INCIDENCE OF MALFORMATIONS FOLLOWING INFLUENZA EPIDEMICS

BY

IAN LECK

From the Department of Social Medicine, University of Birmingham

It is uncertain whether maternal influenza is a cause of human malformations, although defects of the nervous system and axial skeleton have been observed following the administration of the virus to chick embryos and pregnant mice (Hamburger and Habel, 1947; Shear, Heath, Imagawa, Jones and Adams, 1955; Adams, Heath, Imagawa, Jones and Shear, 1956; Williamson, Simonsen and Blattner, 1956). Several attempts have been made to determine whether malformations are commoner in children whose mothers had influenza in pregnancy than in other children, but the results of these inquiries are difficult to interpret. The published series (Table I) include four in which births after influenza were not classified according to the stage in pregnancy at which infection occurred, and nine in which children born after influenza in the first trimester were considered separately. In seven of the nine series in the second group the incidence of malformations in births following first trimester influenza was higher than in other births. In three of the four series in which the time when infection occurred was not recorded, on the other hand, the malformation rate was not increased in births after overt influenza, but this finding cannot be taken to indicate that the rate was uninfluenced by infection: the mothers of most of the controls in two of these three series showed serological evidence of influenza although their histories were negative, and the incidence of malformations among their offspring was higher than in any other control group shown in Table I (opposite).

Although these findings are suggestive, there are two reasons for doubting whether they indicate that influenza causes malformations:

- (i) The malformations described in association with influenza, unlike those due to known teratogenic agents such as rubella and thalidomide, are representative of those found in

the general population and do not constitute a specific syndrome: the authors cited in Table I listed the defects of 38 malformed children born after first trimester influenza, and the only malformations recorded more than once were conditions with a relatively high incidence among all births—anencephalus (4), hydrocephalus (3), congenital heart disease (8), hypospadias (4), syndactyly (3), and talipes (3).

- (ii) The results already quoted suggest that influenza does not only show an association with malformations when it occurs during the first two months of pregnancy, in spite of the fact that most malformations are laid down then. Among children whose mothers had influenza before conception or after the first trimester, the incidence of defects was higher than among cases with a negative history in five of the six series for which this information was available; and estimates of gestational age in months at the time of infection, which were recorded for some of the malformed children, indicate that seven out of 21 first trimester cases occurred in the third month.

If the association between influenza after the second month and malformations is real, it presumably indicates that women whose resistance to influenza is low in early pregnancy are especially liable to produce malformed offspring even if the infection itself does not occur then. This hypothesis can be further explored by examining the malformation rate in the general population: the occurrence of a rise in this rate after each influenza epidemic would be consistent with the view that influenza causes malformations, whereas failure to demonstrate any increase would indicate that the rate is more likely to be influenced by a constitutional factor predisposing to influenza than by the disease itself.

TABLE I
PUBLISHED DATA REGARDING THE RELATIONSHIP OF MATERNAL INFLUENZA TO THE
INCIDENCE OF MALFORMATIONS

Method of Ascertainment of Influenza Cases	Authors	Date	Influenza in First Trimester			Influenza Before or After First Trimester			No Influenza Recorded		
			No. Mal-formed	No. at Risk	Per cent. Mal-formed	No. Mal-formed	No. at Risk	Per cent. Mal-formed	No. Mal-formed	No. at Risk	Per cent. Mal-formed
Tests for Serum Antibodies	Wilson, Heins, Imagawa, and Adams	1959	2	76	2.6	—	—	—	2	53	3.8
	Hardy, Azarowicz, Mannini, Medearis, and Cooke ..	1961	8	69	11.6	15	455	3.3	1	73	1.4
Inquiry before Birth	Campbell	1953	3	122	2.5	1	41	2.4	12	825	1.5
	Coffey and Jessop	1959	8	108	7.4	16	554	2.9	10	663	1.5
	Doll, Hill, and Sakula ..	1960	2	63	3.2	2	66	3.0	—	—	—
	Manson, Logan, and Loy ..	1960	0	41	0.0	7	124	5.6	156	5,611	2.8
	Pleydell	1960	1	10	10.0	2	31	6.5	14	1,030	1.4
	Saxén, Hjelt, Sjöstedt, Hakosalo, and Hakosalo ..	1960	13	446	2.9	17	1,065	1.6	56	2,573	2.2
	McDonald*	1961	9	141	6.4	—	—	—	81	3,038	2.7
			Influenza Recorded, Trimester not Stated								
			No. Malformed		No. at Risk		Per cent. Malformed				
	Hardy and Others	1961	11		326		3.4		13	277	4.7
Inquiry after Birth	Coffey and Jessop	1955	40		519†		7.7		177	12,833†	1.4
	Walker and McKee	1959	6		214		2.8		7	184	3.8
Not Stated	Abramowitz	1958	3		315		1.0		5	414	1.2

* Figures relate to all acute febrile infections; 86 per cent. of these were respiratory.

