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ANENCEPHALUS IN SCOTLAND

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In the search for causes of congenital malformations many methods have been used. Animal experiments have revealed a large number of teratogenic agents and have provided some understanding of the mechanism of maldevelopment. Embryological studies have indicated the probable stage of development when various malformations are initiated. Examination of pedigrees has shown a genetic basis for some of the less common or less lethal human malformations. New cytological techniques have contributed substantially to our understanding of mongolism and a few infrequent abnormalities. But so far these researches have thrown little light on the causal factors of the majority of human malformations.

It is perhaps surprising that population research methods have not been more widely used, particularly in view of the fact that the most notable advance in the field of human teratology — the incrimination of rubella—was achieved by these means. A possible reason is the difficulty of organizing an inquiry on a scale large enough to provide adequate numbers for analysis. It might be expected that national statistics would meet this need, but unfortunately they rarely supply data on stillbirths in sufficient detail for examination. Scotland is the only country which publishes adequate records on stillbirths classified according to cause and distinguishing between the commoner malformations—anencephalus, hydrocephalus, spina bifida, and cardio-vascular abnormalities. A series restricted to stillbirths is hardly adequate for study of the last three malformations, many of which survive birth, but it is well suited for an investigation of anencephalus which is rarely compatible with a post-natal existence even for a few hours. (Of the 349 anencephalics born in Scotland in 1958, all but nineteen were stillborn.) Another characteristic which makes anencephalus a useful subject for investigation on a national scale is its unmistakable appearance, even to an inexpert observer. A third reason is that its relatively high frequency enables a large series to be assembled from the data now available. Indeed the present importance of anencephalus as a cause of stillbirth gives some urgency to the investigation of its aetiology. In 1938–41 the Scottish stillbirth rate was 41·3 per 1,000 total births; by 1956–58 it had been reduced to 23·5, but the anencephalic stillbirth rate had risen in the same period from 2·39 to 2·99. The contribution of anencephalus to the stillbirth rate therefore increased from 5·8 to 12·7 per cent.

An extensive analysis of Scottish data has been reported by Edwards (1958). He confirmed the findings of an earlier survey in Birmingham (Record and McKeown, 1949) that the incidence of anencephalus is higher for first births than for second births and for foetuses born in the late autumn and winter months than for those born in the summer. Edwards found a more pronounced association with maternal age than was shown by the Birmingham data, but could not exclude the possibility that this might be the result of an association with parity. His findings of a marked association with social class was consistent with Aberdeen experience (Anderson, Baird, and Thomson, 1958) but differed from the Birmingham data which showed no variation of incidence with social circumstances. He considered that the secular variation in incidence was due to changing incidence among first births and among winter births. The point is an important one, for if confirmed it would help to narrow the search for aetiological agents. For the same reason an examination of the relation of seasonal variation to parity and social class would be useful

The Registrar General for Scotland does not publish data which permit a study of this detail, but he consented to supply a break-down of the Scottish statistics on anencephalic stillbirths, so that a fuller examination is now possible.

Method

The new data here analysed relate to legitimate anencephalic stillbirths in Scotland for the years 1949–58 classified according to:

(1) Age of mother and number of previous children;
(2) Month of registration of birth and number of previous children;
(3) Month of registration of birth and social class.

Other details of anencephalic stillbirths and data relating to all births (live and stillborn) during the period were obtained from the annual reports of the Registrar General for Scotland. In some parts of the analysis, numbers have been augmented by using data for earlier years (1939–48) from the same source. Incidence in the two periods is compared in Table I.

Results

Since this analysis is based both on new data which relate only to legitimate births and on published statistics which in some instances include illegitimate births, it may be useful to begin by investigating the influence of illegitimacy on incidence. This will be followed by consideration of the influence of maternal age and parity and of seasonal and secular variations in incidence.

Illegitimacy

During the period 1939–58 there were 274 illegitimate anencephalic stillbirths—2·45 per 1,000 total births (Table I). This is 0·14 (approximately 1 standard error) below the population value of 2·59, but since only about 5 per cent. of all births are illegitimate the difference in anencephalic rates between legitimate births and all births is negligible and there seems to be little need to discriminate between the two sets of data.

The slightly low anencephalic rate among illegitimate births is, however, of some intrinsic interest. Standardization for maternal age raises the difference from 0·14 to 0·20, and it seems likely that further standardization for parity and social class (not permitted by the available data) would increase the difference to a significant level.

Part of the difference can be accounted for by the fact that in some areas where the anencephalic rate is low the illegitimacy rate is high. For example, the fifteen counties north of a line joining the Firths of Clyde and Tay experienced in the years 1950–58 an anencephalic rate of 2·0 per 1,000 and an illegitimacy rate of 5.8 per cent., the corresponding rates for the remainder of Scotland being 3·0 per 1,000 and 4·3 per cent. From data for the same period for each of the 33 counties, the coefficient of correlation between the two rates (each value being weighted according to the number of births) was found to be −0·4. Areas of low anencephalic incidence therefore contribute an undue proportion of births to the illegitimate series. It seems unlikely, however, that this accounts completely for the low anencephalic rate among illegitimate births, which has been observed elsewhere (Record and McKeown, 1949). Another explanation, plausible but so far not supported by evidence, is that attempts to procure abortion (presumably a considerable hazard for illicit pregnancies) are more likely to succeed when the foetus is anencephalic than when it is normal.

Maternal Age and Parity

Since 1939, the Registrar General has published data on live births and stillbirths related to maternal age, distinguishing between legitimate and illegitimate births, but the distinction is not maintained when stillbirths are classified according to cause and to maternal age. The published data on parity are based on legitimate births, but the Tables for 1939–45 differ in form from those for 1946–58 so that a satisfactory combination of the two periods is not possible. The published data on age and parity have the further disadvantage that they do not permit a separate

TABLE I
INCIDENCE OF ANENCEPHALIC STILLBIRTHS

Period	Incidence	Legitimate	Illegitimate	Total
1939-48	Total No. of Births	917,135	66,673	983,808
	No. of Anencephalic Stillbirths	2,266	152	2,418
	Incidence per 1,000 Total Births	2·47	2·28	2·46
1949–58	Total No. of Births	916,968	45,037	962,005
	No. of Anencephalic Stillbirths	2,499	122	2,621
	Incidence per 1,000 Total Births	2·73	2·71	2·72
Total	Total No. of Births	1,834,103	111,710	1,945,813
	No. of Anencephalic Stillbirths	4,765	274	5,039
	Incidence per 1,000 Total Births	2·60	2·45	2·59

examination of these rather highly correlated variables. For these reasons, attention will here be restricted to the new data supplied by the Registrar General relating to legitimate births for the years 1949–58.

