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SEASONAL INCIDENCE OF ANENCEPHALUS*

BY

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According to the most recent figures, anencephalus has become the second most common cause of stillbirth in England and Wales and the commonest in Scotland. The most revealing data are those published by the Registrar-General for Scotland, where causes of stillbirth have been registered since 1939 (22 years longer than in England and Wales). Between 1939 and 1963 they show a halving of the overall stillbirth rate and a slight increase in the incidence of stillbirths caused by anencephalus. The proportion of all stillbirths attributed to anencephalus rose from 5·8 per cent. in 1939–41 to 14·8 per cent. in 1961–63. It follows that, in the effort to reduce prenatal mortality further, studies of the aetiology of anencephalus have an increasingly significant part to play.

Among the variables shown to be related to incidence, season of birth is perhaps the most interesting. Anencephalus was found to be commonest among winter births and least common in summer births in a study of Scottish data for 1939–46 and Birmingham data for 1940–47 (McKeown and Record, 1951). Tünte (1965) described a similar variation among births in the Münster region of West Germany in 1950–56. A study of Scottish stillbirths in 1939–58 suggested that the influence of season was independent of the effects of other variables, since each quinquennium, social class, and birth rank group showed a similar seasonal pattern (Record, 1961).

More recent work has failed to reveal any association between season and incidence in Liverpool and Southampton (Smithells, Chinn, and Franklin, 1964; Williamson, 1965), which may indicate that the pattern in England has changed since the original finding of such an association in Birmingham. Negative findings have also been reported from America and France (MacMahon, Pugh, and Ingalls, 1953; Frézal, Kelley, Guillemot, and Lamy, 1964).

In this communication, national data published by the Registrars General for Scotland and for England and Wales, and local records of anencephalics born to Birmingham residents, are used to examine the seasonal pattern in Britain in recent years. This anlysis is followed by an examination of the Birmingham data for evidence concerning the cause of the association between incidence and season.

DATA FOR SCOTLAND

Since 1939 the Annual Reports of the Registrar General for Scotland have included the distribution of all births, and of stillbirths ascribed to anencephalus, by month of registration. Since the last study of these data (Record, 1961), reports covering the quinquennium 1959 to 1963 have appeared, and in Fig. 1 the seasonal incidence of stillbirths ascribed to anencephalus during this period is compared with that observed previously. In place of the trough between May and August exhibited by the 1939–58

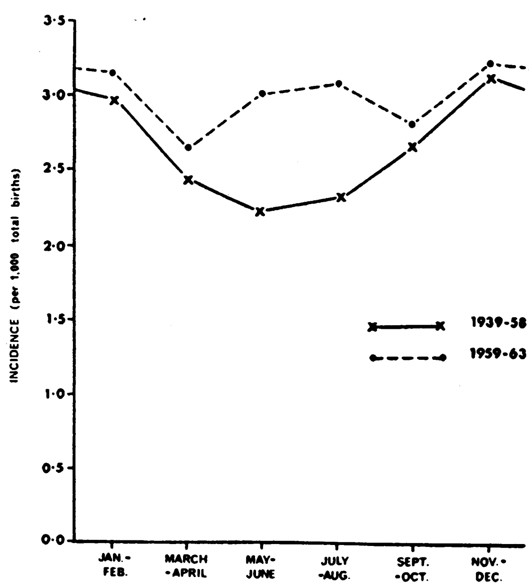

FIG. 1.—Seasonal incidence of anencephalic stillbirths in Scotland, 1939–63.

* This investigation was assisted by a grant from the Association for the Aid of Crippled Children, New York.

data, the more recent figures show a peak almost as high as that for the winter months.

Although the rates for 1959–63 are based on much smaller numbers than those for 1939–58, the change in seasonal pattern is very unlikely to be due to chance. This is demonstrated in Fig. 2, which shows for each period the position and 95 per cent. confidence limit of the peak on a simple harmonic curve fitted to the monthly rates by the method of Edwards (1961)*.