† Estimated.

Most reports on the population incidence of malformations following epidemics relate to the outbreak of "Asian" (A2) influenza in late 1957 and early 1958. After this outbreak anencephalus became commoner in Scotland (Doll, Hill, and Sakula, 1960), and increases in the incidence of all malformations were reported from centres in Chile (Pachaly and Schürmann, 1959), Finland (Saxén, Hjelt, Sjöstedt, Hakosalo, and Hakosalo, 1960), France (Baron, Michiels and Rochas, 1960), and Italy (Avanzini and Giraudo, 1960; Piccioni and Bettocchi, 1960). A similar increase following an epidemic was observed in Baja, Hungary, in 1953 (Kovács and Makay, 1960). But the malformation rate showed no apparent increase in Pennsylvania (Ingalls, 1960), or New York City (Hewitt, 1962; Widelock, Csizmas, and Klein, 1963) following recent outbreaks, and Record and McKeown (1949) and Record (1961) reported that the annual death rate from influenza was not correlated with either the anencephalic still-birth rate (in Scotland) or the death rate from all malformations (in England and Wales).

Except in regard to anencephalus, none of the above inquiries satisfies fully three requirements

which should be met by a study relating changes in the malformation rate to influenza:

- A period of study long enough to include two or more epidemics, in order to permit comparisons between them;
- Details of the types of malformations present in each affected child;
- A population large enough to make it practicable to study each type of malformation separately.

A series recently collected in Birmingham appears to meet these requirements. A full account of it has been given elsewhere (Leck and Millar, 1963). Briefly, data relating to 939 malformed Birmingham children born in 1957-61 were obtained from necropsy reports and other Local Authority records of stillbirths and dead children, and from health visitors and lists of hospital admissions. Attention was restricted to malformations in respect of which the methods used seemed likely to give fairly complete ascertainment. During the period studied there were 102,042 stillbirths and live births to Birming-

ham residents, and three influenza epidemics occurred in the area. The present communication deals with the incidence of malformations following these epidemics and at other times.

RESULTS

As influenza is to-day the only disease which occurs in widespread epidemics among the working population of England, these epidemics can generally be recognized by inspecting the numbers of new claims to sickness benefit received weekly by the Ministry of Pensions and National Insurance. The figures for the Birmingham area showed three major peaks during the period when the children born in 1957–61 passed through early intra-uterine life (Fig. 1), and all three reflected epidemics caused by the A2 or Asian strain of influenza virus. Each peak occurred in the middle of a period of 5 to 7 weeks throughout which the weekly number of new sickness claims was more than 1,500 above the 1953–61 average for the time of year—a level reached at no other time. These three periods are assumed to represent the duration of the influenza epidemics in Birmingham. The numbers of claims to sickness benefit arising out of these epidemics are estimated in Table II.

TABLE II
NEW CLAIMS TO SICKNESS BENEFIT AND ESTIMATED ATTACK RATES DURING THREE INFLUENZA EPIDEMICS IN BIRMINGHAM

Date of Epidemic	Number of New Claims			Attack Rate† (per cent.)
	Received (a)	Expected* (b)	Ascribed to Influenza (a)–(b)	
Sept. 11–Oct. 29, 1957	64,252	22,615	41,637	12–19
Jan. 28–March 3, 1959	53,562	23,312	30,250	9–14
Dec. 21, 1960–Jan. 24, 1961	39,044	21,083	17,961	5–8

* Average of previous 4 years' figures for corresponding season.

† See text for method of estimation.

It is not possible to calculate attack rates from these figures alone, since the size of the population in which the claims occurred is not recorded, and some of those infected were not absent from work for a long enough period to claim benefit. Over the whole of Great Britain it has been estimated that the attack rate in the 1957 epidemic was between 16 and 27 per cent. (Fry, 1958; Woodall, Rowson, and McDonald, 1958; Ministry of Health, 1960); but national figures of new claims to sickness benefit (Ministry of Pensions and National Insurance, 1961) suggest that only 80 per cent. of claims due to this

FIG. 1.—New claims for sickness benefit received each week by the Ministry of Pensions and National Insurance in Birmingham. Bank holiday weeks are distinguished by the letter E (Easter), W (Whitsun), A (August), and C (Christmas). The crosses indicate weeks in which the number of new claims was more than 1,500 above the 1953–61 average for the time of year.

epidemic arose between September 11 and October 29 (the period specified in Table II), and in Birmingham the increase over previous years in the number of new claims received during this period was only 90 per cent. as great as in Great Britain as a whole. The attack rate for Birmingham during this period was therefore estimated by multiplying the national estimates by (0.8×0.9) , with the results given in the last column of Table II. The rates shown there for the other two epidemics were calculated by assuming that the ratio between the attack rate and the number of new claims ascribed to influenza was the same on these occasions as in the 1957 outbreak.