Crude results are shown in Fig. 1. Incidence is high in first pregnancies; it is lowest in second pregnancies, and then rises steadily with advancing parity. Incidence by maternal age shows a similar but more symmetrical pattern, being low in women aged 25–29 and high in the youngest and oldest groups. Since age and parity are positively correlated, one of these patterns could easily be a reflection of the other. The separate effects of the two variables are examined in Table II. In some of the age/parity cells, numbers of births are inevitably small; it has therefore been necessary to combine the two highest age groups of Fig. 1, and also the highest parity groups. The columns of the Table show that the parity effect demonstrated in the Figure is followed consistently by both the older groups. The three younger groups naturally provide less information about the higher parities, but no major inconsistencies are revealed. All five groups show low rates for second pregnancies. Perusal of the rows of the Table suggests that the U-shaped maternal age pattern shown in Fig. 1 is made up of several components, first pregnancies contributing mainly to the descending left arm of the U, and third and later pregnancies to the ascending right arm. The low rates in second pregnancies appear not to vary with maternal age.

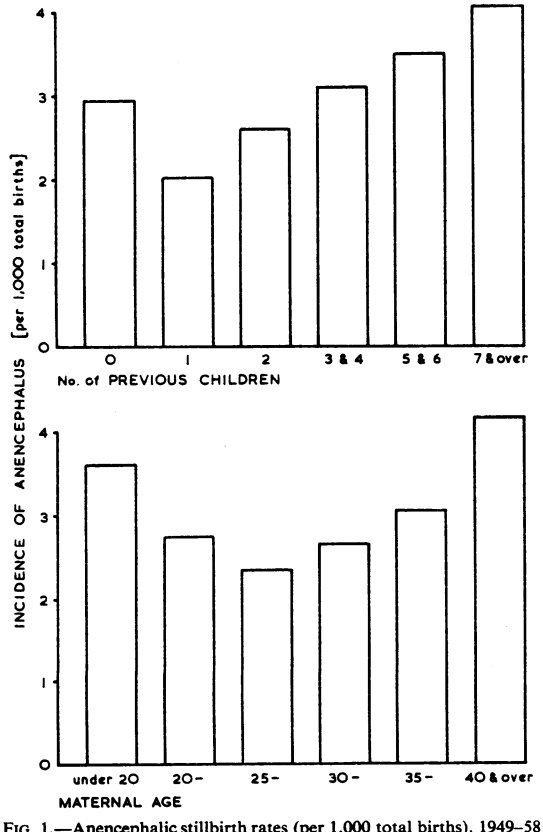

FIG. 1.—Anencephalic stillbirth rates (per 1,000 total births), 1949–58, by maternal age and parity.

TABLE II

ANENCEPHALIC STILLBIRTH RATES (PER 1,000 TOTAL BIRTHS) ACCORDING TO MATERNAL AGE AND PARITY (LEGITIMATE BIRTHS, 1949–58)

No. of Previous Children	Maternal Age (yrs)				
	Under 20	20–	25–	30–	35 and Over
0	3·9	3·1	2·5	2·5	2·7
1	(1·9)	2·2	2·0	2·1	2·0
2	—	1·9	2·4	2·8	3·4
3 and 4	—	(2·8)	2·8	3·0	3·7
5 and Over	—	—	(2·3)	3·4	4·2

Figures in brackets are based on less than 10,000 births

In Scotland there is a very marked social gradient in the incidence of anencephalus which is four times higher in Social Class V than in Social Class I (Edwards, 1958). The social classes also show pronounced differences in reproductive habits, Social Classes I and II being well represented among the lower birth ranks at the higher ages, whereas the higher birth ranks at the lower ages come mainly from Classes IV and V. Social class variation in incidence might therefore account for a positive correlation of incidence with parity and would tend to mask an increase of incidence with maternal age. It follows that standardization for social class would tend to reduce the apparent effect on incidence of high parity and increase the effect of advanced maternal age. In fact, although standardization brings about both these changes (Table III, overleaf), its effect is not so marked that the results outlined in the previous paragraph need re-appraisal.

It is concluded that the incidence of anencephalus varies both with parity and with age, being high among first-born, especially when the mother is very young, and among the higher birth ranks, especially when the mother is old.

TABLE III

ANENCEPHALIC STILLBIRTH RATES STANDARDIZED FOR SOCIAL CLASS

No. of Previous Children	Maternal Age (yrs)				
	Under 20	20–	25–	30–	35 and Over
0	3·6	3·1	2·6	2·9	3·0
1	—	2·1	2·0	2·3	2·1
2	—	1·7	2·3	2·9	3·5
3 and 4	—	—	2·7	3·0	3·8
5 and Over	—	—	—	3·0	4·0

SEASONAL VARIATION

In a previous report (McKeown and Record, 1951), the incidence of anencephalus in Birmingham and in Scotland was shown to be higher in autumn and winter than in spring and summer, the fourth quarter of the year (October–December) having the highest rate and the second quarter (April–June) the lowest. In that investigation, division of the year into orthodox quarters was necessary because of the form of the Birmingham data, but it does not reveal the full extent of the seasonal variation. In fact, it is the least efficient of the three possible ways of dividing the year into trimesters in order to examine fluctuations in incidence; the maximum range and variance are obtained if the first trimester starts in February (Table IV). This is the basis for the grouping of the months used in the analysis which follows.

