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Epidemic mechanisms of Type A influenza

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SUMMARY

The antigenic varieties of influenza A virus isolated from 1968 to 1976 in a surveillance of a small, rather remote population were similar to those from England and Wales as a whole, despite frequent antigenic changes during the period. Household studies in the first two H3N2 influenza A epidemics found low attack rates within households, a high proportion (70%) of affected households with only one case of influenza, similar distributions of affected households in the two epidemics by the number of cases of influenza and similar distributions of the influenza cases by the day of their onset in the household outbreak. No serial interval could be demonstrated by cumulating household outbreaks. More than one minor variant was causing influenza contemporaneously in the same villages in several seasons, and different variants were on one occasion found on successive days in bedfellows. The regular occurrence of epidemics in winter was often accompanied by the disappearance of the epidemic variants and their replacement, after a virus-free interval, by new variants.

These epidemiological findings seem best interpreted on the following tentative hypothesis. Influenza A sufferers do not transmit the virus during their illness; instead it rapidly becomes latent in their tissues so that they become symptomless carrier-hosts and develop specific immunity. Next season an extraneous seasonally mediated stimulus reactivates the latent virus residues so that the carrier-host becomes briefly infectious, though symptomless. Antigenic drift occurs because particles reconstituted to be identical with the progenitor virus cannot escape the specific immunity it has provoked in the carrier host. He can shed only mutants also determined by the progenitor virus. From the assortment of mutants shed by the carrier-host, his non-immune companions select that (those) which is best fitted to survive, and it rapidly causes influenzal illness. Epidemics consist largely or entirely of such persons sick with influenza caused by reactivated virus caught from symptomless carrier-hosts.

INTRODUCTION

It was not long after human influenza virus had been discovered in 1933 that workers began to find difficulty in explaining the epidemic behaviour of influenza on a simple model, like that of measles, in which the agent is surviving by endless chains of transmissions passing directly from the sick to their non-immune

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Table 1. *Some type A influenza problems requiring explanation*

Problem	
1	Seasonal occurrence
2	Antigenic drift of virus
3	Antigenic shift of virus
4	World-wide conformity of many seasonal virus changes, often within one year
5	World-wide disappearance of predecessor virus, often sudden
6	Prolonged absences of virus between epidemics
7	Reappearance after long absence, often explosively over wide areas at the same time
8	Rapid termination of epidemic despite the availability of abundant susceptible persons
9	Low attack rate within households often contrasting with high attack rate within institutions
10	Absence of serial interval in cumulated household outbreaks
11	Anomalous age distribution
12	World-wide distribution of influenza throughout recorded history, at all inhabited latitudes and longitudes, in all climates, at all altitudes among all the races of mankind, in persons of all ages

companions who forthwith fall ill and continue the chains (e.g. Burnet, 1945; Andrewes, 1971). Most of the features giving rise to epidemiological difficulties are listed in Table 1. One of them, seasonal occurrence, so regular and familiar that it tends to be taken for granted, can be followed on a global scale in successive issues of the Weekly Epidemiological Record of the World Health Organization, in which influenza A epidemics appear to be travelling to and fro across the world almost annually. Outbreaks south of the tropic of Capricorn precede or succeed their northern counterparts by six months, coming in the colder months in both areas so that they are spoken of as 'winter epidemics', and a 'winter factor' has been invoked in their epidemiology (Andrewes, 1952). Season, however, rather than climate is their determinant as shown by seasonal epidemics of influenza in the tropics during the monsoons in areas where the mean daily temperature may vary as little as 1·1 °C throughout the year. The earth is a unity for influenza A virus in a manner not yet found for any other parasite. Epidemics occur in all inhabited parts of the globe regardless of latitude, longitude, altitude, climate, rainfall, temperature, humidity, race and sex. Latitude, however, expresses the seasonality of the disease by determining broadly the time of year in which epidemics may be expected in any locality. The method by which the influence of season is mediated so as to control influenzal outbreaks is as yet unidentified, but its importance cannot be doubted. It is concerned in most of the phenomena in Table 1 and may indeed provide the key to understanding them. It cannot itself be explained by a hypothesis of direct spread.