It seems likely that, if influenza were a cause of malformations, the effect would be limited to infections less than 2 months after conception—38 to 30 weeks before term. The susceptible period for some malformations—*e.g.* anencephalus—would probably be considerably shorter. But as many births (especially of malformed children) do not occur at term, it is assumed in this communication that children who develop malformations during influenza epidemics may be born at any time between 26 and 40 weeks later. The total number of births occurring 26 to 40 weeks after each epidemic in the present series is given in Table III. The number for the three epidemics combined was 22,698.

TABLE III

INDIVIDUALS WHO MAY HAVE BEEN EXPOSED TO INFLUENZA IN EARLY INTRA-UTERINE LIFE

Date of Influenza Epidemic	Births 26–40 weeks after Epidemic	
	Date of Birth	Number of Births
Sept. 11–Oct. 29, 1957	March 12–Aug. 5, 1958	7,968
Jan. 28–March 3, 1959	July 29–Dec. 8, 1959	6,779
Dec. 21, 1960–Jan. 24, 1961	June 21–Oct. 31, 1961	7,951
Total		22,698

The incidence of the various malformations among these 22,698 births and the other 79,344 births in the series is compared in Table IV, which gives the ratio between the two rates for each malformation. In Fig. 2 (overleaf) these ratios are plotted against the numbers of affected births on which they are based. The curves indicate the limits below which 95 and 99 per cent. of ratios would be expected to fall if there were no association between influenza epidemics in early pregnancy and the incidence of malformations.*

* The 95 and 99 per cent. confidence limits shown in Fig. 2 relate to one tail of the expected distribution only, and therefore correspond to differences of 1.645 and 2.326 standard errors between the rates compared.

TABLE IV

INCIDENCE OF MALFORMATIONS (PER 1,000 TOTAL BIRTHS) 26 TO 40 WEEKS AFTER INFLUENZA EPIDEMICS AND AT OTHER TIMES, 1957–61 (BIRMINGHAM)

Type of Malformation	Births 26 to 40 weeks after Epidemics		All Other Births		Ratio <i>a : b</i>
	No.	Incidence (<i>a</i>)	No.	Incidence (<i>b</i>)	
Neural					
Anencephalus (with or without spina bifida)	50	2.20	213	2.68	0.82
Spina bifida, cephalocele (without anencephalus)	60	2.64	213	2.68	0.99
Alimentary					
Cleft lip (with or without cleft palate)	35	1.54	81	1.02	1.51
Cleft palate (without cleft lip)	10	0.44	43	0.54	0.81
Oesophageal atresia, tracheo-oesophageal fistula	16	0.70	23	0.29	2.41
Anal atresia*	12	0.53	20	0.25	2.12
Genito urinary					
Renal agenesis or hypoplasia (bilateral)*	10	0.44	25	0.32	1.38
Hydronephrosis, hydroureter, urinary obstruction	16	0.70	34	0.43	1.63
Hypospadias	9	0.77†	21	0.51†	1.51
Reduction Deformities of Limbs					
Sirenomelia	0	0.00	4	0.05	0.00
Defects limited to thumbs and/or radii	5	0.22	8	0.10	2.20
Other defects‡ { Both arms and/or both legs affected	3	0.13	8	0.10	1.30
{ One arm and/or one leg affected	6	0.26	15	0.19	1.37
Other					
Exomphalos	17	0.75	31	0.39	1.92
Diaphragmatic hernia	9	0.40	30	0.38	1.05
Total Affected Individuals	225	9.91	714	9.00	1.10
Total Births	22,698	—	79,344	—	—

* Excluding cases with sirenomelia.

† Per 1,000 male births.

‡ Excluding defects limited to fingers or toes.

FIG. 2.—Ratio of incidence of each malformation 26–40 weeks after influenza epidemics to its incidence at other times, plotted logarithmically against the number of cases in the whole series.