TABLE IV

INCIDENCE OF ANENCEPHALUS IN VARIOUS TRIMESTERS OF THE YEAR LEGITIMATE AND ILLEGITIMATE BIRTHS, 1949–58

Trimester	Incidence (per 1,000 total births)	Range	Variance
January–March	2·82	0·73	0·08
April–June	2·42		
July–September	2·53		
October–December	3·15		
February–April	2·57	1·02	0·14
May–July	2·30		
August–October	2·74		
November–January	3·32		
March–May	2·39	0·79	0·10
June–August	2·47		
September–November	2·89		
December–February	3·18		

Parity.—The numbers of anencephalics, grouped according to parity, who were born in each trimester are shown in Table V. For each parity the relative incidence according to season was calculated by dividing the proportion of anencephalics born in each trimester by the proportion of all births born in the same period. For example, for the first parity,

TABLE V

NUMBERS OF LEGITIMATE ANENCEPHALIC STILLBIRTHS, ACCORDING TO SEASON AND PARITY, 1949–58

No. of Previous Children	Trimester of Birth				Total
	February–April	May–July	August–October	November–January	
0	221	205	251	295	972
1	132	120	128	152	532
2 and 3	153	135	157	193	638
4 and Over	86	84	81	101	352
Not Stated	3	2	—	—	5
Total ..	595	546	617	741	2,499
Total Births	245,740	248,641	233,563	234,061	962,005

the relative incidence in the period February–April was

$$\frac{221}{972} \Big/ \frac{245740}{962005} = 0{\cdot}89.$$

The four parity groups show a consistent pattern (Fig. 2). In all of them incidence is highest in the period November–January and lowest in May–July. The seasonal fluctuation is least marked for the highest parities (four or more previous children), but this may be due merely to the smaller size of this group.

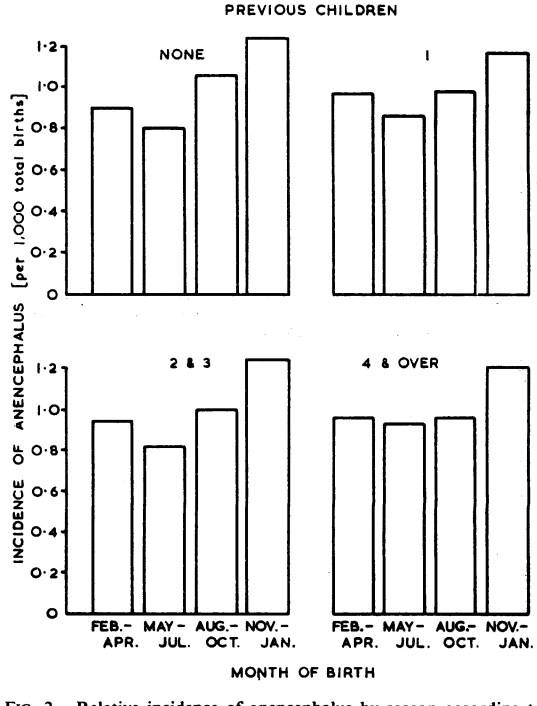

FIG. 2.—Relative incidence of anencephalus by season according to parity, 1949–58.

Unfortunately, there are no published data on the seasonal distribution of all births classified according

to parity and it has been necessary, therefore, to assume that the seasonal pattern of human reproduction does not vary with parity. The validity of this assumption was explored by examining data relating to all births in Birmingham where the necessary information is collected. Births occurring in 1950 were distributed in the same parity and season groups as before and for each parity group the percentage of births in each trimester was calculated (Table VI). There is very little difference between the four parity groups, all showing the lowest proportion of births in November–January and the next lowest in August–October. The only inconsistency is among first parities where most births occur in May–July whereas the maxima of the other three groups are in February–April. These differences are so trivial when compared with the marked seasonal fluctuation shown in Fig. 2 that it seems unnecessary to attempt to apply corrections.

TABLE VI

PERCENTAGE DISTRIBUTION BY SEASON OF BIRTHS (LIVE AND STILL), ACCORDING TO PARITY BIRMINGHAM, 1950

No. of Previous Children	No. of Births	Trimester of Birth				Total
		February–April	May–July	August–October	November–January	
0	7,142	25·2	26·1	24·7	24·1	100
1	5,395	26·2	25·7	24·1	24·0	100
2 and 3	4,500	26·8	25·7	24·6	22·9	100
4 and Over	1,879	26·7	26·4	23·7	23·2	100
Total ..	18,916	26·1	25·9	24·4	23·7	100

Social Class.—Results of a similar analysis in respect of social class are shown in Table VII and Fig. 3.

TABLE VII

NUMBERS OF LEGITIMATE ANENCEPHALIC STILL-BIRTHS, ACCORDING TO SEASON AND SOCIAL CLASS, 1949–58

Social Class	Trimester of Birth				Total
	February–April	May–July	August–October	November–January	
I and II	48	50	42	73	213
III	313	308	359	409	1,389
IV	112	98	115	136	461
V	122	90	101	123	436
Total ..	595	546	617	741	2,499

Social Classes I and II have been combined because of their relatively small numbers of anencephalics. Classes III, IV, and V have seasonal patterns which closely resemble each other; in all, the highest rates occur in November–January and the lowest in May–July, and each class shows about the same

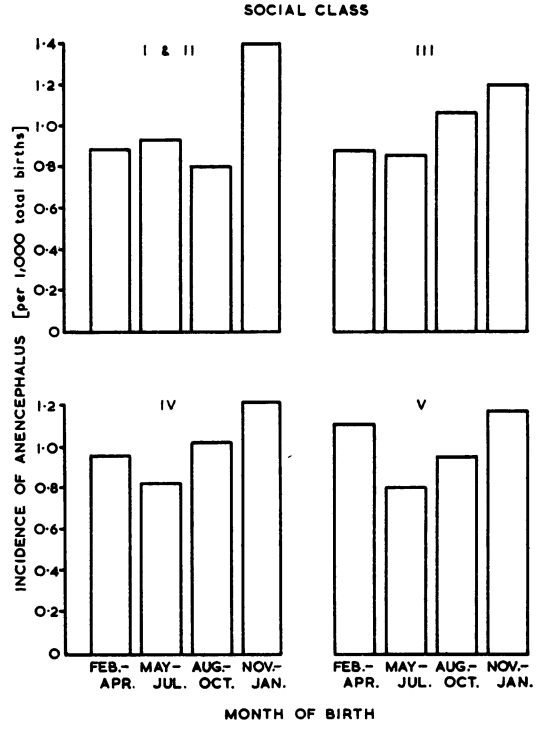

FIG. 3.—Relative incidence of anencephalus by season according to social class, 1949–58.

range, the highest rate being 1·4 to 1·5 times the lowest. Social Classes I and II also show the highest incidence in November–January, but the rate is almost constant in the other three periods. It is possible that the relatively small size of this group has caused the low May–July incidence shown by the other classes to be obscured by random variation.