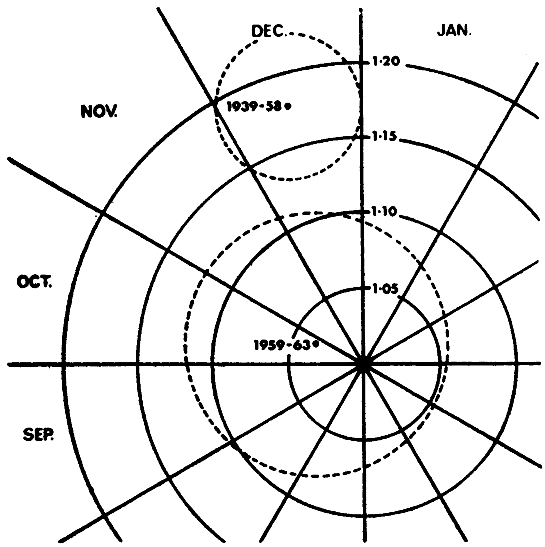

FIG. 2.— Results of fitting simple harmonic curves (Edwards, 1961) to the Scottish monthly rates for anencephalic stillbirths in 1939–58 and 1959–63.

The radius on which each point lies indicates when the peak on the appropriate curve occurred, and the distance of the point from the centre shows the ratio of the peak incidence to the mean. The 95 per cent. confidence limits of the points are represented by interrupted circles.

The consistency between the seasonal fluctuations observed during the four quinquennia from 1939 to 1958 (Fig. 3) also illustrates the resistance of such fluctuations to distortion by random variation.

Examination of monthly totals for 1939 to 1958 (given by Record, 1961) indicates that over this period incidence was lower in March to August (2·31/1,000) and higher in September to February (2·90/1,000) than in any other consecutive 6 months. In order to identify the specific years in which the seasonal pattern was disturbed, the whole period from 1939 to 1963 was therefore divided into half-years starting in March and September, and the incidence of anencephalus in each half-year was computed.

* In his original account of this test, Edwards applied it to absolute numbers. Except when estimating variance we used rates instead, so as to eliminate variations attributable to the seasonal trend in total births.

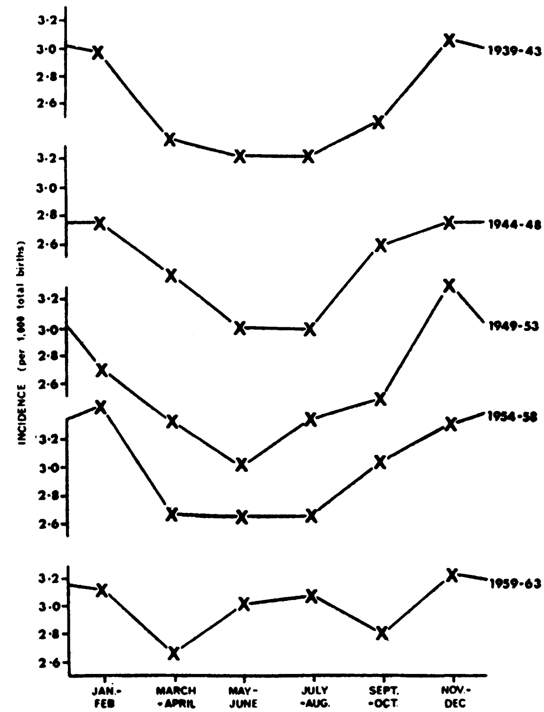

FIG. 3.—Seasonal incidence of anencephalic stillbirths in Scotland, by quinquennia.

In Fig. 4 (opposite) these rates are plotted with lines connecting the points which relate to the same halves of adjacent years, so that when the normal seasonal pattern is reversed the line representing incidence in March to August rises above that relating to September to February.

During the years 1939–57, the rate for March to August was always the lower except for two brief periods in 1939–40 and 1947–48; but, after again rising in 1958 to a peak which exceeded the figure for the previous winter, it remained high through 1959–61. There was no corresponding increase in the rate for September to February.

DATA FOR ENGLAND AND WALES

The Annual Reports of the Registrar General for England and Wales give the number of stillbirths attributed to anencephalus for each month only since the beginning of 1961, when causes of stillbirth were first registered. Compared with the Scottish figures, these data have however the advantage of including month of birth instead of month of registration.