The observations reported in this paper, made during a prolonged virological and clinical surveillance of the diseases in a small population living in and around a provincial market town, fall into two groups. The observations in the first

Table 2. *Hypothesis of influenza A virus epidemic mechanisms*

Proposition 1. Influenza A virus, having caused influenzal illness, rapidly becomes latent in the tissues 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.

group were made in a search for evidence of direct spread in the relationship between the local and national experience of type A influenza over a period of 8 years, in the expectation that differences between the findings in the two sorts of population might betray the invasions of successive viruses into the country, travelling through it by direct spread. The observations in the second group were looking for evidence of direct spread in more detailed studies, especially of the behaviour of influenza within affected households. None of the observations are thought to provide evidence of direct spread, and some of them suggest the operation of alternative mechanisms, most of which have already been proposed by others. They have therefore been synthesized into an hypothesis that seems better able to explain most of the epidemiological difficulties in Table 1. The new hypothesis is tentatively offered for consideration and criticism in Table 2.

METHODS

Pereira & Chakraverty (1977) analysed all the influenza A viruses received at the PHLS Central Influenza Reference Laboratory, Colindale, London, from all parts of England and Wales from 1968 to 1976 (Colindale analysis).

The dates in the Colindale analysis are those on which specimens containing influenza A virus were obtained from influenzal patients throughout the UK. The analysis with which the Colindale study is compared is that of the influenza A viruses found during a survey of the illnesses in a general practice population of about 3800 living in and around Cirencester, a small town in Gloucestershire, England (Cirencester analysis). Specimens from patients with acute respiratory disease were examined at the PHLS Epidemiological Laboratory at Cirencester by procedures already described (Hope-Simpson & Higgins, 1969). Many of the

Table 3. *Isolations of type A influenza virus by winter* (1968–1976) *and antigenic variety*

(Cirencester analysis compared with Colindale analysis of specimens from the UK (Pereira & Chakraverty, 1977). Numbers in parentheses indicate influenza A (H3N2) viruses not fully characterized.)

Winter	Virus (all H3N2)	Cirencester isolates		Colindale isolates	
1968–69	A/Hong Kong/68	3 (+73)		881	
1969–70	A/Hong Kong/68	(114)		809	
1970–71	A/Hong Kong/68	0		51	
1971–72	A/Hong Kong/68	54		751	
1972–73	A/England/42/72	26		1290	
1973–74	A/Port Chalmers/73	9		575	
1974–75	A/Port Chalmers/73	25		241	
	A/Intermediate/74	0	31 (+2)	343	941
	A/Scotland/74	6		357	
1975–76	A/Victoria/75	15		1923	
	A/England/864/75	2	17 (+2)	118	2041

specimens found to contain influenza A virus were sent to Colindale for more detailed antigenic characterization, and form a contribution to the Colindale figures varying from none in winters 1969–70 and 1971–2 to 7 % of the UK total in winter 1975–6. The importance that might attach to full antigenic analysis of all specimens was unfortunately not at first appreciated.

Household studies during H3N2 influenza A virus epidemics of 1968–9, 1969–70 and 1971–2 were carried out as described (Hope-Simpson, 1970). The household findings of other epidemics were recorded fortuitously during the surveillance of the population of the general practice.

RESULTS

Comparison of UK and Cirencester analyses (Table 3)

Winter 1968–9. The new influenza A virus, A/Hong Kong/68 (H3N2), differed greatly from its H2N2 predecessor of winter 1967/8 especially in the haemagglutinin antigen. Instead of the severe epidemic expected from the novelty of the virus and its reported behaviour in other parts of the world, the UK experienced a long desultory epidemic with low weekly morbidity. The outbreak in Cirencester was similar, lasting for 13 weeks, but imperceptible among the usual seasonal colds so that few people knew of its presence. Nevertheless more than 4 % of the practice population suffered an attack of influenza (Hope-Simpson, 1970). Unfortunately only 5 of the 76 specimens from Cirencester containing influenza A virus were sent to Colindale and the remainder were jettisoned after having been identified as influenza A virus, H3N2.

Winter 1969–70. In Cirencester, as in Britain as a whole, the influenza epidemic was very severe. More than twice as many persons in the general practice population

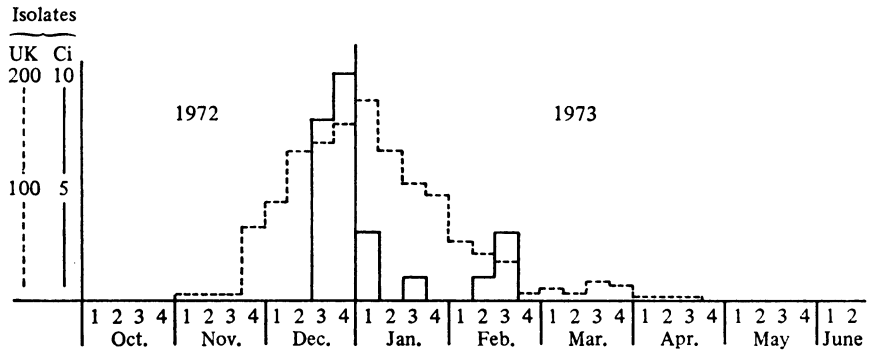

Fig. 1. Influenza season of 1972–3. A/England/42/72-like virus. Ci and continuous line = viruses in Cirencester analysis. UK and broken line = viruses in Colindale analysis. (From Pereira and Chakraverty, 1977.)

