothesis has been tentatively proposed according to which the virus is not immediately transmitted by the influenzal patient, but instead it becomes latent in his tissues until, perhaps a year later, it is reactivated by a seasonal stimulus to brief infectiousness in the symptomless carrier host (Hope-Simpson, 1979). The detailed suppositions are recapitulated in the Appendix. Observations of several sorts that had suggested the new hypothesis were reported and discussed, but the relevance of the seasonal characteristics of influenza could be mentioned only summarily.

This paper presents observations concerning the seasonal behaviour of epidemic influenza, both local and on a global scale, that confirm the existence and importance of a seasonal influence in its natural history and seem to support the operation of some mediating mechanism such as that proposed in the new hypothesis.

METHOD AND RESULTS

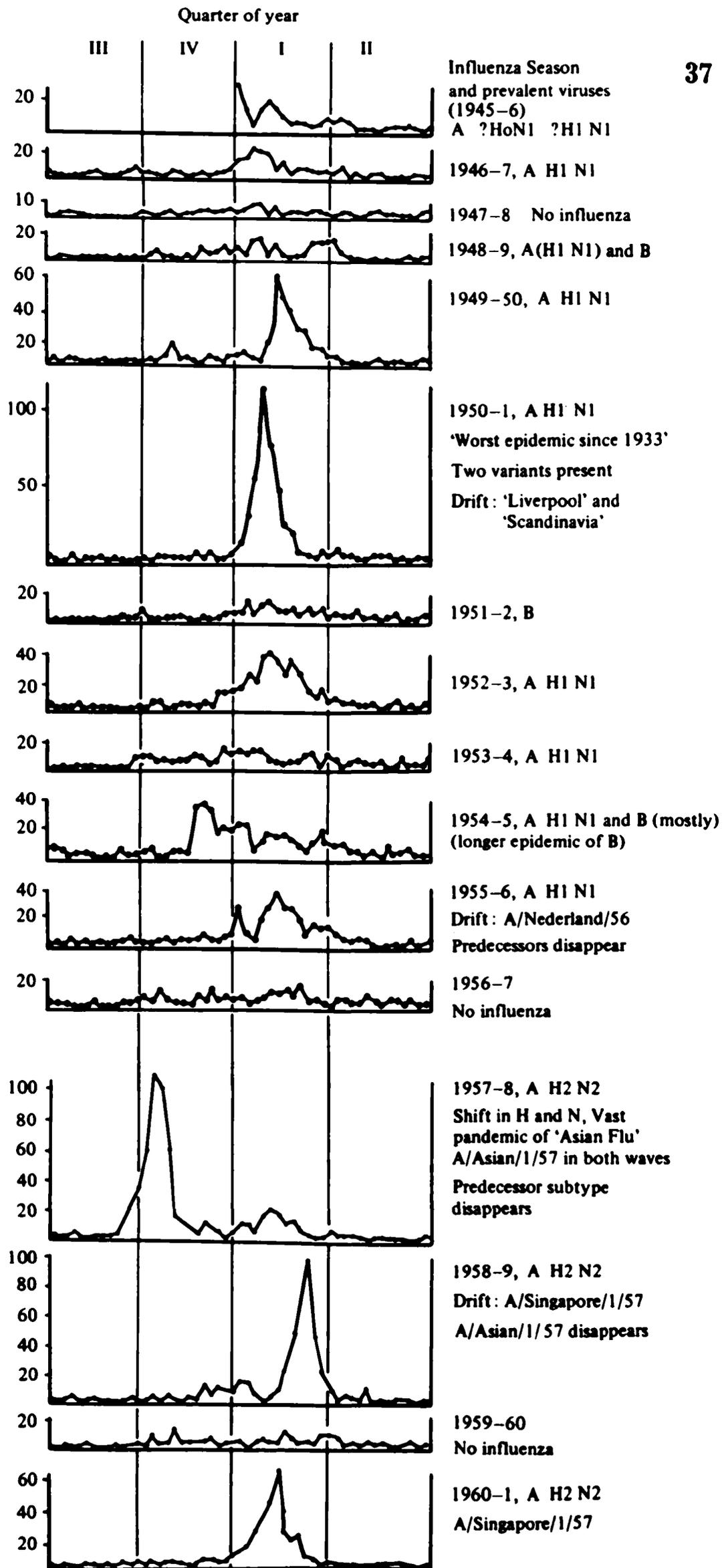
Many influenza records from various sources were analysed and compared in order to determine the influence of latitude and time of year and of other factors that might be affecting the epidemiology of the disease. Records were selected that illustrated characteristic seasonal tendencies exhibited by epidemic influenza, and the information they contain has been summarized in the four figures in this paper.