Fig. 5 (opposite) shows the seasonal incidence of stillbirths due to anencephalus in the 4 years for

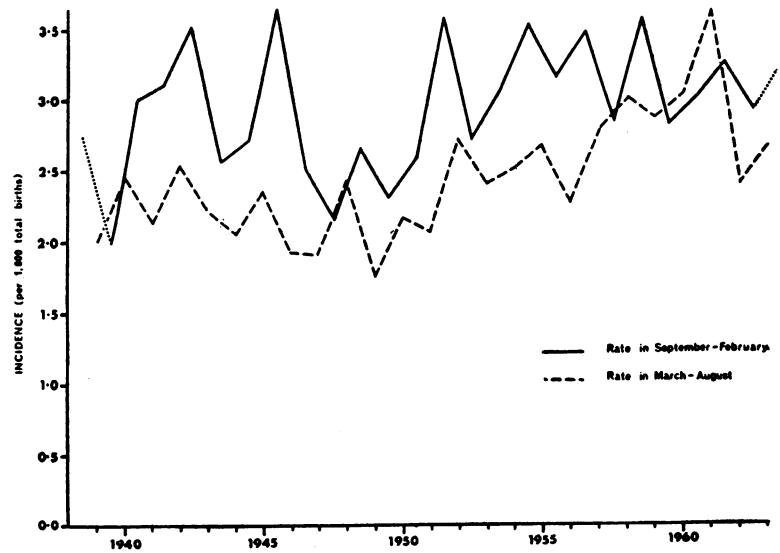

FIG. 4.—Secular variations in the September to February and March to August rates for stillbirths due to anencephalus in Scotland.
The lines from the first and last points are dotted because these points do not relate to complete half-years, but only to the first two months of 1939 and the last four of 1963.

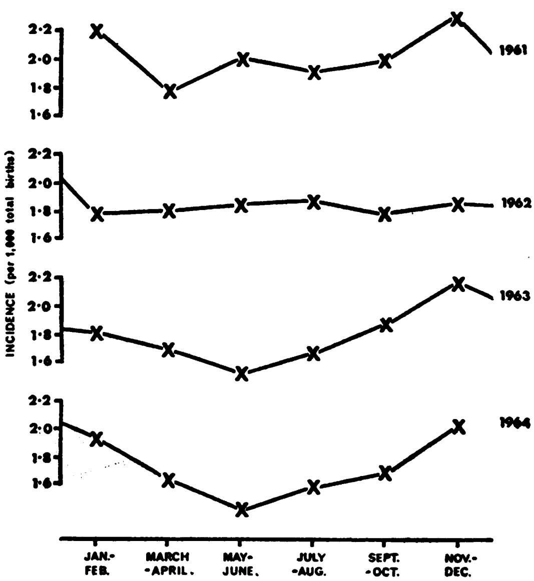

FIG. 5.—Seasonal incidence of anencephalic stillbirths in England and Wales, 1961–64.

which data are available. There was little seasonal variation in 1961, and none in 1962; but in 1963 and 1964 fluctuations like those formerly seen in Scotland were observed.

DATA FOR BIRMINGHAM

MATERIAL

For many years the Public Health Department of the City of Birmingham has maintained registers of information supplied by doctors and midwives in respect of all stillbirths and neonatal deaths among Birmingham residents. The data include sex, date of birth, duration of gestation in weeks, and details of malformations and other conditions contributing to death. Particulars of every case of stillbirth or neonatal death ascribed to anencephalus between January, 1940, and April, 1965, were obtained from this source. In addition, the mothers of many of the propositi born in 1940–47 had been interviewed and their hospital records examined (Record and McKeown, 1949 and 1950; MacMahon and McKeown, 1952), so that in these cases we had information about the birth months of sibs, the presence or absence of hydramnios, and the mode of onset of labour.

Additional data were also available in respect of anencephalics born in 1952–62: the Birmingham Public Health Department's own birth records were greatly improved during the period 1949–51 (Charles, 1951), and thereafter the particulars obtained from doctors and midwives included date of onset of last menstrual period, mode of onset of labour, birth weight, and more complete data on associated defects.

The number of births each month in the related population was known precisely for the years 1950–54; and for the more recent years we used the numbers notified to the Medical Officer of Health (normally within two days of birth), after adjusting them to allow for births not notified in Birmingham. For each of the years 1940–49, it was necessary to assume that the distribution of Birmingham births by month corresponded to that for England and Wales given by the Registrar General. In support of this assumption, it should be noted that, between local and national monthly totals obtained by summing the figures for 1950–54, the coefficient of correlation was $+0 \cdot 98$.

According to our records 509,673 children (including stillbirths) were born to Birmingham residents between January, 1940, and April, 1965, and 1,102 (2·16/1,000) of these children were anencephalics.