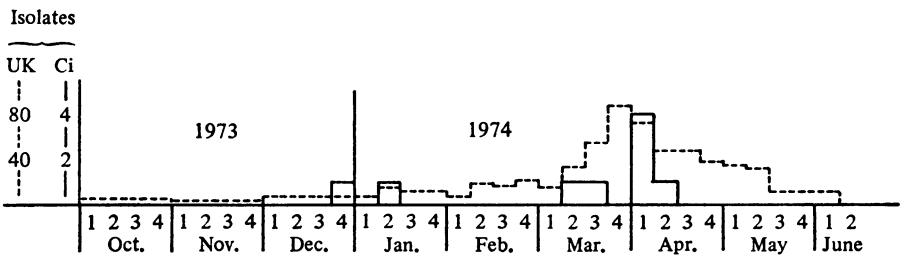

Fig. 2. Influenza season of 1973–4. A/Port Chalmers/73 virus. Conventions as in legend for Fig. 1.

were attacked in less than 6 weeks as in the 13 weeks of the epidemic of 1968–9. Table 3 shows that Colindale received fewer positive specimens than last season, an anomaly that may have arisen from the severity of the epidemic. None of the 114 specimens containing influenza A virus obtained at Cirencester were sent to Colindale.

Winter 1970–1. No recognizable epidemic of type A influenza occurred in Britain this season, only 51 specimens, all similar to A/Hong Kong/1/68 virus, were received at Colindale and no type A influenza was found at Cirencester.

Winter 1971–2. Viruses similar to A/Hong Kong/1/68 virus reappeared in the UK at the end of November, caused widespread illness for several months and disappeared in late February. In Cirencester a desultory epidemic of acute febrile respiratory disease ran for 3 months from late November. A/Hong Kong/68 virus was found from the first week in January to the third week in February.

Winter 1972–3 (Fig. 1). Among the 751 viruses examined at Colindale in the previous season only one was found to be a variant strain, A/England/42/72 virus. A few months later, during our summer of 1972, this variant was causing widespread influenza in the southern hemisphere. It reappeared in the UK in November 1972 and caused a sharp epidemic, peaking in early January 1973 and fading out in mid-February. At Cirencester the experience was similar. A/England/42/72-like virus was first found there in mid-December, caused a sharp epidemic,

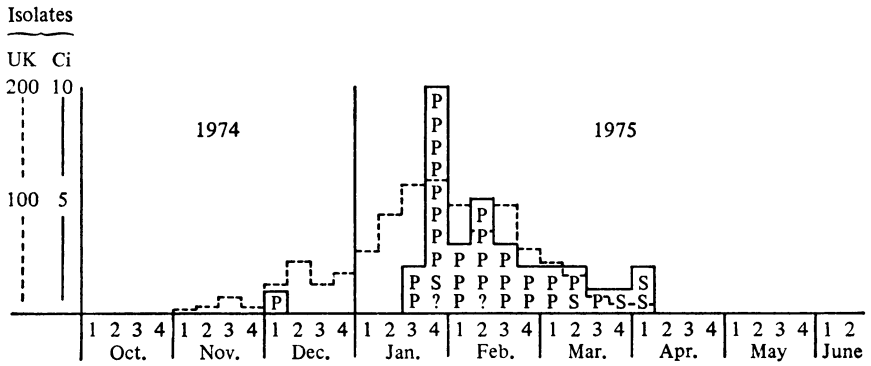

Fig. 3. Influenza season of 1974–5. A/Port Chalmers/73 and A/Scotland/74 and A/Intermediate/74 viruses. Conventions as in legend for Fig. 1, and also, in Cirencester viruses, P = A/PC/73 virus, S = A/Sco/74 virus and ? = an influenza A (H3N2) virus not fully characterized.