Incidence following epidemics was more than twice as high as at other times in the case of oesophageal atresia, anal atresia, and reduction deformities of the thumbs and radii; and cleft lip, hydronephrosis, hypospadias, and exomphalos also showed increases of over 50 per cent. The probability of ratios as high as those observed arising by chance was below 1 per cent. for oesophageal atresia and below 5 per cent. for cleft lip, anal atresia, and exomphalos. Anencephalus, spina bifida, cleft palate, and diaphragmatic hernia were the commonest other malformations examined, and these showed little or no increase after epidemics. A slight but not significant increase was shown by the incidence of all individuals affected by the malformations studied.

Some if not all malformations show seasonal and secular variations in incidence which are certainly not related to influenza (McKeown, 1961; Record, 1961), and it seems possible that variations of this kind may have affected the ratios reported above, since the children born after influenza were not representative of the related population in respect of

season or year of birth. A simple way of reducing the risk of this type of bias is to restrict attention to children born between March 12 and December 8 in 1958 and 1959. It may be seen from the data given in Table III that the births 26 to 40 weeks after the 1957 and 1959 influenza epidemics occupied approximately the first half of the period March 12–December 8, 1958, and the second half of the corresponding period in 1959. By combining all the births in these two periods, it is possible to obtain a group of children born after influenza epidemics and a control group with a similar seasonal distribution, each including roughly equal numbers of 1958 and 1959 births. The frequency of malformations in these two groups is compared in Table V (opposite).

The results for the most of the malformations studied were broadly similar to those recorded in Table IV and Fig. 2, suggesting that seasonal and long-term secular variations in incidence were not an important source of bias in these cases. There were however two exceptions to this generalization: anal atresia and exomphalos occurred slightly less

TABLE V
MALFORMATIONS IN BIRTHS BETWEEN MARCH 12 AND DECEMBER 8, 1958 AND 1959

Type of Malformation	Number born between March 12 and December 8, 1958 and 1959		Ratio of Incidences $\left(\frac{a}{14,747} \div \frac{b}{14,612}\right)$
	(a) 26-40 weeks after Epidemics (14,747 births)	(b) at Other Times (14,612 births)	
Neural			
Anencephalus (with or without spina bifida)	36	39	0.91
Spina bifida etc. (without anencephalus)	41	36	1.13
Alimentary			
Cleft lip (with or without cleft palate)	18	10	1.78
Cleft palate (without cleft lip)	8	12	0.66
Oesophageal atresia, etc.	10	4	2.48
Anal atresia	5	6	0.83
Genito urinary			
Renal agenesis, etc.	6	6	0.99
Hydronephrosis, etc.	12	7	1.70
Hypospadias	8	3	2.64
Reduction Deformities of Limbs*			
Defects limited to thumbs and/or radii	5	2	2.48
Other defects (affecting one limb only)	5	3	1.65
Other			
Exomphalos	7	7	0.99
Diaphragmatic hernia	4	7	0.57
Total Affected Individuals	149	131	1.13

* Sirenomelia did not occur and other defects affecting more than one limb occurred only once between the dates stated.

often after the 1957 and 1959 epidemics than in the rest of the periods covered by Table V, although in the whole series they were about twice as common after influenza epidemics as at other times.

To interpret these findings, separate malformation rates for each epidemic and each intervening period are required. These rates are shown in Table VI (and in Fig. 3, overleaf), for the seven malformations which showed increases in incidence of

more than 50 per cent. following epidemics. The rates for cleft lip, oesophageal atresia, anal atresia, and exomphalos were all more than twice as high after the 1960-61 epidemic as in the preceding 18 months; in addition, the incidence of cleft lip showed a substantial rise after the epidemic of 1959, and the rate for oesophageal atresia increased markedly after the 1957 epidemic and slightly after that of 1959, but the incidence of anal atresia and exomphalos showed no

TABLE VI
SECULAR DISTRIBUTIONS OF MALFORMATIONS WHICH INCREASED IN INCIDENCE AFTER INFLUENZA EPIDEMICS BY MORE THAN 50 PER CENT.