CHANGING EFFECT OF SEASON ON INCIDENCE

The seasonal incidence of anencephalus in Birmingham is shown in Fig. 6. In view of the change in seasonal pattern observed in Scotland from 1958 onwards, the rates for this period are shown separately from those occurring previously. In 1940–57 there was a marked cyclic trend, with the peak in November to December and the trough in May to June. More recently the rate among births between May and August has increased, in spite of the overall decline in incidence. Apart from the decline, these findings are similar to those for Scotland.

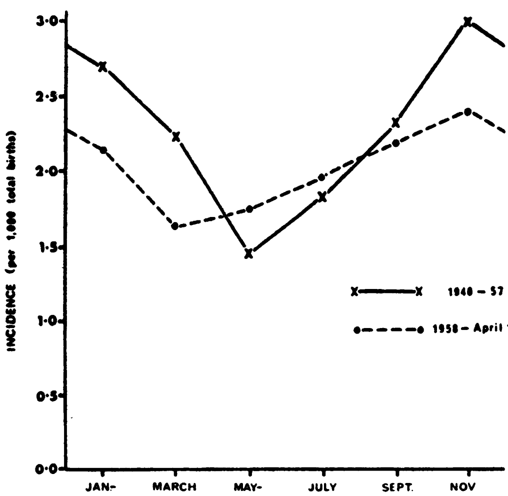

FIG. 6.—Seasonal incidence of anencephalus in Birmingham: January, 1940, to April, 1965.

As most anencephalics are born a month or two earlier than normal children conceived at the same time, one source of inaccuracy in this presentation (and in the national statistics) is that the number of anencephalics born in each month has been related to the total number of births in the same month. Where length of gestation is known, it is more accurate to allocate each anencephalic to the month in which birth would have occurred in the event of a 280-day gestation and to relate the resulting figure for each month to the total number of children born then. The results of applying this procedure to the Birmingham series are shown in Table I and Fig. 7. 1,052 of the 1,102 affected births are included; gestation length was unknown in 34 of the remainder, and sixteen births due during January to March, 1940, and April to May, 1965, were omitted because the data for these months excluded affected births occurring outside the period surveyed and were therefore incomplete.

TABLE I

ANENCEPHALIC BIRTHS TO BIRMINGHAM RESIDENTS ALLOCATED TO THE MONTHS IN WHICH THEY WOULD HAVE OCCURRED IF ALL AFFECTED PREGNANCIES HAD BEEN OF 40 WEEKS' DURATION

(Estimate based on recorded length of gestation in weeks)

Month	April, 1940, to March, 1958			April, 1958, to March, 1965		
	Total Births	Anencephalic Births due: No.	Anencephalic Births due: Incidence (per 1,000 total births)	Total Births	Anencephalic Births due: No.	Anencephalic Births due: Incidence (per 1,000 total births)
January ..	29,826	89	2·98	13,008	26	2·00
February ..	27,863	74	2·66	11,954	26	2·18
March ..	31,479	80	2·54	13,666	27	1·98
April ..	30,183	72	2·39	12,822	20	1·56
May ..	31,367	65	2·07	13,397	20	1·49
June ..	29,587	58	1·96	12,571	25	1·99
July ..	30,204	32	1·06	12,993	16	1·23
August ..	28,991	45	1·55	12,480	21	1·68
September	29,142	71	2·44	12,249	27	2·20
October ..	28,348	61	2·15	12,477	19	1·52
November	26,674	52	1·95	11,653	35	3·00
December ..	28,444	67	2·36	12,143	24	1·98
Total ..	352,108	766	2·18	151,413	286	1·89

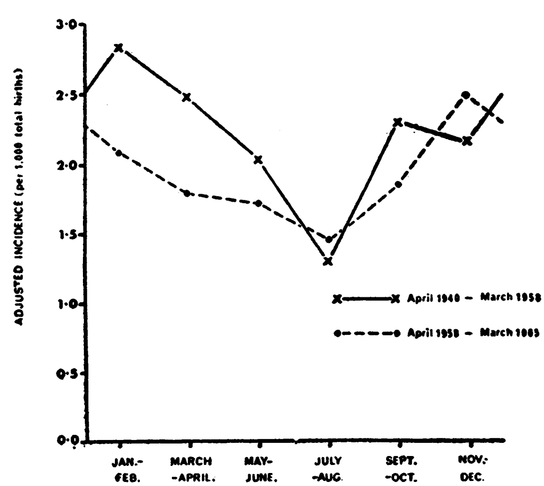

FIG. 7.—Seasonal incidence of anencephalus in Birmingham, adjusted as in Table I for variations in gestation length: births due in April, 1940, to March, 1965.