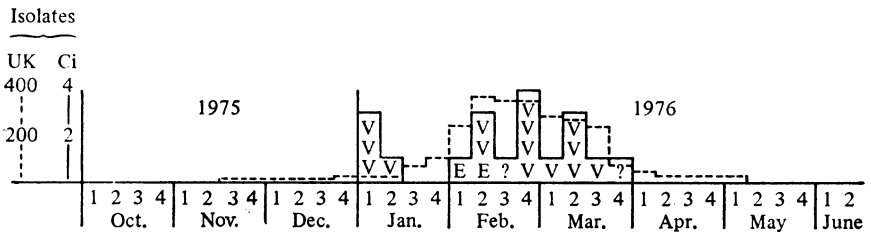

Fig. 4. Influenza season of 1975–6. A/Victoria/3/75-like virus and A/England/864/75-like virus. Conventions as in legend for Fig. 1, and also, in Cirencester, V = A/Vic/75 virus and E = A/Eng/864/75-like virus, and ? = influenza A (H3N2) virus not fully characterized.

peaking a week before the maximum of UK isolations, and disappeared in late February.

Winter 1973–4 (Fig. 2). Virus like A/England/42/72 does not reappear in the Colindale analysis. A new variant of H3N2 influenza virus, A/Port Chalmers/73, which had been causing influenza in the southern hemisphere, began to be found in small numbers in many parts of the UK from October 1973, but no epidemic came until mid-March, rising to a peak at the end of the month and declining more slowly, the last isolates coming from specimens taken in early June.

A/Port Chalmers/73 virus was first found in Cirencester on 28 December 1973. Most of the isolates came from specimens taken in March and April when Colindale was receiving the most isolates from the UK. The pattern of acute febrile respiratory illness in the Cirencester general practice population was complicated by a large outbreak of type B influenza, part of a nationwide epidemic.

Winter 1974–5. Of the 575 influenza A viruses examined at Colindale in the previous season 11 had shown an identical drift (Fig. 3), and when the variant reappeared as one of three influenza A viruses circulating together this season

Table 4. *Households serially attacked in different seasons during the dominance of H2N2 subtype of influenza A virus*

('?' indicates that the virus was not fully characterized, the attribution being assumed because this was the only variant recorded in Britain during that season.)

Household	Season	Sex	Age	Virus	Season	Sex	Age	Virus
2	1962–63	F	32	A/Singapore/1/57	1963–64	M	8/12	A/England/12/64
3	1962–63	F	39	A/England/61	1965–66	M	5/12	A/England/12/64
7	1962–63	M	38	? A/Singapore/1/57	1967–68	F	9/12	? A/England/68/68
1	1963–64	M	13	A/England/12/64	1967–68	F	12	A/England/68/68
8	1963–64	M	3	A/England/12/64	1967–68	F	1	A/England/68/68
6	1965–66	F	26	? A/England/12/64	1967–68	M	11/12	A/England/68/68
		M	28	? A/England/12/64				

Table 5. *Households serially attacked in different seasons during the dominance of H3N2 subtype of influenza A virus*

Household	Season	Sex	Age	Virus	Season	Sex	Age	Virus
2	1968–69	F	24	A/Hong Kong/1/68	1969–70	F	39	A/Hong Kong/1/68
						M	6	A/Hong Kong/1/68
					1973–74	F	16	A/Port Chalmers/1/73
11	1968–69	M	40	A/Hong Kong/1/68	1968–70	F	2	A/Hong Kong/1/68
					1971–72	M	43	A/Hong Kong/1/68
13	1968–69	F	45	A/Hong Kong/1/68	1969–70	M	49	A/Hong Kong/1/68
16	1968–69	F	51	A/Hong Kong/1/68	1969–70	M	53	A/Hong Kong/1/68
						F	20	A/Hong Kong/1/68
						F	19	A/Hong Kong/1/68
17	1968–69	F	29	A/Hong Kong/1/68	1969–70	M	6	A/Hong Kong/1/68
						F	4	A/Hong Kong/1/68
20	1968–69	F	18	A/Hong Kong/1/68	1971–72	M	58	A/Hong Kong/1/68
21	1969–70	M	64	A/Hong Kong/1/68	1975–76	M	38	A/Victoria/3/75
						M	42	A/Victoria/3/75
5	1974–75	F	59	A/Port Chalmers/1/73	1975–76	F	29	A/Victoria/3/75
18	1974–75	F	22	A/Port Chalmers/1/73	1975–76	F	10	A/England/864/75
19	1974–75	F	50	A/Port Chalmers/1/73	1975–76	F	13	A/Victoria/3/75
						M	22	A/Victoria/3/75
						F	75	A/Victoria/3/75

it was designated A/Scotland/74. A/Port Chalmers/73 was again present and a new variant showing less drift than A/Scotland/74 named A/Intermediate/74. These three variants were present to an equal degree throughout the season from December 1974 to March 1975.