There is no information on social class variation in the seasonal distribution of the total population of births, and it has been assumed that there are no class differences in this respect. To justify this assumption, data on Birmingham births have again been examined. These data are not quite so helpful as before, since they permit identification of only three social classes. Social Classes I and II of the Registrar General are approximately equivalent to Group A in the Birmingham series, III and IV to B, and V to C. The seasonal distributions of births thus classified are very similar (Table VIII, overleaf).

It is concluded that the seasonal trends of anencephalus shown in Fig. 3 approximate reasonably closely to the true values.

Reasons for Seasonal Variations.—There can be no doubt that the incidence of anencephalus fluctuates

TABLE VIII

PERCENTAGE DISTRIBUTION BY SEASON OF BIRTHS (LIVE AND STILL), ACCORDING TO SOCIAL CLASS BIRMINGHAM, 1951–2

Social Class	No. of Births	Trimester of Birth				Total
		February–April	May–July	August–October	November–January	
A	4,895	25·9	26·7	24·3	23·0	100
B	26,825	25·7	25·8	24·4	24·0	100
C	4,929	25·3	26·4	24·1	24·2	100
Total ..	36,649	25·7	26·0	24·4	23·9	100

widely with season and it seems that this variation extends to all classes and to all parities—even to the more privileged classes and to second pregnancies, where the general incidence is low. A satisfactory exploration of the reasons for the seasonal variation would involve consideration of the many aspects of the environment which vary with season. This is too wide a subject for full investigation at present and attention will here be restricted to certain climatic phenomena and some of the more common infectious diseases.

Before attempting to correlate the seasonal variation of possible influences with monthly anencephalic rates, it must be recognized that, because the duration of gestation of anencephalic foetuses is so variable, the date of birth is only a rough guide to the date when the causal agent acted upon the embryo. Also, since gestation is usually shorter than normal and since there is a seasonal variation in the total number of births, some error is introduced when the anencephalics born in any month are related to the total births in that month; a substantial proportion should be related to the births of the following month and some to the month after that. (The error is, of course, less when a 3-monthly grouping is adopted as in the first part of this section.) Examination of Birmingham data indicates that, in round figures, only one-sixth of anencephalics are born in the month expected (counting from the date of the last menstrual period), one-half being born one month early and one-third 2 months early.

In order to calculate monthly incidence figures, it is necessary, therefore, to advance one-half of the anencephalics born in a given month to the following month, and one-third to the month after that. The time of operation of the causal factor, supposing that it acts when the embryo is about 3 weeks old, would then be 8 months before the adjusted month of birth. In using this method, it is necessary, because the number of days in a month is not constant, to convert the monthly figures to daily numbers before carrying out the adjustment. Results of analysis of all the available Scottish data (1939–58) are shown in Table IX. These suggest that, unless the factor responsible for the seasonal incidence has a delayed action affecting primarily the mother rather than the embryo, it operates most strongly from March to July and least strongly from September to December.

The adjusted anencephalic rates of Table IX, related to the month when the influence was presumed to operate, have been charted in Fig. 4 (opposite) against the mean monthly figures for mean air temperature, daily hours of daylight, and hours of sunshine in West Scotland. (This area was chosen because it contains the greater proportion of the population.) The scales have been adjusted to make the ranges approximately the same; comparison should be based, therefore, on the inflexions of the curves and the position of the modes rather than on the proximity of the lines. The daylight and sunshine curves are, of course, very similar; both fit the anencephalic variation more closely than the tempera-

TABLE IX

MONTHLY ANENCEPHALIC STILLBIRTH RATES—SCOTLAND, 1939–58

Month of Birth	Jan.	Feb.	Mar.	Apr.	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.
Total No. of Days ..	620	565	620	600	620	600	620	620	600	620	600	620
Total Births in Month ..	165,618	150,929	171,629	169,420	177,221	164,552	167,058	157,821	151,554	164,762	147,200	158,049
Total Births per Day ..	267·13	267·13	276·82	282·37	285·84	274·25	269·45	254·55	252·59	265·74	245·33	254·92
Anencephalic Stillbirths in Month	509	429	412	413	369	386	342	401	379	455	436	508
Anencephalic Stillbirths per Day	0·8210	0·7593	0·6645	0·6883	0·5952	0·6433	0·5516	0·6468	0·6317	0·7339	0·7267	0·8194
Anencephalic Stillbirths per Day corrected for Short Gestation*	0·7887	0·8102	0·7641	0·7000	0·6649	0·6343	0·6119	0·5980	0·6126	0·6537	0·6987	0·7446
Monthly Corrected Anencephalic Stillbirth Rate	2·95	3·03	2·76	2·48	2·33	2·31	2·27	2·35	2·43	2·46	2·85	2·92
Month of Operation of Influence	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.	Jan.	Feb.	Mar.	Apr.

*Corrected numbers are obtained by advancing half the anencephalics 1 month and one-third 2 months.