The rate for the earlier years again shows the more marked seasonal trend, although both peak and trough are 2 months later than those observed before adjusting for length of gestation. During these years, adjusted incidence was higher in December to May (2·49/1,000) and lower in June to November (1·84/1,000) than in any other consecutive 6 months. To determine when the reduction in seasonal variation occurred in Birmingham, separate rates for each half-year beginning in June or December were therefore computed and these are depicted (in Fig. 8) in the same way as the half-yearly rates for Scotland (Fig. 4). The change in seasonal pattern was again largely due to an increase in the summer rate. The resulting reversal of the normal summer-winter relationship began in 1955, 3 years earlier than the corresponding effect in Scotland.

It has been suggested that there may be aetiological differences between craniorrhachischisis and anencephalus without spinal involvement, and between cases with no additional malformation (other than talipes) and those exhibiting further defects. We have therefore examined the seasonal incidence of these varieties separately (Table II). The last decade is here distinguished from the earlier years surveyed, because of our finding that it was only during the earlier of these two periods that incidence in December to May was almost always higher than in June to November. Table II shows that all varieties of anencephalus contributed to the change in seasonal pattern. The improvements in documentation which began in 1949 are probably responsible for the fact that the proportion of anencephalics reported to have other defects was higher in the second period than in the first.

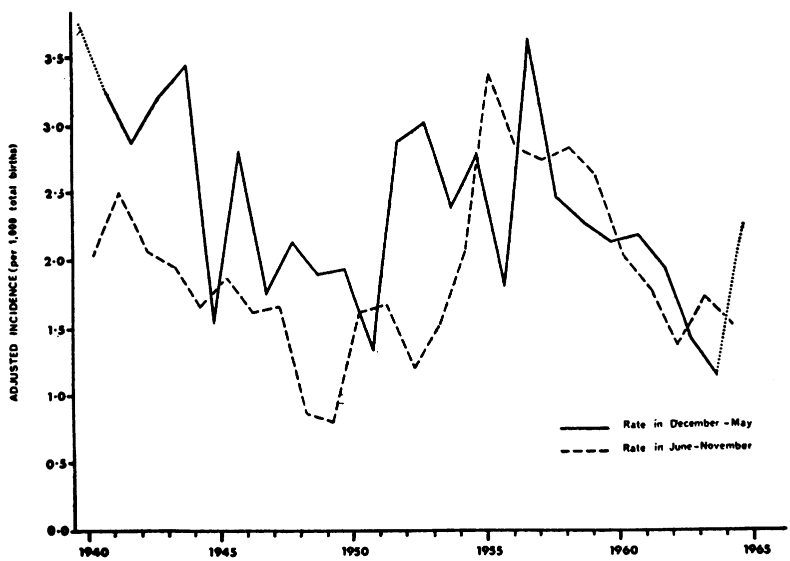

FIG. 8.—Secular variations in the incidence of anencephalus (adjusted as in Table I for variations in gestation length) among Birmingham births in December to May and June to November.

TABLE II

BIRMINGHAM ANENCEPHALIC BIRTHS DISTRIBUTED ACCORDING TO MORPHOLOGY AND SEASON
(adjusted as in Table I for variations in gestation length)

Morphology		Births due April, 1940, to March, 1955			Births due April, 1955, to March, 1965		
		(a) December to May (150,187 births)	(b) June to November (145,030 births)	Ratio of Incidences $\left(\frac{a}{150,187} \div \frac{b}{145,030}\right)$	(a) December to May (105,965 births)	(b) June to November (102,339 births)	Ratio of Incidences $\left(\frac{a}{105,965} \div \frac{b}{102,339}\right)$
Anencephalus (without mention of rhachischisis)	Alone	301	190	1·53	140	140	0·97
	With Other Defects	12	7	1·67	25	26	0·93
Craniorrhachischisis	Alone	45	31	1·40	35	39	0·87
	With Other Defects	13	9	1·40	19	20	0·92