Figure 1 illustrates how influenza behaved during a sequence of 28 years in a small locality by showing weekly the number of patients treated for acute febrile respiratory diseases in a general practice population of about 3700 in Cirencester, South-west England, from 1946 to 1974. The years are shown from July through June in order to display the cold season in continuity. From 1947 specimens for virus examination and paired sera were collected from an increasing proportion, reaching between 40 and 90% of such patients after 1961. In each influenza season the type of influenza virus is indicated and also where known, the prevalent variant.

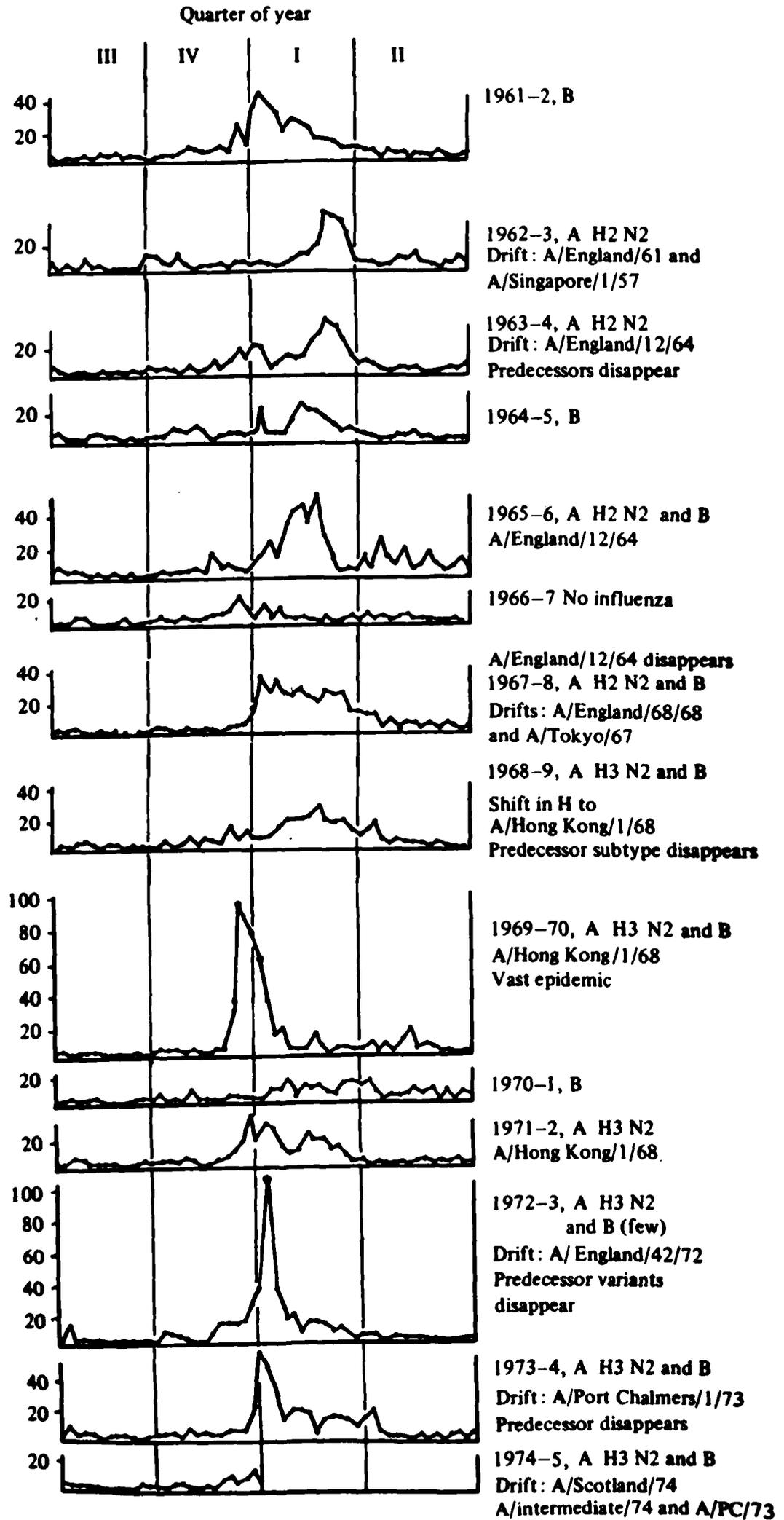
Influenza broke out in 24 (85.7%) of the seasons, sometimes more than once, 20 outbreaks occurring in the first quarter of the year and one in the second quarter. The 1957 'Asian' epidemic of type A influenza stands out uniquely in the first weeks of the fourth quarter with its origin at the end of September, a timing identical with that of the great autumn outbreak of 1918 in this area. In many of the seasons new antigenic variations, some of them major, supplanted the previously prevalent influenza A virus.