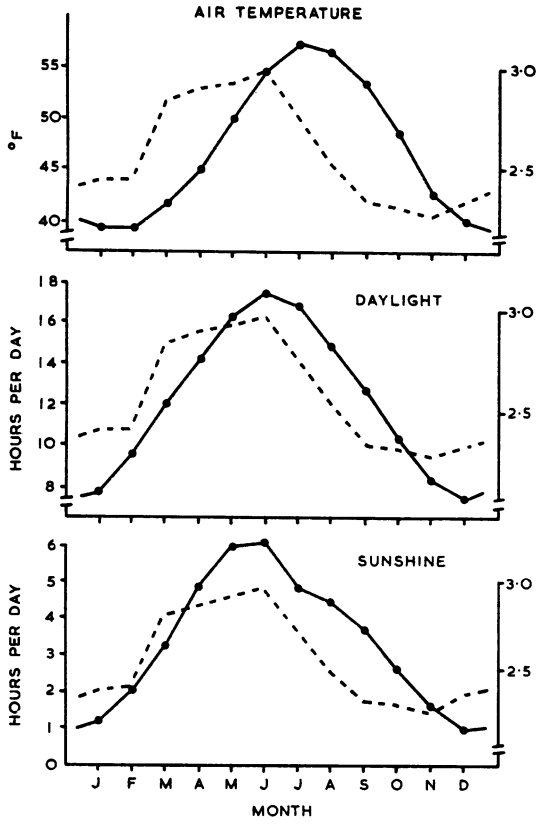

FIG. 4.—Comparison of mean air temperatures, daylight hours, and sunshine hours (continuous lines) with anencephalic stillbirth rates 8 months later (broken line).

ture curve does, but although the positions of the modes coincide the agreement is not perfect.

There is much less agreement, however, with some of the commoner infectious diseases (Fig. 5, overleaf). Choice of the diseases investigated depended on the availability of weekly notifications and, since the Registrar General does not publish these figures, data for Glasgow (published in the *Glasgow Medical Journal*) have been used. There seems little objection to using figures for Glasgow, which is the centre of the largest conurbation in Scotland with a seasonal distribution of disease presumably not very different from that of other heavily populated areas which are not far away. The chief limitation of the data is that not all infectious diseases are notifiable, and only a few of those that are occur with a frequency which makes an investigation of the seasonal trend useful. Scarlet fever, whooping cough, chicken pox, and poliomyelitis show no correspondence with the anencephalic curve. Measles fits more closely and rubella is even closer, but this is presumably a chance association because the teratogenic effects of rubella have been thoroughly investigated and there is no evidence that it causes anencephalus.

Influenza deserves special consideration in view of the evidence provided by Coffey and Jessop (1959) of its association with anencephalus. It is not a notifiable disease, but a reliable guide to the prevalence of virus A, which is the type most likely to be concerned, is provided by mortality data. These show a seasonal pattern quite unlike the seasonal variation of anencephalus (Fig. 6, overleaf). The implication of this observation is supported by an examination of secular variations of the two conditions. Between 1938 and 1958 there were seven epidemic winters (arbitrarily distinguished by more than 500 deaths from influenza in the period October to March); only two (in 1939–40 and 1957–58) were followed the next May to October by an anencephalic incidence above the normal value. The fact that the second of these epidemics was the one investigated by Coffey and Jessop raises the possibility that the causal virus, known to differ antigenically from its predecessors, also differed in its teratogenic potentialities. Two contemporary American studies, however, showed no obvious association with anencephalus (Wilson, Heins, Imagawa, and Adams, 1959; Walker and McKee, 1959). Doll, Hill, and Sakula (1960), in London, also obtained negative results, but concluded, after examining Scottish statistics, that Asian influenza in early pregnancy "can increase the risks of anencephaly, but that the extent of the hazard is normally small".

Further study of the Scottish data suggests that the risk is negligible. If influenza has any teratogenic action, the duration of the illness and of the period during which the embryo is at a stage when it is susceptible to the development of anencephalus suggest that the danger to the embryo lasts for at least 3 or 4 days. In Scotland, therefore, where there are about 8,000 births each month, at least 1,000 embryos are at risk at any time. The 1957 epidemic was largely restricted to the months of October and November, during which about 25 per cent. of women of reproductive age were attacked. There were therefore about 500 embryos exposed to maternal influenza at the relevant time; three-quarters of those which developed anencephalus would be expected to be born in the following May and June. The actual number of anencephalic stillbirths registered in these months (62) was greater than the numbers in 1957 and 1959 when there was no preceding autumn epidemic (36 and 54 respectively) but