A/Port Chalmers/73 virus reappeared in Cirencester in the first week in December 1974, and from mid-January to early April 1975 it was found concurrently with A/Scotland/74 virus as at Colindale. A/Intermediate/74 virus was not found at Cirencester.

In several earlier seasons of the Cirencester surveillance, before the period covered by this comparative analysis, more than one minor variant had been causing influenza in the same epidemic, sometimes in the same villages. In winter 1967–8 two small brothers who shared a bed in a rural household developed influenza simultaneously, and A/England/68/68 virus was isolated from one of them on 25 January, and next day A/Tokyo/67 was isolated from his brother.

Winter 1975–6 (Fig. 4). The three variants of the season before disappeared in March 1975 and were replaced throughout the UK this season by two new variants. A/England/864/75 virus was first found in November 1975 and similar strains were isolated in small numbers until March 1976. The other new variant, similar to A/Victoria/3/75 virus, had drifted considerably from A/Hong Kong/68 virus and had already been causing much influenza in the southern hemisphere so that it was the variant expected in Britain. It was not found in the UK until the last day of December 1975, and next day, New Year's Day 1976, it was found in a small village near Cirencester. It caused a severe epidemic throughout the UK before disappearing in April 1976. In Cirencester A/Victoria/75 virus also continued to be found until the end of April 1976, and A/England/864/75-like virus was only found twice.

Households affected serially in different epidemics

The surveillance recorded six households in which one member had been attacked by H2N2 influenza A virus and in which another member had been attacked by virus of the same major subtype in a later epidemic. In each of these households the second H2N2 virus differed antigenically from the first (Table 4).

Ten households each with one case of type A influenza caused by an H3N2 virus were recorded in which H3N2 virus attacked one or more other members in later seasons. Altogether 17 persons were attacked in these households in a second season and two more in a third season (Table 5). These subsequent attacks did not always occur in the next influenza season. The H3N2 viruses obtained in the winters of 1969–70 and 1971–2 in households previously attacked showed no apparent antigenic drift from the earlier virus. Thereafter the subsequent viruses all differed antigenically from their predecessor in the same household. Out of 19 viruses obtained in Cirencester in winter 1975–6, five came from households in which H3N2 virus of a different antigenic character had been found in a previous season.

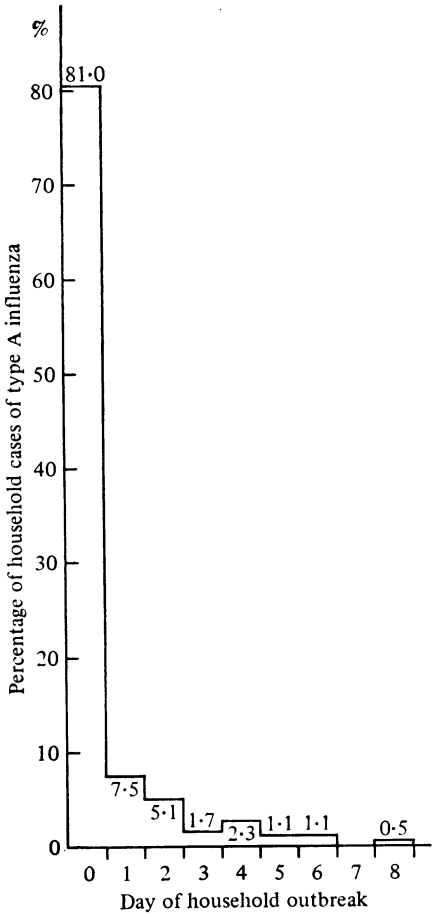

Fig. 5. Cumulation of 134 household outbreaks of type A influenza to show the proportion of cases occurring on each day of household outbreak. No serial interval, dividing introducing cases from those infected by them, can be found.

Apparent spread of influenza within households

When multiple cases occurred within a household in epidemics caused by H3N2 influenza virus they were always closely aggregated, with seldom more than a few days between successive cases. In the longest household outbreak of four cases, the last case began 9 days after the first. To obtain evidence of direct spread within the household the serial interval (case interval, generation time, transmission interval) must be determined by cumulating household outbreaks with the first case in each household on day 0, so that the interval between infecting case and infected case becomes apparent (Hope-Simpson, 1948). Fig. 5 shows that no serial interval was demonstrable in the cumulated influenza households.