For contrast with the local behaviour illustrated by Fig. 1, Fig. 2 summarizes the global pattern of epidemic influenza by latitude and by calendar month. Reports

Fig. 1. The weekly totals of acute febrile respiratory diseases seen in a general practice population of 3511–3919 from 1946 to 1974 in Cirencester, England. Major subtype and minor variety of prevalent influenza viruses are indicated where known. Influenza outbreaks occurred in 24/28 (85.7%) of the years at about the same time of year. Both major and minor variants showed the phenomenon of seasonal disappearance and replacement.



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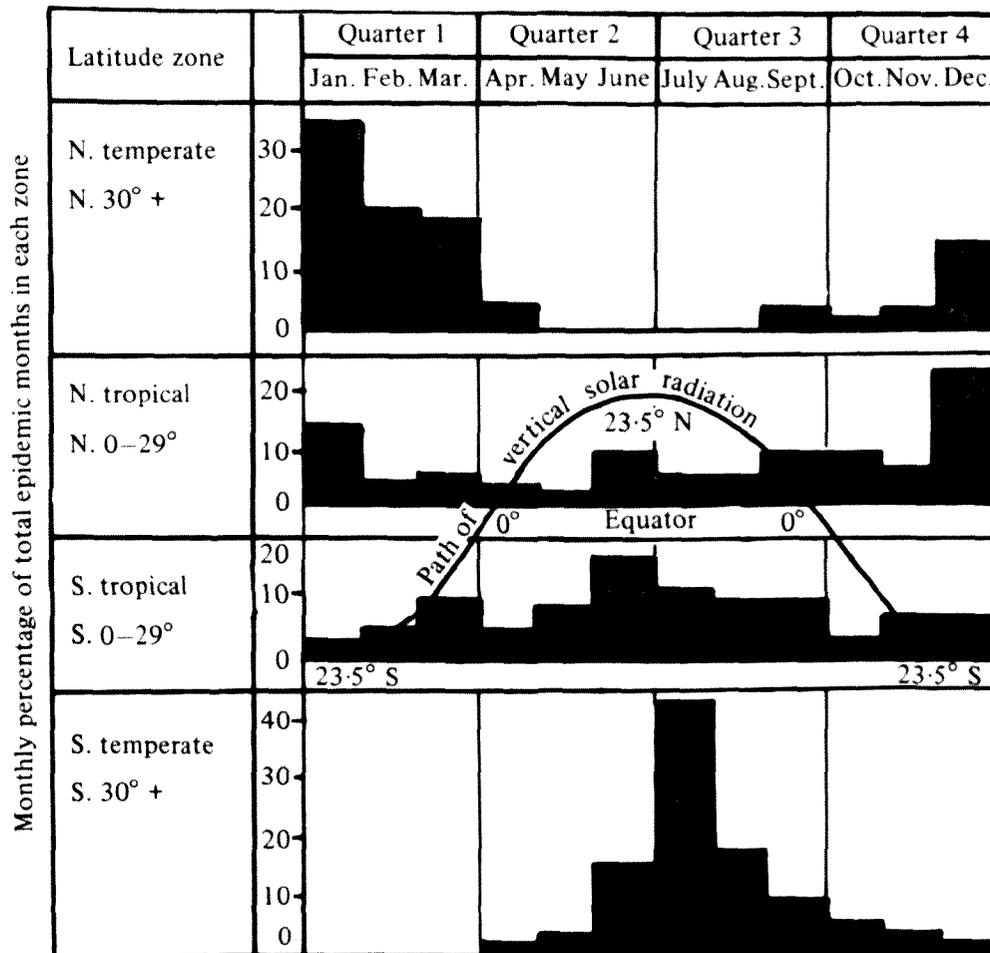


Fig. 2. The seasonal and latitudinal distribution of outbreaks of type A influenza in the world, 1964–75, summarized from the Weekly Epidemiological Record of the World Health Organization into major zones. The diagrams show for each calendar month the percentage of each zone's total outbreaks. In both north and south temperate zones the epidemics are distributed around the local midwinter, whereas the tropical zones show a transition, each approximating towards the distribution of its own temperate zone. The curve indicates the 'midsummer' path taken annually by vertical solar radiation. The 'epidemic path' seems to parallel it, but to lag six months behind it.

of influenza outbreaks received by the W.H.O. from 1964 to 1975 were classified by date, longitude and latitude. Analysis by longitude revealed no clear pattern. Outbreaks classified by date and latitude were summarized into four major zones as shown, and the number of epidemic-containing months was totalled separately for each zone. Figure 2 shows the percentage occurring in each calendar month of the total of epidemic months in that zone.