The figures in heavy type relate to births 26 to 40 weeks after epidemics

Type of Malformation	Incidence (per 1,000 total births)						
	Jan. 1, 1957- March 11, 1958 (22,978 births)	March 12- Aug. 5, 1958 (7,968 births)	Aug. 6, 1958- July 28, 1959 (19,834 births)	July 29- Dec. 8, 1959 (6,779 births)	Dec. 9, 1959- June 20, 1961 (32,935 births)	June 21- Oct. 31, 1961 (7,951 births)	Nov. 1- Dec. 31, 1961 (3,597 births)
Cleft lip (with or without cleft palate) ..	1.35	0.88	0.76	1.62	0.94	2.14	1.11
Oesophageal atresia, etc. ..	0.22	0.88	0.30	0.44	0.36	0.75	0.00
Anal atresia ..	0.13	0.38	0.35	0.30	0.30	0.88	0.00
Hydronephrosis ..	0.48	0.50	0.45	1.18	0.39	0.50	0.28
Hypospadias* ..	0.93	1.46	0.29	0.58	0.29	0.24	1.08
Reduction deformities (thumbs, radii) ..	0.22	0.38	0.10	0.30	0.00	0.00	0.28
Exomphalos ..	0.26	0.50	0.66	0.44	0.30	1.26	0.56

* per 1,000 male births.

FIG. 3.—Malformation rates (per 1,000 total births) after each epidemic (stippled) and at other times (hatched) for defects showing an increase of more than 50 per cent. after the three epidemics combined.

obvious relationship to these two epidemics. Hypo-spadias and reduction deformities of the thumbs and radii appeared to be more common following the 1957 and 1959 epidemics than at other times, but data published elsewhere (Leck and Millar, 1963) indicate that the high rates recorded for these conditions after the first epidemic were maintained throughout late 1957 and early 1958, and cannot therefore be ascribed to influenza. Hydronephrosis showed only one marked increase, which occurred after the 1959 epidemic.

The four malformations which doubled in incidence following the 1960-61 epidemic—cleft lip, oesophageal atresia, anal atresia, and exomphalos—were also the only four to show significant increases in incidence when all births 26 to 40 weeks after epidemics were considered together (Fig. 2). It may be concluded that, if a syndrome of malformations associated with influenza exists, it is more likely to include these four defects than any of the others studied here. The relationship of all recorded combinations of these four malformations to the influenza epidemics was therefore explored, with the results shown in Table VII. Combinations were reported in nine of the 22,698 births that occurred 26 to 40 weeks after epidemics, and in two of the 79,344 other births.

TABLE VII
FREQUENCY OF ASSOCIATION BETWEEN CLEFT LIP,
OESOPHAGEAL ATRESIA, ANAL ATRESIA, AND
EXOMPHALOS

Individuals with More than One of the Listed Malformations	Born 26 to 40 weeks after Influenza Epidemics			Born at Other Times (79,344 births)
	March 12–Aug. 5, 1958 (7,968 births)	July 29–Dec. 8, 1959 (6,779 births)	June 21–Oct. 31, 1961 (7,951 births)	
Number Observed . . .	1*	2†	6‡	2§
Incidence Observed (per million births)	126	295	755	25
Incidence Expected (per million births)	2.01	0.77	3.91	1.16
Ratio (Observed:Expected)	63	383	193	22

* Oesophageal atresia, anal atresia.

† Oesophageal atresia, anal atresia, exomphalos; anal atresia, exomphalos.

‡ Cleft lip, exomphalos (2); oesophageal atresia, anal atresia (3); anal atresia, exomphalos.

§ Oesophageal atresia, anal atresia (2).

After each of the three epidemics the ratio of the observed combination rate to that expected if all combinations were fortuitous* was several times higher than in the remainder of the 5-year period. The commonest combination was between oeso-

phageal atresia and anal atresia, but exomphalos with anal atresia (and oesophageal atresia in one case) and exomphalos with cleft lip also occurred.

DISCUSSION

Reference has already been made to the substantial increases in the malformation rate reported in various places after influenza epidemics (Pachaly and Schürmann, 1959; Avanzini and Giraudo, 1960; Baron and others, 1960; Kovács and Makay, 1960; Piccioni and Bettocchi, 1960; Saxén and others, 1960). But in the present series, which was considerably more extensive than those quoted, only a statistically insignificant increase of 10 per cent. occurred in the incidence of all affected individuals. Such a difference between results from different places could of course be caused by variations in the influenza attack rate, and a comparison between the four series for which attack rates are available suggests that some of the difference may be accounted for in this way. Two of these series, showing increases in the malformation rate of 100 per cent. or more, came from places where more than half the population was attacked (Pachaly and Schürmann, 1959; Piccioni and Bettocchi, 1960). In Helsinki, with an attack rate of 32 per cent., the malformation rate increased by 60 per cent. (Saxén and others, 1960). The 10 per cent. increase observed in the present series was associated with an estimated attack rate of less than 20 per cent. during each period when influenza was regarded as epidemic.