Seasonal Distribution of Sibs of Anencephalics

Although the seasonal variation in the incidence of anencephalus appears to suggest that the environment is of aetiological importance in this condition, this conclusion may be criticized on the ground that even the incidence of a genetically-determined trait would vary in this way if there were seasonal fluctuations in either the fertility of carriers or the abortion rate among those affected. These points were investigated by examining data obtained by interviewing mothers of anencephalics born in 1940–47. From this source we ascertained the months of birth of 554 viable sibs and the months of abortion and gestational ages of 55 aborted sibs of anencephalics. The seasonal distributions of these sibs and of the related anencephalics are reproduced in Table III, which also includes the parameters obtained by fitting simple harmonic curves to these distributions (again by Edwards's method). Both the anencephalics with viable sibs and those related to aborti showed marked seasonal fluctuation around a peak during the first quarter, and may therefore be regarded as fairly typical of their period.

The viable sibs were evenly distributed throughout the year, which suggests that there was no abnormal association between season and fertility in these families. The aborted sibs on the other hand showed a seasonal distribution like that of anencephalus itself when they were allocated to the months when birth was due. Far from supporting the view that the low incidence of anencephalus among summer births may be due to a relatively high abortion rate, this finding suggests that anencephalic abortions (like affected births) may be relatively uncommon in pregnancies due to terminate in summer: the abortion rate is known to be increased among sibs of anencephalics (Record and McKeown, 1950) and it seems possible that many of those aborted are themselves anencephalic.

Effect of Season on Duration of Gestation

As our data on abortions were limited to 55 cases, it seemed desirable to seek additional evidence as to the plausibility of the suggestion that the seasonal variation in the incidence of anencephalus is due to differential survival. We therefore examined the relationship of season to gestation length in our series of anencephalic births, because it seemed possible that an influence which promoted the loss of anencephalic foetuses in early pregnancy might also have some effect on the gestation periods of those who survived to the last trimester.

In Fig. 9 (opposite) Birmingham anencephalics due to be born in the 6 months of highest incidence are compared with the remainder in respect of gestation length as recorded in weeks. During the period between 1940 and 1955, length of gestation tended to be shorter in the months when incidence was high; and after eliminating births of less than 28 weeks' gestation (which being unrepresentative are excluded from all the data that follow) the difference between the mean durations for December to May (243·8 days) and for June to November

TABLE III

ANENCEPHALIC BIRTHS TO BIRMINGHAM RESIDENTS IN 1940–47, AND OTHER MEMBERS OF THE SAME FRATERNITIES, DISTRIBUTED ACCORDING TO MONTH OF BIRTH

Month		Fraternities including Aborti		Fraternities including Viable Births	
		Anencephalics*	Aborti†	Anencephalics*	Viable Births
January		3	3	42	48
February		3	7	49	44
March		10	8	52	56
April		4	3	61	42
May		8	2	70	49
June		2	2½	48	42
July		1	4½	24½	52
August		1	7	41	50
September		7	1	41	41
October		5	5	32	52
November		4	6½	40½	40
December		7	5½	63	48
Parameters of Fitted Simple Harmonic Curve	Month of Peak	February	January	March	April
	Ratio of Peak to Mean	1·39	1·29	1·24	1·02

* The months of birth of anencephalics were adjusted for variations in gestation length as in Table I. In order that the comparison of anencephalics and their sibs might not be biassed by any association between season of birth and family size, each anencephalic with n sibs in the next column was counted n times (or $\frac{n}{2}$ times if the fraternity included two anencephalics).

† Each abortus was allocated to the month when birth was due, as estimated from month of abortion and length of gestation. The halves in the totals for some pairs of months represent cases in which the data were equally consistent with birth in either month.