In both north and south temperate zones, outbreaks were grouped around the time of local midwinter, whereas in the tropical zones the outbreaks showed transition between the timings in the temperate zones, as shown in Table 1.

Figure 3 illustrates the tendency for outbreaks caused by the same virus to occur simultaneously in widely separated areas at a similar latitude. The morbidity from acute febrile respiratory diseases in Cirencester (51.43° N, 1.59° W) is compared with that in Czechoslovakia (Prague, 50.05° N, 14.25° E) from 1969 to 1974 (Strnad *et al.* 1976). Outbreaks caused by the same viruses regularly occurred at about the same time in the two localities.

Table 1. *Percentage of total epidemic months of each zone falling in each half year*

Zone	October–March	April–September
1. North latitudes 30–70°	91.8	8.2
2. North latitudes 0–29°	58.9	41.1
3. South latitudes 0–29°	35.8	64.2
4. South latitudes 30–70°	10.5	89.5

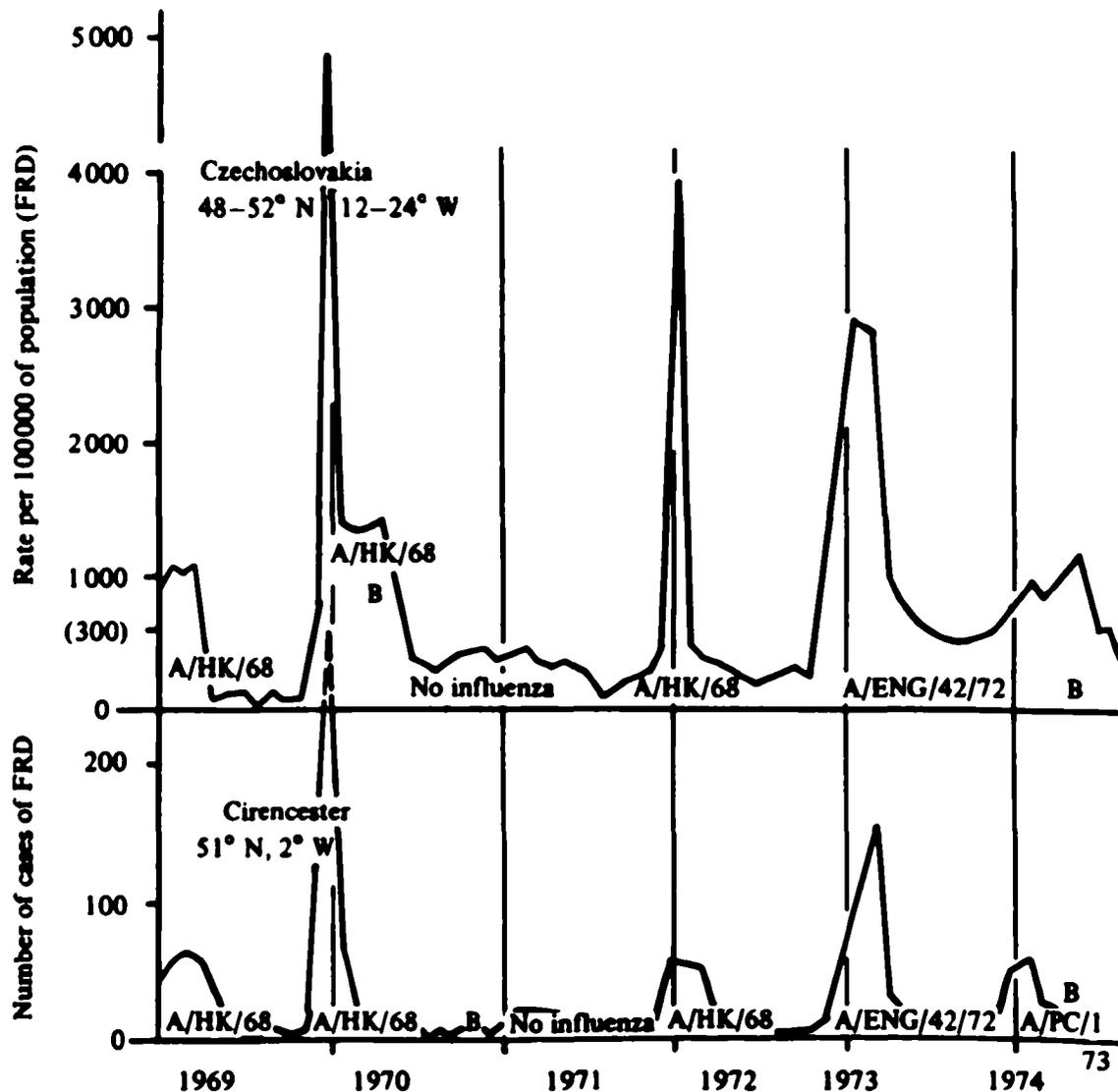


Fig. 3. The Cirencester acute febrile respiratory diseases at 51.43° N, 1.59° W, compared with notifications of such diseases in Czechoslovakia (Prague, 50.05° N, 14.25° E), 1969–74, to show the correspondence of influenza epidemics at widely separated localities at a similar latitude. Each season the epidemics in the two localities are almost synchronous and, despite antigenic change in influenza A virus, are caused by the same organism (Czechoslovak figure adapted from Strnad *et al.* 1976).

Figure 4, for contrast, illustrates the tendency for corresponding epidemics in temperate zones on opposite sides of the equator also to be caused by the same virus but to be separated by six months. The mortality from influenza in England and Wales is compared with that in New South Wales from 1967 to 1973 (Gill & Murphy, 1976). The synchronism of Fig. 3 is replaced by parallelism, Fig. 4 show-