Although these figures suggest that the present series may be regarded as confirming the positive results of earlier surveys, analysis of the types of malformations responsible for the increase does not support this view. Although the earlier reports did not include separate figures for each type of defect, the information given seems to indicate either a general increase or one affecting mainly the central nervous malformations. The increase reported here, on the other hand, did not involve the neural defects examined (anencephalus, spina bifida) and could be due entirely to the formally significant changes in the incidence of cleft lip, oesophageal atresia, anal atresia, and exomphalos. The differences in behaviour following epidemics between the various specific malformation rates for Birmingham are unlikely to be due to chance: a χ^2 of 22.18 is given by the figures for specific malformations shown in Table IV (treating the limb defects as a single group to avoid small numbers), which with 11 degrees of freedom indicates a probability of about 0.025.

As the Birmingham data did not show either a general increase in incidence or one affecting the central nervous malformations it seems possible that

* The expected rates are those that would occur if the incidence of every combination of malformations was equal to the product of the rates at which these malformations occurred separately.

the increases of these kinds reported elsewhere were unrelated to the influenza epidemics which they followed. The number of places where increases were reported is so small that these increases could well be local phenomena. It is interesting, however, that most of them occurred in 1958, since in this year an unusually high proportion of all Birmingham births was affected by the types of malformations included in the present series (Leck and Millar, 1963). This increase in Birmingham in 1958 was too prolonged to be ascribed to influenza.

Apart from the present series, few data are available in respect of the incidence of specific types of malformations after influenza epidemics. Possibly the best sources of information are the national statistics of stillbirths and deaths by cause and month of registration which are published by the Registrar General for Scotland. From examination of the figures for 1950-60 (the most recent years for which they are available) it appears reasonable to assume that influenza was epidemic in months for which the influenza death rate exceeded the average for the time of year by more than two deaths per day. Epidemics satisfying these criteria occurred in January and February, 1951; September-November, 1957; and February and March, 1959. The incidence of stillbirths due to malformations among all births 6 to 9 months after these epidemics is compared with their incidence during the remainder of the period 1951-60 in Table VIII. Neither the specific defects for which data were available—anencephalus, spina bifida, and hydrocephalus—nor the remaining defects (considered together) were more common after epidemics.

It was noted earlier in this communication that figures like the above are liable to be influenced by seasonal and secular variations unrelated to influenza. For this reason Table VIII also includes the results obtained when births in March-July, 1958, and September-December, 1959 (6 to 9 months after epidemics) are compared with those in September-

December, 1958, and March-July, 1959. The results of this procedure should be virtually free from seasonal and secular bias, since the two groups are alike in respect of seasonal distribution and both include comparable numbers of 1958 and 1959 births. The defects examined showed a rather lower incidence in the group born after epidemics than in the control group.

Analysed in this way, the Scottish data do not appear to support the interpretation put upon them by Doll and others (1960), who noted that the incidence of anencephalus in May-December, 1958, was unusually high, and suggested that this was due to the influenza epidemic of the previous winter. This increase in incidence had little effect on the figures in Table VIII, for two reasons:

- (i) It occurred 8 to 13 months after the period of highest influenza mortality, and as the gestation period is often short in anencephalus it is assumed in the Table that any cases due to influenza would be born 6 to 9 months after infection.
- (ii) In 1959 a similar increase occurred in April-July, and influenza was not prevalent when the children born in these months passed through early intra-uterine life.

As the Scottish figures relate only to stillbirths they cannot be regarded as representative of all malformations; but taken with the results of the present inquiry they strongly suggest that influenza is not a cause of anencephalus or spina bifida. It is, however, possible that some of the maternal influences which predispose to these two defects are also related to an increased susceptibility to influenza: these defects occurred in fourteen of the 662 births after influenza and four of the 653 controls in the series of Coffey and Jessop (1959), and were also well represented among the other births following influenza in the reports listed in Table I.

TABLE VIII
INCIDENCE (PER 1,000 TOTAL BIRTHS) OF STILLBIRTHS DUE TO MALFORMATIONS IN SCOTLAND

Type of Malformation	All Births in 1951-60			Births in March-July and Sept.-Dec. (1958 and 1959)		
	(a) Rate 6 to 9 mths After Epidemics* (127,745 births)	(b) Rate at Other Times (845,880 births)	Ratio (a : b)	(c) Rate 6 to 9 mths After Epidemics* (75,047 births)	(d) Rate at Other Times (78,174 births)	Ratio (c : d)
Anencephalus	2.87	2.88	1.00	2.86	3.24	0.88
Spina bifida	0.28	0.28	1.00	0.21	0.27	0.78
Hydrocephalus	1.01	1.30	0.78	1.00	1.02	0.98
Other Malformations ..	0.65	0.76	0.86	0.67	0.68	0.99
All Malformations ..	4.81	5.22	0.92	4.74	5.21	0.91

* Influenza epidemics are assumed to have occurred in January and February, 1951; September-November, 1957; and February and March, 1959.