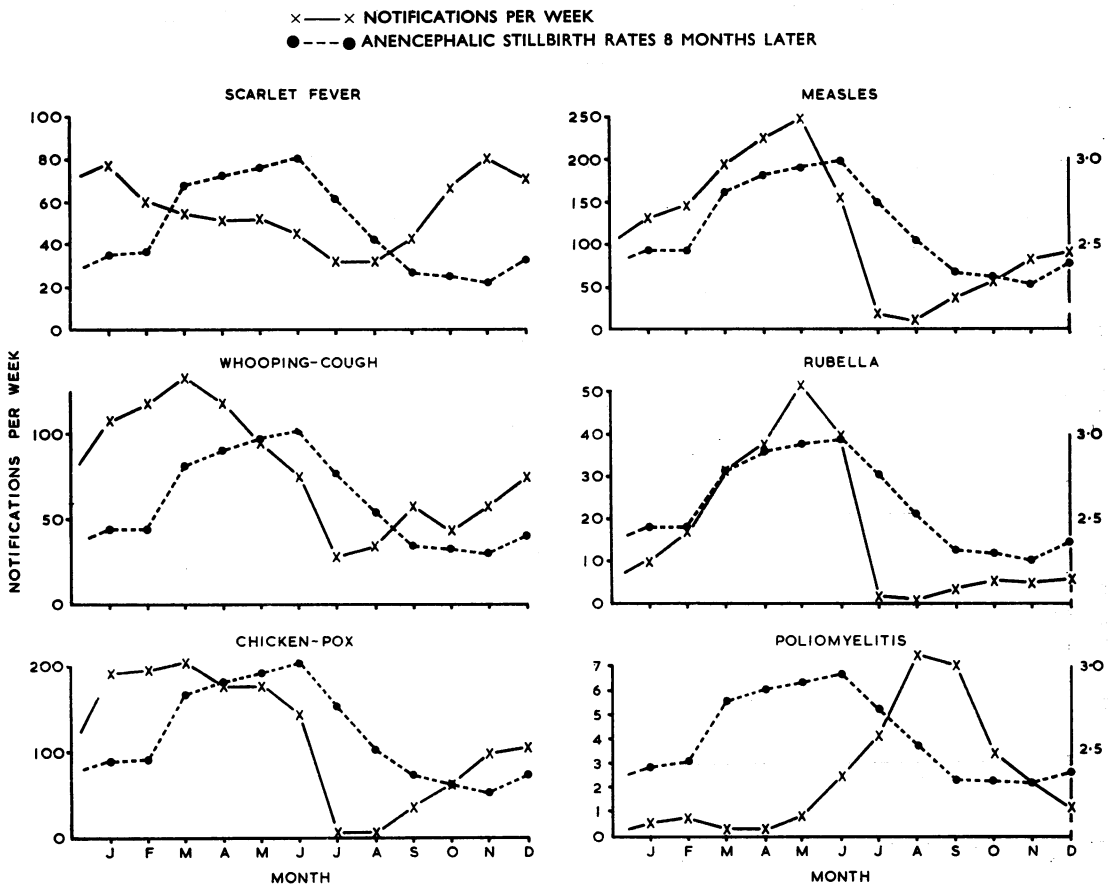

FIG. 5.—Comparison of monthly frequency of infectious diseases in Glasgow in 1945–54 (continuous lines) with adjusted anencephalic stillbirth rates 8 months later (broken line).

was very much less than the number which would have occurred if influenza were an important influence.

A second epidemic due to the same virus strain in February and March, 1959, provided a further opportunity to study its effect. The number of anencephalic stillbirths born in the following September and October was 42; the previous year, when there was no prevalence of influenza in late winter, 58 anencephalic births were recorded in these months.

These results support the view that influenza cannot be regarded as a specific cause of anencephalus. If there is any association, it is possible that this occurs, as Doll and others (1960) suggest, only when other circumstances are suitable.

SECULAR VARIATION

Annual anencephalic rates in Scotland from 1939 to 1956 were examined by Edwards (1958), who considered that much of the fluctuation from year to year was due to changes in incidence among first births and among winter births, rates for multiparae and for summer births showing little more than random variation. It is worth noting, however, that annual rates may be misleading because anencephalic foetuses are usually born prematurely; a substantial proportion of those born towards the end of a year would, if normal, have been born in the following year and should therefore be related to the births of that year. No error arises, of course, if the annual

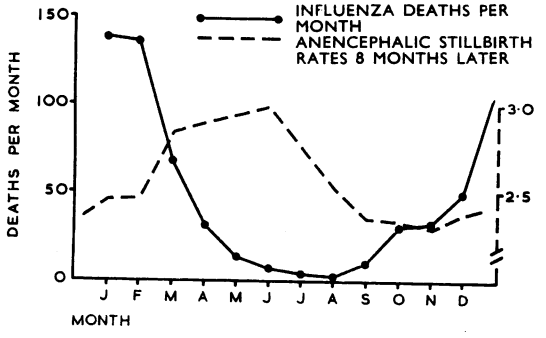

FIG. 6.—Comparison of monthly frequency of deaths from influenza in Scotland (continuous line) with adjusted anencephalic stillbirth rates 8 months later (broken line).

number of total births is constant, but if, as in 1945, the number of births in one year is smaller than the number in the following year, the anencephalus rate is overstated. The error can be minimized by grouping consecutive years as has been done in a later part of this analysis.

In attempting to explain changes in the annual rates in terms of variation in the environment, it is more useful to know incidence according to the year when the malformation was initiated than to the year of birth. These rates can be readily calculated if it is assumed, as was done in the examination of seasonal variation, that the malformation is laid down about 3 weeks after conception (approximately 8 calendar months before term). Normal infants born in the period September–December therefore pass through this stage in the same year as the year of birth, and infants born in January–August pass through it in the previous year. The same rule can be applied to anencephalic foetuses if their month of birth is first adjusted as in the previous section to take account of their shorter period of gestation.

Rates derived in this way are shown in Fig. 7.

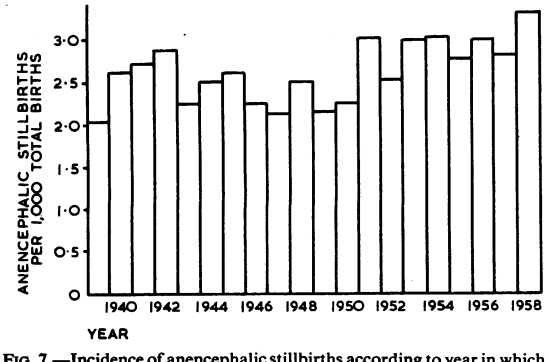

FIG. 7.—Incidence of anencephalic stillbirths according to year in which the malformation was initiated.

Minor fluctuations from year to year are of doubtful significance (the standard errors are in the range 0·15–0·18 per 1,000) and only the broader trends merit attention. It appears that incidence increased during the early war years and then settled to a low level which persisted until 1950; since then rates have been high, especially in 1958. At first sight this pattern suggests a direct relationship between anencephalic rates and food intake. (Although food rationing was introduced at an early stage of the war it became more severe and persisted well into the post-war period, fat consumption for example reaching its lowest level in 1947.) It has not been possible, however, to find any close correlation between anencephalic rates and the national intake of the major nutrients. Similar attempts to correlate incidence with the prevalence of the notifiable infectious diseases considered in the previous section were equally unrewarding. Nor is there any relationship between rates and the more obvious meteorological phenomena.

A full investigation of the many environmental factors subject to annual variation which might be concerned in the causation of anencephalus would be very laborious and is hardly justifiable unless the number of possible agents can be narrowed. At present the most useful line of inquiry seems to be an investigation of secular trend in relation to those variables which have been shown to have some influence on incidence—season, maternal age and parity, and social class.

The available data permit examination of the secular influence of season of birth and maternal age for the whole period 1939 to 1958 (Table X, overleaf). To reduce random error due to the small numbers which occur in some cells when the series is divided according to these variables, a 5-year grouping has been adopted. The anencephalic rate was highest in 1954–58 and lowest in 1944–48. Each of the four seasons of birth also showed their highest rates in 1954–58, but only two (May–July and November–January) were consistent with the general pattern in having their lowest rates in 1944–48. These two seasons also provided the greatest range in the quinquennial rates. It seems that the seasons with the lowest and the highest rates (May–July and November–January respectively) show the greatest secular variation.