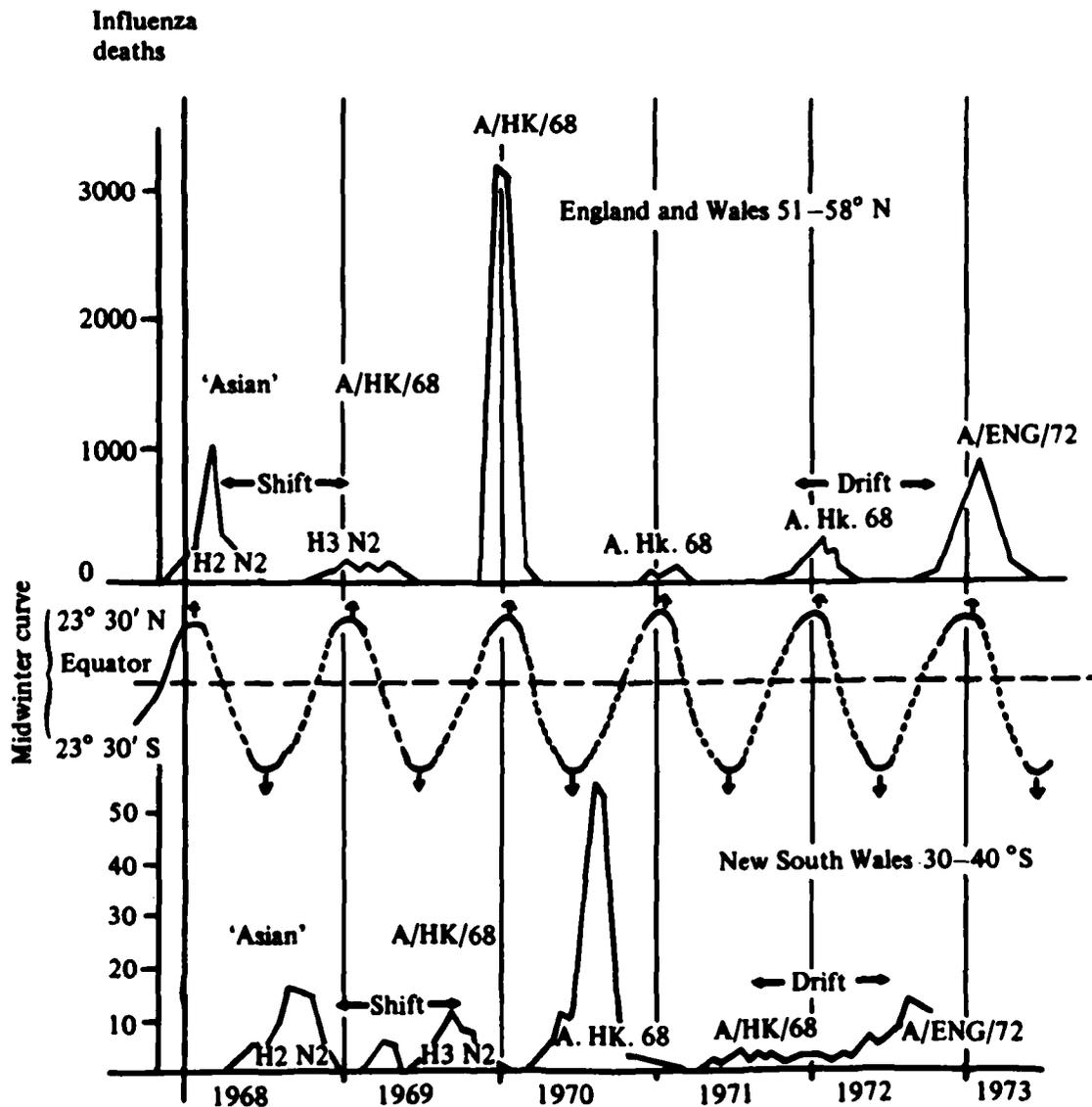


Fig. 4. Influenza mortality in England and Wales at latitude 51–58° N compared with that in New South Wales, Australia, 30–40° S, (adapted from Gill & Murphy, 1976). In contrast to Fig. 3 the effect of the widely separated latitudes is to produce a regular difference of about six months in the timing of epidemics caused by the same virus in the two hemispheres. The shift from H₂N₂ to H₃N₂ subtype of influenza A virus and the drift of minor variant from A/HK/68 to A/Eng/72 both appear punctually in the corresponding epidemic in the opposite hemisphere, and in both places the earlier ubiquitous virus is completely replaced after the inter-epidemic interval by the new variant.

ing that the 'midwinter' timing summarized in Fig. 2 is an annually recurring sequence of events.

Analysis of the records from the World Health Organization shows this north and south procession of influenza in every one of the years from 1964 to 1975.

DISCUSSION

The evidence summarized in the figures leaves no doubt that a seasonal influence is controlling the epidemicity of influenza. The use of the term 'seasonal influence' may, however, obscure the fact that season itself is a result of the operation of extraterrestrial forces and, before considering in detail the significance of the seasonal pattern, it may be valuable to recapitulate the general nature of seasonal

phenomena, seeking to understand what mechanisms are likely to be mediating the 'seasonal influence' on influenza.

Seasonal phenomena are caused by variations in solar radiation. This is a natural law from the inexorable logic of which there would appear to be no exceptions. Seasons occur because the axis of the Earth's daily rotation is not perpendicular to the plane of its annual elliptical orbit around the sun. The plane of the daily rotation is tilted some $23\frac{1}{2}^{\circ}$ in relation to the plane of the orbital journey, consequently the vertical radiation from the sun, instead of circling the Equator year after year, follows a sinuous path, reaching its north extremity, the Tropic of Cancer, each 21 June and its south extremity, the Tropic of Capricorn, each 21 December, and crossing the Equator at the spring and autumn equinoxes. Figures 2 and 4 suggest that this path travelled annually by maximum solar radiation is paralleled by that taken by epidemic influenza. The variations in intensity and composition of solar radiation resulting from the tilt of the earth cause the seasons and associated seasonal phenomena all over the surface of the globe. Polar ice-caps, glaciers and the snowcaps of mountain ranges expand