There are almost no published data on which to explore the relationship of other specific malformations to influenza epidemics. The monthly numbers of deaths from malformations given in national statistics are useless for this purpose because the majority of these deaths do not occur in the month of birth. However, Babbott and Ingalls (1962) reported that tracheo-oesophageal fistula was exceptionally common after the 1957 epidemic in Pennsylvania, and data are also available in respect of 98 instances of oesophageal atresia (or tracheo-oesophageal fistula) which occurred in Birmingham in 1950–55 and in the Newcastle-upon-Tyne area in 1950–58 (Knox, 1959). The annual reports for 1949–58 of the Registrar General for England and Wales indicate that the monthly death rate from influenza exceeded the average for the time of year by more than twenty deaths per day in April, 1949, January–February, 1951, February, 1953, and September–November, 1957; and in Table IX the numbers of cases in Knox's series born 6 to 9 months after these epidemics and at other times are compared. Although Knox's own analysis showed that the instances of oesophageal atresia in his series tended to occur in clusters as if due to an infectious disease, Table IX suggests that there was no clustering in relation to influenza epidemics. It therefore seems rather doubtful whether there was a causal connexion between the influenza epidemics and the rises in incidence of oesophageal atresia which followed each of them in the present series, although this association was more significant statistically than that shown by any other malformation.

TABLE IX
FREQUENCY OF OESOPHAGEAL ATRESIA IN SERIES
PRESENTED BY KNOX (1959)

Period of Birth	Locality	Infants with Oesophageal Atresia/ Tracheo-Oesophageal Fistula			
		Born 6 to 9 mths after Epidemics*		Others	
		Number	Rate (per month)	Number	Rate (per month)
1950–55	Birmingham, Newcastle ..	7	0.7	61	1.0
1956–58	Newcastle ..	6	1.0	24	0.8

* Influenza epidemics are assumed to have occurred in April, 1949; January and February, 1951; February, 1953; September–November, 1957.

The rates for cleft lip, anal atresia, and exomphalos also showed increases significant at the 5 per cent. level when all births 26 to 40 weeks after epidemics were considered, but as in the case of oesophageal atresia there is some evidence that these increases were not directly due to the influenza

virus. Although the 1961 epidemic was less extensive than the others, it was associated with the highest rates of these three defects. Each of these rates rose after only one of the other two outbreaks, and the rates for anal atresia and exomphalos were no higher 26 to 40 weeks after these two outbreaks than in the intervening months.

As combinations of oesophageal atresia, cleft lip, anal atresia, and exomphalos were apparently several times more common following each influenza epidemic than at other times, it seems likely that the overall increases in incidence shown by these defects after epidemics were related in some way to each other and to the epidemics even if they were not directly due to the influenza virus. As the increases were most marked after the 1961 epidemic, they could for example be due to the use of increasing quantities of some teratogen in the treatment of influenza. There is however no other evidence that any factor associated with influenza causes the four defects mentioned.

SUMMARY

Although several authors have reported that malformations are more common in births to mothers who have had influenza in pregnancy than in other births, it has not been established whether the malformation rate in the general population increases after influenza epidemics.

Since 1956 three major influenza epidemics have occurred in Birmingham, with peaks in October, 1957, February, 1959, and January, 1961. In this communication the incidence of various malformations in Birmingham among births 26 to 40 weeks after these epidemics is compared with their incidence in the remainder of 1957–61.

When the births following the three epidemics were combined, formally significant increases in incidence were demonstrated in respect of oesophageal atresia, cleft lip, anal atresia, and exomphalos. A fuller analysis showed that all four malformations more than doubled in incidence following the 1961 epidemic, but that only one of them—oesophageal atresia—was especially common after each of the earlier outbreaks. The incidence of births with two or more of these four defects increased very markedly after each epidemic.

The rates for the other malformations considered, and the incidence of all malformed individuals included in the inquiry, were not significantly increased after the epidemics. The negative findings in respect of anencephalus and spina bifida were confirmed by an analysis of the instances notified each month among stillbirths in Scotland.

Most of the data used in this inquiry were abstracted from Local Authority and hospital records by Mrs. Eileen Armstrong, Miss Ann Cooper, Miss Ida Giles, and Mrs. Betty Mann. These records were collected and made available by Dr. E. L. M. Millar and his staff, and by Dr. K. W. Cross, Mr. O. T. Mansfield, and the pathologists and records officers of local hospitals. I am grateful to all these people for their ready co-operation.