The influenza epidemic of 1969–70, much larger and briefer than its predecessor of 1968–9, attacked many more households. Yet within the households attacked the two epidemics behaved similarly. No further case occurred in nearly 70% of households into which the virus had gained entry and the proportion of cases

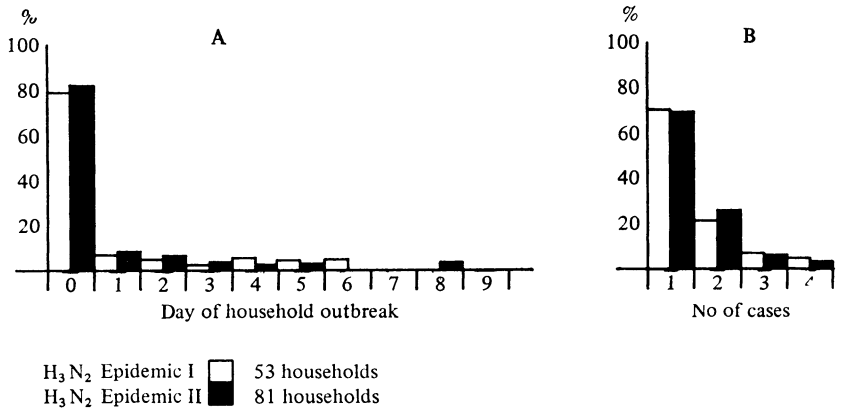

Fig. 6. Household outbreaks of type A (H3N2) influenza in a mild epidemic (1968–9) and in a severe epidemic (1969–70). (A) Proportion of cases falling on each day of household outbreak, showing similar distribution in the two epidemics with about 80% falling on day 0. (B) Distribution of households by number of persons attacked in them, showing almost identical distribution in the two epidemics: 70% of households in both epidemics have only one case of influenza.

falling on days 0, 1, 2, etc., of household outbreak was similar in the two epidemics (Fig. 6A). The distributions of households by the number of cases of influenza within them were also closely similar (Fig. 6B).

It is necessary to separate co-primary from secondary cases in order to calculate the secondary attack-rate (or the more accurate exposure attack-rate, Hope-Simpson, 1952) and it is impossible to do so without knowing the serial interval. An attempt was therefore made to obtain some measure of the infectiousness of the virus within households by using a 'Subsequent attack-rate', arbitrarily choosing one first-day case in each household outbreak as the primary and all other cases as 'secondary' to it, even when they also fell on day 0 or on day 1. Although the method should give a figure which is too high, because co-primaries are included with secondaries, the 'subsequent attack rate' was low, namely 17% for the epidemic of 1968–9 and only 14% for the far more severe epidemic of 1969–70. These rates should be compared with the exposure-attack-rates for mumps (30%), chickenpox (61%) and measles (75%) (Hope-Simpson, 1952).

DISCUSSION

The findings reported in this paper come from several different approaches, yet none can readily be explained by an epidemic mechanism of direct transmission of influenza A virus from the sick to their non-immune companions who rapidly develop the disease. Some of the observations indeed seemed to show positively that such direct spread was not occurring. Taken together the findings have combined to suggest the operation of the alternative epidemic mechanisms in Table 2, which also seem to explain most of the other epidemiological problems listed in Table 1 except those posed by antigenic shift.

Comparison of Cirencester analysis with Colindale analysis

The findings from the Cirencester general practice population, fewer than 1/10000 of that of England and Wales, living in a semi-rural area of less than 50 square miles, reproduced in miniature for eight successive seasons from 1968 to 1976 the patterns of influenza A (H3N2) viruses antigenically characterized by Colindale from specimens coming from all parts of the country. The pattern was complex. The first of the seven antigenic varieties found by Colindale appeared to cause all the type A influenza for the first four winters, but thereafter the six variants came and went rapidly, three being present only for a season. Five viruses disappeared from the UK between February 1972 and March 1975 (Table 3). Winter 1975–6 shows how rapidly a new variant can appear in a remote area. Season after season the small local epidemic reproduced the complicated changes affecting the UK as a whole except for the absence of one of the three viruses present in winter 1974–5. Such close concordance seems unlikely to have been caused by a virus invading the UK from outside its borders anew each season and reaching all parts of the country by chains of transmissions, each link being a person with an influenzal illness.

Both analyses illustrate most of the problems in Table 1, and some problems recur. For example, A/Hong Kong/68 virus, having caused perhaps half a million cases of influenza in Britain in winter 1971–2, disappeared in March and next season A/England/42/72 virus appeared in November 1972 and began an epidemic that caused a further half-million cases. Similar seasonal disappearance and replacement of successive minor variants recurred in 1973 and in 1975.

Subclinical immunizing infections are often invoked to explain why epidemics cease unexpectedly, as in winter 1968–9 when H3N2 influenza A virus appeared as a novel major variant in an inexperienced population and attacked fewer than 5% (Hope-Simpson, 1970). Although serological findings seemed to support the explanation, a much more severe epidemic caused by the same virus struck the supposedly immunized community only 8 months later.