and contract so that oceans rise and fall, belts of light and temperature around the earth shift repeatedly north and south so that climates change, winds and ocean currents shift and alter course, and the length of days and nights changes continually. More complex than such direct effects are the countless adaptations evolved by plants and animals to evade the rigours or seize the opportunities of seasonal changes.

Seasonal disease in man is no exception to the law that all seasonal phenomena are caused by variations in solar radiation. Intermediate mechanisms through which the prime cause is operating may be suggested by the geographical distribution and the annual timing, as in the parasitic diseases mentioned in the Introduction in which the vectors of the parasites undergo a seasonal life cycle. Colds were found to have a different type of seasonal distribution in a United Kingdom study (Hope-Simpson, 1958) in which the morbidity was closely though inversely related to seasonal temperature throughout the four years of the investigation. The seasonal character of influenza, however, bears little resemblance to any of these examples.

Figure 1 is typical of the behaviour of influenza in small communities all over the world, breaking out for several weeks at approximately the same season almost every year, perhaps twice annually in the Tropics. Table 1 and Fig. 2, which gather local experiences over a number of years from all over the world into a single diagram, show that, although in any one locality influenza outbreaks are briefly episodic, when the world population is considered as a whole, epidemic influenza is occurring smoothly in sequence at different latitudes. Fig. 4 confirms that it is travelling annually north and then south across the surface of the earth. If it were spreading directly from the sick the progress should be multidirectional following lines of travel. This does not happen. Epidemic influenza appears to follow each year a path that parallels that of maximum solar radiation, lagging six months behind.

Influenza epidemics occur all over the inhabited globe. The ubiquity of influenza is evidence that the influence of season cannot be operating by means of any mediating mechanisms that have a limited geographical distribution such as

plants, arthropods, climates, ethnic factors, social behaviour or seasonal temperature changes. Latitude alone broadly determines the timing of epidemics in the annual cycle, a relationship that suggests a rather direct effect of some component of solar radiation acting positively or negatively upon the virus, the human host or their interaction.