Dividing the series according to maternal age gives a rather different pattern. All groups had their highest rates in 1954–58 and all but the youngest had their lowest rates in 1944–48, but the amount of secular variation was small for the group with the lowest incidence (25–29 years), and the group with the

TABLE X

SECULAR VARIATION IN ANENCEPHALIC RATES (PER 1,000 TOTAL BIRTHS) ACCORDING TO SEASON OF BIRTH AND MATERNAL AGE

Quinquennium		1939–43	1944–48	1949–53	1954–58	Ratio of Highest to Lowest
Trimester of Birth	February–April	2·51	2·54	2·33	2·80	1·20
	May–July	2·18	1·88	1·99	2·60	1·38
	August–October	2·44	2·50	2·54	2·94	1·20
	November–January	3·05	2·68	3·21	3·42	1·28
Maternal Age	Under 25	2·20	2·35	2·59	3·07	1·40
	25–29	2·22	2·19	2·23	2·50	1·14
	30–34	2·71	2·31	2·36	2·97	1·29
	35 and Over	3·40	2·89	3·03	3·58	1·24
All Births		2·53	2·39	2·51	2·94	1·23

highest incidence (35 and over) showed less variation than the youngest group.

Incidence according to maternal parity could be examined only for the years after 1945 because in the earlier years birth ranks of stillbirths and live-births were estimated in different ways. The first quinquennium of Table X has therefore been omitted and a 3-year period (1946–48) has been substituted for the second quinquennium. Incidence was low in this period; it increased in 1949–53 and was highest in 1954–58 (Table XI). The first three birth ranks were consistent with this pattern, but later-born children showed an irregular trend. Secular variation in incidence appeared to be most marked for second pregnancies (in which rates are lowest). This contrasts sharply with the secular pattern according to maternal age where the group with the lowest rate showed the least variation. Further exploration of this point was attempted by comparing incidences in the last two quinquennia in respect of both age and parity, but numbers in some cells were too small to establish any consistent pattern.

TABLE XI

SECULAR VARIATION IN ANENCEPHALIC RATES ACCORDING TO MATERNAL PARITY (LEGITIMATE BIRTHS)

No. of Previous Children	Period			Ratio of Highest to Lowest
	1946–48	1949–53	1954–58	
0	2·31	2·84	3·04	1·32
1	1·52	1·77	2·34	1·54
2	2·04	2·29	2·96	1·45
3 and 4	3·10	2·69	3·55	1·32
5 and Over	3·64	3·82	3·69	1·05
Total	2·25	2·50	2·94	1·31

Examination of secular variation according to social class was possible only for the period 1949–58, and in order to maintain adequate numbers a 5-year grouping was adopted and Classes I and II were amalgamated. The results show that the increased incidence in 1954–58 was experienced by all social classes (Table XII).

TABLE XII

SECULAR VARIATION IN ANENCEPHALIC RATES ACCORDING TO SOCIAL CLASS (LEGITIMATE BIRTHS)

Social Class	Quinquennium		Ratio $\frac{b}{a}$
	1949–53 (*a*)	1954–58 (*b*)	
I and II	1·35	1·76	1·30
III	2·57	2·91	1·13
IV	2·73	3·32	1·22
V	3·25	3·93	1·21
Total	2·50	2·94	1·18

DISCUSSION

This investigation confirms previous observations that the incidence of anencephalus varies with maternal age and parity, social class, and season. It is now clear that each of these variables has an independent effect; association with maternal age, for example, cannot be explained by the influence of parity, and the composite effect of age and parity is not due to the social class variation. Furthermore, association with one variable does not nullify the effect of another; the relationship with season of birth, for example, appears to be manifested by all parity groups and by all social classes, and a consistent secular variation is shown by most of the subgroups derived by dividing the series according to maternal age, parity, social class, or season of birth.

Before considering the implications of these findings, it is necessary to examine the possibility that they might be the result of bias due to incomplete ascertainment.

Anencephalus is so easily recognized that it seems unlikely to be missed or confused and there is little doubt that the only cases not recorded are those born alive, and those born dead before the 28th week of pregnancy. The proportion born alive appears to be small. It was 5 per cent. in Birmingham in 1940–47; the same figure was recorded for Scotland in 1958 (the only year for which this information is available).

This proportion is too small to bias results seriously even if survival at birth was dependent to a large extent on one of the variables under consideration.

The abortional loss is certainly greater and requires closer scrutiny. Some idea of its magnitude may be obtained from a survey of all pregnancies in Belfast in 1957 (Stevenson, Dudgeon, and McClure, 1959). In 84 cases of abortion in which the foetus was available for examination, five were anencephalic. If this frequency is representative of the whole series of 1,127 abortions (which occurred in 9,526 pregnancies) it can be estimated that the loss of anencephalics is seven per 1,000 pregnancies. This is higher than the anencephalic rate in pregnancies which reach a viable stage (4·6 per 1,000 total births). A substantial proportion of cases are missed, therefore, when attention is restricted to pregnancies which have reached a viable stage (28 weeks), and we must consider whether the association with the variables examined in the present study might be due to selective elimination of malformed foetuses at an early stage of pregnancy.

For example, the variation in incidence by maternal age could be accounted for, even if the initial incidence were unrelated to age, if women aged 25–29 had a greater tendency to abort anencephalic foetuses than younger or older women. Although there is no direct evidence on this point, there are grounds for believing that this supposition is highly unlikely. The data published by Stevenson and others (1959) provide estimates of the relative incidence of abortions according to age. Comparison with the Scottish anencephalic statistics shows a remarkable similarity in trend when both series are standardized to remove variation due to parity (Fig. 8). (Standardization is necessary because the incidence of anencephalus but not of abortion is raised in first pregnancies.) This strongly suggests that loss by abortion cannot account

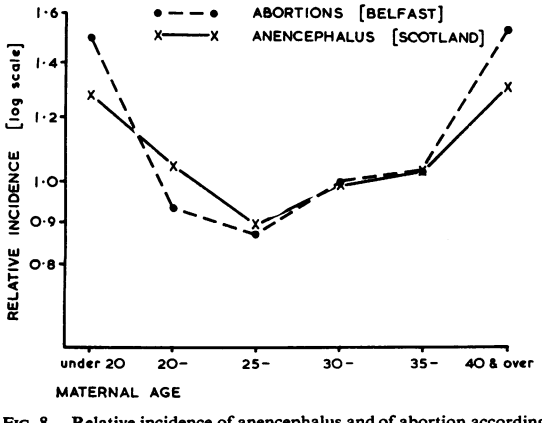

FIG. 8.—Relative incidence of anencephalus and of abortion according to maternal age.

for the observed variation of anencephalic incidence with age; on the contrary it would probably tend to obscure the true extent of the variation.