Serial interval

The epidemiological evidence that a disease is being transmitted directly from case to case in a particular environment is the demonstration of the serial interval between the primary introducing cases and the secondary cases they have caused (Hope-Simpson, 1948). Fig. 5 shows no serial interval between first and second cases in cumulated household outbreaks of type A influenza. Its absence shows that in those households influenza was not spreading from the sick, and that one of two other possible mechanisms must have been operating. Either the household cases were caused by reactivation of virus previously latent in the influenza victims as suggested by Petrescu *et al.* (1976), or all the household cases were caught from some inapparent focus of infection within the household, e.g. a symptomless carrier.

Secular aggregation of influenza within households

If the first alternative – reactivation of virus previously latent in the sufferers – were correct, multiple cases within a household would be expected to be distributed throughout the duration of the epidemic. This was not so. The first H3N2 epidemic lasted for more than 90 days, yet the multiple cases within any household were always closely aggregated within a few days. Their influenza therefore was not caused by virus previously latent in them.

Low household attack rates

The small proportion of housemates attacked after the initial household case may be seen as evidence of the second alternative, namely that all household cases including the first were in fact secondary to a symptomless introduction. If this explanation is correct, the household attack rate in the small first H3N2 epidemic (1968–9) quoted as 17% was in fact 25%, while that in the large second H3N2 epidemic (1969–70) quoted as 14% was in reality 54%. These higher values accord well with the observed characters of the two epidemics and with their attack rates in institutions such as schools. The virus had more than doubled its infectiousness in the 1969–70 epidemic, a finding consistent with antigenic drift in the neuraminidase antigen detected in 1969 (Werner, Schudrowitz & Kohler, 1975).

Distribution of households by number of cases of influenza

The high proportion of affected households in which only one case of influenza occurred, nearly 70% in both epidemics, is further evidence that the disease was not spreading within the household. Had the first case of influenza been introducing a highly infectious virus into each household it would not have failed to infect any other housemate in such a high proportion of households, especially in the severe second epidemic. Little difference is recorded in the intrafamilial behaviour of the disease in two epidemics of such different character. The two distributions shown in Fig. 6A are almost identical as are those in Fig. 6 B. This picture accords well with the suggested mechanism of a symptomless carrier transmitting all the overt household infections. The number of households affected was much greater in the second epidemic, but within affected households the secondary response to the symptomless introducer was similar in the two epidemics.

Alternative hypotheses previously suggested

Limitation of space precludes a consideration here of the vast literature of the present subject, and the reader is referred for a discussion of the situation as it was in 1972 to the summary of Influenza Workshop IV (National Institutes of Health, 1973). More than 30 years ago Burnet (1945) found himself compelled to the view that influenza virus must undergo some form of latency in the tissues of its human host in order for it to survive between epidemics, and many others have come to the same conclusion. Other propositions have from time to time been put forward to explain isolated difficulties (Petrescu *et al.* 1976; Langmuir &

Schoenbaum, 1976; Marine, McGowan & Thomas, 1976), but there have been few published attempts to draw these suggestions into a coherent hypothesis, unifying the explanation of all the problems. Andrewes (National Institutes of Health, 1973) suggested the following:

(1) Large infecting doses give clinical disease and solid immunity, while smaller doses cause subclinical infections and only temporary immunity.

(2) In an epidemic most householders are infected at the same time so that those receiving small doses do not pick up clinically evident disease from a stricken housemate.

(3) Those who were ill remain immune but those infected subclinically become susceptible in following years.

Evidence in favour of this attractive hypothesis may be seen in the usual decline in antibodies after an epidemic, and in the varied response to different challenge doses of virus by mice and human volunteers. It also provides a better basis for antigenic drift than the indefinite 'herd immunity' or 'antibody pressure on the virus by a partially immunized community' often suggested. Those with waning immunity from subclinical infection might next season still possess sufficient specific immunity to deter the identical virus and select a minor mutant. The low household attack-rate found here and by some (but not all) others is explained, but it is not clear in the propositions whence the housemates obtain their simultaneous infection. No explanation is given of survival of virus between epidemics and Andrewes (1951) was one of the earliest to propose that latency must be occurring. Seasonal occurrence remains unexplained, and no reason is offered for the disappearance of successive antigenic varieties. The truth may well be found, as Andrewes has suggested, in a combination of his propositions with those in Table 2.

The hypothesis in Table 2

The propositions in the hypothesis in Table 2 arose from the observations reported in this paper and from those in a study of the seasonality of type A influenza reported elsewhere (Hope-Simpson, 1979).