Figure 3 illustrates the tendency of epidemics of influenza to occur contemporaneously at the same latitude even in localities widely separated by longitude. The explanation must be that the epidemic process is approximately synchronous over vast areas at similar latitudes. Exceptions are easy to find. Epidemics often occur in different months in neighbouring communities, but the tendency to latitudinal synchrony is evident and could have been illustrated from many other communities including series as far apart as North America and Europe.

Epidemicity is not the only seasonal characteristic of influenza illustrated by these figures. Figures 1, 3 and 4 demonstrate that antigenic variation of the type A influenza virus is frequently occurring seasonally in a puzzling manner. During the 28 years illustrated in Fig. 1 it shifted twice, first from H1N1 to H2N2 in 1957 and then to H3N2 in 1968–69, and on both occasions the predecessor major subtype, that had caused all the identified type A influenza for more than a decade, disappeared and was entirely replaced next season by viruses belonging to the successor subtype. Moreover, during the years of dominance of each subtype, minor antigenic ‘drifted’ variants supplanted one another seasonally. Even in the incomplete series of identifications in Fig. 1 the prevalent virus can be seen to have disappeared and to have been replaced next season by one or more minor variants on at least four occasions. Figure 3 shows that this process of virus disappearance and seasonal replacement was occurring simultaneously in widely separated localities at the same latitude, indicating that the virus substitution had taken place seasonally over an enormous territory synchronously affecting vast numbers of people. For example the virus, A/Hong Kong/68 (H3N2), that had been causing all the type A influenza in England and Wales and in Czechoslovakia in the winter of 1971–72 disappeared from these populations during the subsequent interepidemic months and was replaced in the winter of 1972–73 by viruses similar to A/England/42/72 (H3N2). A similar situation in places in temperate latitudes north and south of the Equator is depicted in Fig. 4, corresponding epidemics being caused by identical viruses, but with the important difference, that the antigenic shift from H2N2 to H3N2 in 1968–69 and the antigenic drift from A/Hong Kong/68 to A/England/72 are mirrored six months later in the Antipodes.

When two apparently diverse influenzal processes, epidemicity and antigenic variation, occur so often both simultaneously and seasonally in huge populations living in vast areas at approximately the same latitude, and when both participate in the annual north and south progression across the surface of the earth about six months after ‘midsummer’, the association cannot be occurring by chance and is most simply explained if virus variation and epidemicity are both part of the same single epidemic process.

It is also necessary to explain the repeated phenomenon of the abrupt disappearance of a virus uniquely prevalent over a wide area and its replacement next season

by a new variant. The most probable, perhaps the only, explanation would seem to be that, by a metamorphosis of some sort, the first virus had been transformed into its successor. A possible mechanism by which such a transformation might take place is suggested by the new hypothesis (Appendix, propositions 5 and 6) whereby residues of the first virus latent in those in whom it had caused influenza are reactivated next season when their carrier-hosts have developed specific immunity. The reactivated virus would then be in a situation analogous to that by which antigenic drift is induced in the laboratory (Archetti & Horsfall, 1950). The role of season is suggested as providing the stimulus that initiates reactivation of latent virus around the time of minimal solar radiation.

If epidemicity and virus variation are both integral features of a single seasonally controlled process, the problems posed by annual epidemics, unusual seasonal timing of epidemics, antigenic drift, viral disappearances and replacements and many other epidemiological difficulties are simply explained. Antigenic shift remains difficult to understand, but it shares the same seasonal character as epidemicity and drift, so that the new hypothesis must predict that the mechanisms causing the seasonal behaviour of major antigenic shift will be found to be similar to those controlling that of minor antigenic drift.

The regular annual excursions of influenza north and south across the inhabited surface of the earth cannot be interpreted in terms of a continuous chain of direct transmissions from the sick to their companions. Such an explanation of the observations illustrated in Figs 2 and 4 strains credibility. In the new hypothesis the illustrations are interpreted as showing the annual movement north and south of the seasonal stimulus that reactivates latent virus in the innumerable carriers who are everywhere present, so creating the opportunity for epidemics to occur in the wake of its passage. This stimulation would be responsible for causing the usual seasonal outbreaks. Epidemics generated out of season might be caused by symptomless travellers harbouring virus that had been reactivated from latency in a distant area. Such events may be expected to occur more frequently in these days of rapid and universal travel and would explain, for example, the outbreak of Asian type A influenza in a military establishment in Cheshire, England, in May and June 1957, months before any further outbreaks in this country. That outbreak may have signalled the arrival in camp of a symptomless carrier whose latent virus had been reactivated to infectiousness by the seasonal trigger operating when he was thousands of miles away in a southern latitude. Many puzzling outbreaks recorded in the literature would be similarly explained. Fothergill in 1775 recorded the dates of onset, maxima and decline of the then current influenza in various parts of England and Wales (reported in Fothergill, 1784). The speed of spread of the epidemic 200 years ago was similar to that of twentieth-century epidemics. Direct spread of the disease would have been much slower in days of limited and slow travel, but the movement across the Earth of a seasonal trigger would be unaffected by speed of travel.