REFERENCES

- Abramowitz, L. J. (1958). *S. Afr. med. J.*, **32**, 1155.
- Adams, J. M., Heath, H. D., Imagawa, D. T., Jones, M. H., and Shear, H. H. (1956). *Amer. J. Dis. Child.*, **92**, 109.
- Avanzini, P., and Giraudo, G. (1960). *Minerva pediat. (Torino)*, **12**, 120.
- Babbott, J. G., and Ingalls, T. H. (1962). *Amer. J. publ. Hlth*, **52**, 2009.
- Baron, F., Michiels, Y., and Rochas, J. E. (1960). *Gynec. et Obstét.*, **59**, 271.
- Campbell, W. A. B. (1953). *Lancet*, **1**, 173.
- Coffey, V. P., and Jessop, W. J. E. (1955). *Irish J. med. Sci.*, 6th series. No. 349, p. 30.
- (1959). *Lancet*, **2**, 935.
- Doll, R., Hill, A. Bradford, and Sakula, J. (1960). *Brit. J. prev. soc. Med.*, **14**, 167.
- Fry, J. (1958). *Brit. med. J.*, **1**, 259.
- Hamburger, V., and Habel, K. (1947). *Proc. Soc. exp. Biol. (N.Y.)*, **66**, 608.
- Hardy, J. M. B., Azarowicz, E. N., Mannini, A., Medearis, D. N., and Cooke, R. E. (1961). *Amer. J. publ. Hlth*, **51**, 1182.
- Hewitt, D. (1962). *Ibid.*, **52**, 1676.
- Ingalls, T. H. (1960). *Ibid.*, **50**, 50.
- Knox, G. (1959). *Brit. J. prev. soc. Med.*, **13**, 222.
- Kovács, I., and Makay, L. (1960). *Zbl. Gynäk.*, **82**, 1335.
- Leck, I., and Millar, E. L. M. (1963). *Brit. J. prev. soc. Med.*, **17**, 1.
- McDonald, A. D. (1961). *Ibid.*, **15**, 154.
- McKeown, T. (1961). In "First International Conference on Congenital Malformations, London, 1960", ed. M. Fishbein, p. 45. Lippincott, Philadelphia.
- Manson, M. M., Logan, W. P. D., and Loy, R. M. (1960). "Rubella and Other Virus Infections during Pregnancy". Ministry of Health Reports on Public Health and Medical Subjects, No. 101. H.M.S.O., London.
- Ministry of Health (1960). "The Influenza Epidemic in England and Wales, 1957-1958." Reports on Public Health and Medical Subjects, No. 100. H.M.S.O., London.
- Ministry of Pensions and National Insurance (1961). "Digest of Statistics analysing Certificates of Incapacity 1957-58." Ministry of Pensions and National Insurance, London.
- Pachaly, L., and Schürmann, R. (1959). *Beitr. path. Anat.*, **121**, 309.
- Piccioni, V., and Bettocchi, S. (1960). *Minerva pediat. (Torino)*, **12**, 126.
- Pleydell, M. J. (1960). *Brit. med. J.*, **1**, 309.
- Record, R. G. (1961). *Brit. J. prev. soc. Med.*, **15**, 93.
- and McKeown, T. (1949). *Brit. J. soc. Med.*, **3**, 183.
- Saxén, L., Hjelt, L., Sjöstedt, J. E., Hakosalo, J., and Hakosalo, H. (1960). *Acta path. microbiol. scand.*, **49**, 114.
- Shear, H. H., Heath, H. D., Imagawa, D. T., Jones, M. H., and Adams, J. M. (1955). *Proc. Soc. exp. Biol. (N.Y.)*, **89**, 523.
- Walker, W. M., and McKee, A. P. (1959). *Obstet. and Gynec.*, **13**, 394.
- Widelock, D., Csizmas, L., and Klein, S. (1963). *Publ. Hlth Rep. (Wash.)*, **78**, 1.
- Williamson, A. P., Simonsen, L., and Blattner, R. J. (1956). *Proc. Soc. exp. Biol. (N.Y.)*, **92**, 334.
- Wilson, M. G., Heins, H. L., Imagawa, D. T., and Adams, J. M. (1959). *J. Amer. med. Ass.*, **171**, 638.
- Woodall, J., Rowson, K. E. K., and McDonald, J. C. (1958). *Brit. med. J.*, **2**, 1316.