In the same way, again using Stevenson's data, it can be shown that the parity trend of abortions is inconsistent with the view that the parity pattern of anencephalus can be explained by differential abortion loss.

This evidence, of course, does not dispose of the possibility that the age and parity pattern may be different for abortions which occur very early, perhaps even before the fact of pregnancy is established. Such abortions are probably frequent and there is evidence (though derived only from women with genital disease) that a high proportion of such embryos are abnormal (Hertig, Rock, Adams, and Menkin, 1959). All that can be said at present is that, if there is a differential loss of embryos at this stage, it must show a very unusual pattern if it can account for any of the variations in anencephalic incidence so far reported.

Since it is unlikely that the association between anencephalus and the variables examined in this paper can be explained in terms of differential survival of affected foetuses, the relationships here demonstrated are presumably of aetiological significance. It has been shown that these variables are independent of each other in their influence and are to some extent additive in their effect. For example, in Scotland, the risk of an anencephalic stillbirth is always considerable for a woman in poor social circumstances, but the risk is increased if conception takes place in early summer.

It seems likely, therefore, that anencephalus may be due to a number of causes. This conclusion is consistent with laboratory experience; Giroud (1960) listed sixteen agents which can produce anencephalus in experimental animals. It is also quite possible that anencephalus is not an entity and that different types may originate in different ways. Some cases may arise by failure of fusion of the anterior part of the neural folds and sometimes might be associated with spina bifida. These would, perhaps, show the epidemiological features of spina bifida rather than of anencephalus (for example, they might show no seasonal variation in incidence), and spina bifida may be as likely as anencephalus among subsequent members of the sibship. In other cases the neural folds may fuse normally and the anencephalic state may arise later by destruction of nervous tissue. If this were so, the causal agent would act a little later than was supposed in the analysis of seasonal variation, and the dotted curves of Figs 4, 5, and 6 should be shifted slightly to the right. The possibility that anencephalus could arise in this way should stimulate search for a neurotropic virus with a teratogenic

action. Investigation of the viruses of poliomyelitis and mumps by Manson, Logan and Loy (1960) and of ECHO 9 by Peterson and Glicklich (1960) have yielded negative results, but there are many more known neurotropic viruses (and perhaps many not yet discovered) which await study.

The present analysis provides some evidence consistent with the hypothesis that some cases of anencephalus may be due to an infective agent. Incidence was high among:

(1) Young mothers (whose immunity might be supposed to be lower than that of older persons);

(2) Mothers of high parity (the presence of many children in the home would increase the risk of infection);

(3) Mothers in poor social circumstances (which would favour transmission of infection).

The seasonal and secular variations could also be compatible with an infective cause. Findings which do not support an infective cause are the increased incidence among primiparae and at high maternal ages. These associations suggest hormonal disturbance as a possible factor, but other hypotheses worth considering are the less efficient uterine circulation of primiparae and the greater risk of faulty gametogenesis in older women.

Although the malformation has been initiated in experimental animals by excess of vitamin A, and by deficiency of pantothenic acid, vitamin E, and folic acid, epidemiological studies provide little support for the view that anencephalus in man is due to nutritional factors. It is difficult to account in nutritional terms both for the social class gradient and for the low incidence during the years when rationing was most severe, or for the very different experience immediately after the war in parts of Germany, where the rate reached an unprecedented level, and in Scotland, where it was low, and in the last year of the war in Holland where, in spite of severe famine, no obvious increase in anencephalus occurred.

It may be remarked that no mention has been made in this paper of the possible influence of inheritance. The reason is not that hereditary causes are regarded as totally unimportant, but that the nature of the present investigation precluded any examination of a genetic basis for this malformation. It is worth noting, however, that there are several twin studies which provide strong evidence against a simple genetic explanation. Furthermore, the lethal nature of the malformation is not easily reconciled with the perpetuation of a gene or genes, which, in order to account for this condition, would be quite common, at least in some countries. Perhaps the genetic constitution of the embryo is less important than the maternal genotype, which may influence the environment of the early embryo so as to produce conditions favourable for the development of the abnormality. It would be unwise to disregard the possible importance of genetic factors so long as ethnic variations in incidence cannot be adequately explained in environmental terms. For this reason, population studies in other countries could make an important contribution to our understanding of this malformation.

SUMMARY

Unpublished data on anencephalic stillbirths in the years 1949–58 provided by the Registrar General for Scotland, and less detailed statistics from his Annual Reports for the years 1939–48, were examined in relation to information on all births contained in the Annual Reports covering these periods.

The anencephalic rate was slightly lower than normal among illegitimate births. Variations of incidence with age and with parity showed U-shaped trends, being lowest for mothers aged 25–29 years and for second pregnancies. The effects of these two variables were independent of each other and of social class influences.

Incidence was highest in infants born in the period November–January, and this was shown by all parity groups and all social classes. Adjustment of rates to the probable time when the malformation was initiated indicated that the seasonal influence was strongest from March to July. Comparison of this pattern with that of the more frequent notifiable infectious diseases showed little resemblance; daylight and sunshine hours gave a closer correspondence.

Secular variation of the whole series was compared with that of sub-groups obtained by dividing according to season of birth, maternal age, parity, and social class. A high incidence in the last quinquennium was consistently shown by all these sub-groups.

It is concluded that several factors are probably involved in the aetiology of anencephalus, but that much of the present evidence would be consistent with an infective agent as the cause. There is less evidence to support a nutritional hypothesis.

I am most grateful to the Registrar General for Scotland for providing detailed statistics of anencephalic stillbirths for the years 1949–58.

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