The nature of the seasonal stimulus remains undiscovered. If its effect is immediate it must be operating around the time of minimal solar radiation, a timing that favours the suggestion that U.V. rays inhibit direct transmissions which are

therefore facilitated in winter, so that epidemics are more likely to occur then (Shadrin, Marinich & Taros, 1977). Ultraviolet rays are lethal for influenza virions, but the occurrence of tropical epidemics of influenza does not support this explanation, which also fails to explain the other problems of influenzal epidemiology.

Solar radiations consist of complex and varied emissions from the sun comprising the whole spectrum of electromagnetic radiations, and streams of alpha- and beta-particles are also carried to Earth on the solar wind. Reflections from Earth's magnetosheath and molecular collisions in the atmosphere also give rise to secondary effects on the surface of the Earth. Studies are in progress in many parts of the world to determine the effect of such emissions on human and animal physiology and upon microorganisms (Tromp & Bouma, 1979). Proposition 5, that antigenic variation occurs in each influenza season, seems to be belied by those successive seasons in which none has been detected. Changes missed by earlier analyses are sometimes detected by later techniques. The proposal may, however, oversimplify the process. At times, as after an antigenic shift, several cycles of latency and reactivation may precede the escape of a successful minor variant.

The world influenza reports summarized in Fig. 2 vary in quality and completeness from one country to another, and some areas, several of which are large or contain great populations, are not represented. The records also vary from year to year, the accuracy and completeness improving over the years. The movement of epidemic influenza over the surface of the earth, clearly perceptible in Fig. 2, must therefore be accepted with the recognition that more complete data may strengthen or modify the inferences drawn in this paper. In view of the evident importance of season in the epidemiology of influenza, it is to be hoped that increasingly accurate and comprehensive world data will continue to be collected and made available for analysis.

The prolonged survey was carried out with the help successively of Drs P. G. Higgins, G. E. Urquhart and B. Roome and of the staff of the Cirencester and Gloucester Public Health Laboratories. The influenza viruses were identified in detail by Dr Marguerite Pereira and her staff at the Influenza Virus Reference Laboratory of the Central Public Health Laboratory at Colindale, London. These and numerous others have helped by discussion, criticism and encouragement. I have had outstanding help from my secretaries, Miss Joyce Dawson and Mrs Bettie Neal, from Miss Helen Spurrier and her small staff at the Medical Library, Princess Margaret Hospital, Swindon, and from the Photographic Department of the hospital.

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Figures 3 and 4 are reproduced from Tromp & Bouma (1979) by kind permission of the publisher.

Dr P. J. Delon of the World Health Organization kindly supplied me with the half-yearly summaries of the influenza material from the Weekly Epidemiological Record for the years summarized in Fig. 2.

APPENDIX

Hypothesis of influenza A virus epidemic mechanisms

(Reproduced by permission of the Publishers of the Journal of Hygiene from Hope-Simpson (1979).)

Proposition 1. Influenza A virus, having caused influenzal illness, rapidly becomes latent in the tissue of the human host causing him no further disturbance, and inaccessible to discovery by present techniques of virus isolation. He develops specific immunity and becomes a non-infectious carrier-host.

Proposition 2. The latent virus residues are reactivated seasonally in their carrier-hosts by an extraneous stimulus that, being ultimately dependent on seasonal variation in solar radiation, affects all parts of the globe, the timing of its operation in a particular locality depending broadly upon the latitude.

Proposition 3. When latent virus is reactivated, the carrier-hosts become for a short time intensely infectious to their non-immune companions who, if infected, rapidly develop influenza. The carrier-hosts suffer no illness from the reactivation.

Proposition 4. Epidemics of type A influenza consist largely or entirely of persons who have caught the disease from reactivated virus shed by symptomless carrier-hosts. During the epidemic the sick do not infect their non-immune companions.

Proposition 5. Virus reactivated from latency always differs antigenically from its progenitor virus because the immune state of the carrier-host induces antigenic drift.

Proposition 6. The antigenic character of reactivated virus is nevertheless determined by the progenitor virus. Carrier-hosts of latent residues of the same progenitor will tend to shed the same assortment of mutants from which their non-immune companions will select the fittest to survive and so continue the species.

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