Virus latency is the fundamental assumption. The absence of evidence for direct spread suggested that latency must be occurring too rapidly for the sick person to be able to infect his companions. The absence of serial interval (Fig. 5) and the aggregation of multiple cases within households suggested that reactivation in the carrier host must be symptomless. The seasonal occurrence of epidemics suggested that the powerful and worldwide seasonal control of the timing of influenza A epidemics must operate through an extraneous stimulus initiating the reconstitution of latent residues into infectious virus seasonally. The carrier host would thus have time to develop immunity specific against his infecting and now latent virus, so that when reactivation was stimulated the reactivating virus would encounter a situation similar to that used in the laboratory for inducing antigenic drift (Archetti & Horsfall, 1950; Isaacs, 1951; Fazekas de St Groth & Hannoun, 1973). For example, in Household 19 (Table 3) Mrs F.N., the first case of A/Port Chalmers/73 influenza in the local epidemic was, that

season, the only person to suffer in her household, but a year later her daughter B.N., her son W.N. and her mother E.B., all living with Mrs F.N., were the first persons attacked in the local A/Victoria/3/75 influenza epidemic. The explanation, according to this hypothesis, is that Mrs F.N., having become immune, could not shed virus particles reconstituted to be identical with her A/Port Chalmers/73 virus. From the limited assortment of mutants that she was able to shed, her family selected A/Victoria/3/75 because it was the variant best fitted to survive, perhaps because of its abundance and power of spread. The same happenings with the same result were occurring in the households, not only of Mrs F.N.'s fellow sufferers in the local epidemic, but also over a large part of the world. Some such explanation seems to be required to account for the disappearance of a ubiquitous virus, and its ubiquitous replacement next season by a new virus. The latent residues left by a particular virus in the carrier-host must be considered to determine rigorously the antigenic natures of the assortment of mutants that will be shed at the time of reactivation. The immunity it has provoked will be similar in all hosts carrying its residues. The best mutant will be unconsciously selected by the companions infected, so that a particular progenitor virus will tend to determine a particular successor. More than one mutant of equal potentiality will inevitably issue from some of the progenitor variants, causing epidemic seasons in which more than one successor variant will be isolated contemporaneously. The incident reported in this paper of the isolation of A/England/68/68 (H2N2) virus from a small boy and of A/Tokyo/67 (H2N2) virus next day from his brother sharing the same bed is best explained by both boys catching their infection from a common donor of two variants of good potential.

Objections to the hypothesis in Table 2 are numerous and cogent. Virus isolated from cases of human type A influenza is transmissible to chicken embryos, certain cells, tissues and organs in culture, animals and human volunteers. Experimental studies provide little evidence to support the postulate and much of the rapidly advancing understanding of the cell–viral relationship does not favour the likelihood of latency. On the other hand both animal and human influenza A viruses persist as a symptomless infection in healthy swine and may become manifest as illness perhaps under adverse environmental conditions (Menšík *et al.* 1976; Wallace, 1977). Gavrilov *et al.* (1972) have produced prolonged persistence of influenza A virus in tissue-culture, and Golubev *et al.* (1975) found that such persistent influenza A virus underwent spontaneous antigenic drift in the absence of added antibody, producing both forward and backward mutants some of which overleapt the boundaries of antigenic shift. Frolov *et al.* (1978) have isolated H0N1 influenza A virus from the blood of healthy individuals in the non-influenza months of 1976 – a major subtype last found to be causing influenza more than 30 years ago. The Fort Dix outbreak of type A influenza in 1976 was also caused by virus of a long-vanished subtype, and in 1977 H1N1 influenza A viruses after 20 years absence are currently causing influenza.

Experiments in mice and in human volunteers (National Institutes of Health, 1973) and with live influenza vaccine (Shadrin, Marinich & Taros, 1977) have

confirmed an effect of season and latitude independent of artificial environment. Such findings, taken with the epidemiological evidence, are thought to justify publication of the new hypothesis. If correct, it carries important theoretical and practical consequences. The population of the world is seen at all times and everywhere seeded with persons carrying latent residues of influenza A virus. A seasonally operated stimulus is pictured as moving to and fro across the surface of the globe, reactivating the virus latent in the symptomless carriers, so initiating influenza epidemics in its course and creating the false impression that the disease itself is travelling. Like every other seasonal process on earth, the cause of its seasonal occurrence must ultimately be traced, however remotely mediated, to the annual cycle of variations in solar radiation caused by the $23\frac{1}{2}°$ inclination of the earth's equatorial plane to the plane of its orbit round the sun.

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