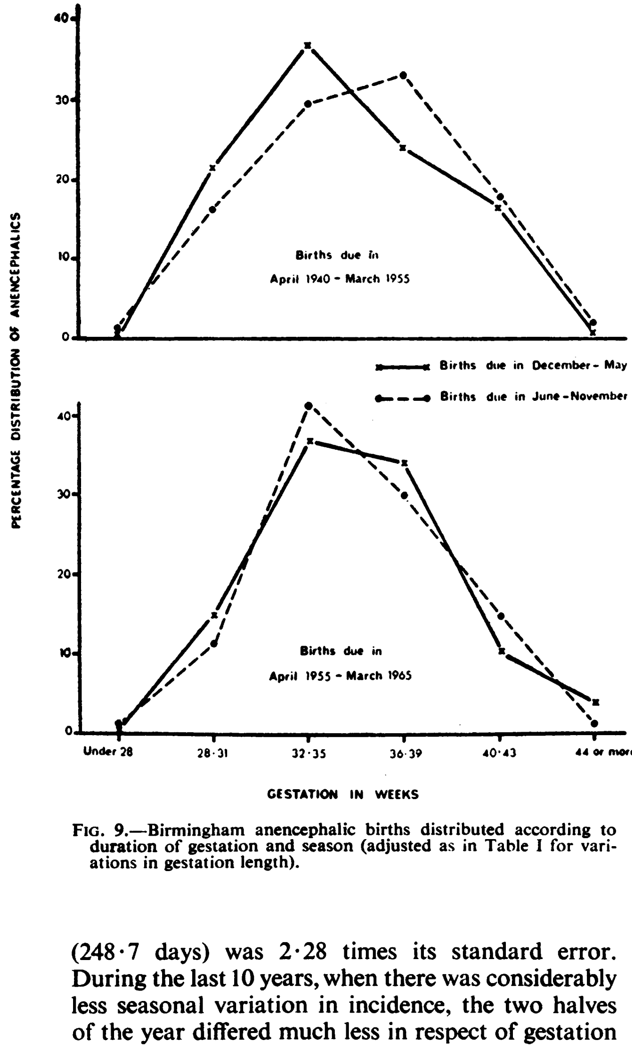

FIG. 9.—Birmingham anencephalic births distributed according to duration of gestation and season (adjusted as in Table I for variations in gestation length).

(248·7 days) was 2·28 times its standard error. During the last 10 years, when there was considerably less seasonal variation in incidence, the two halves of the year differed much less in respect of gestation length: the means were 248·9 days for December to May, and 248·7 days for June to November.

These results however are based on the recorded length of gestation measured to the nearest week, and we have shown elsewhere that seasonal variations in this measurement can readily arise from inaccuracies in the methods by which it is calculated (Record and Leck, 1963). To establish whether the observed variations in gestation length were of this kind, we made use of the fact that date of onset of last menstrual period was recorded for 453 of the 517 anencephalics born in 1952–62. Five of these gestations were excluded because they were of less than 28 weeks' duration; the exact duration of the remainder in days from the last menstrual period was compared with their length as recorded in weeks. The means based on the more exact data exceed the others by 1·0 to 1·5 days, but they show an almost identical seasonal variation. Mean birthweight varied in a parallel manner: among births due before April, 1955, but not in the more recent group, the figure for December to May was lower (by about 7 per cent.) than that for June to November (Table IV).

The duration of anencephalic gestations is often reduced by hydramnios and by artificial induction of labour. Our data suggest however, that neither of these occurrences was especially frequent during the seasons when gestation length was short. There was on the contrary some evidence that labour was induced less often in winter than in summer, both in 1940–47 (Table V, overleaf) and in more recent years (Table IV).

According to the 1940–47 data, there was no material difference in respect of the incidence of hydramnios (Table V) between births due in December to May and those due in June to November. The results shown in Table V must however be regarded as tentative, in view of the large number of individuals whose records were incomplete.

TABLE IV

BIRMINGHAM ANENCEPHALIC GESTATIONS TERMINATING IN 1952–62, AND OF KNOWN DURATION FROM LAST MENSTRUAL PERIOD

(Mean duration and related characteristics)

Basis for Estimate of Gestation Length and of Month when Birth was Due	Variable	Births due before April, 1955: Due in December to May	Births due before April, 1955: Due in June to November	Births due after March, 1955: Due in December to May	Births due after March, 1955: Due in June to November
Recorded Gestation Length in Weeks	Number of Cases	79	39	155	175
	Mean Length of Gestation (days)	246·5	251·5	248·3	247·9
Date of Onset of Last Menstrual Period	Number of Cases	80	39	157	172
	Mean Length of Gestation (days)	247·9	253·0	249·8	248·9
	Mean Birthweight (kg.)	1·54	1·65	1·57	1·52
	Onset of Labour: Number Induced (including elective Caesarean sections)	37	17	72	91
	Onset of Labour: Percentage Induced	46	44	46	53

TABLE V

FREQUENCY OF INDUCED LABOUR AND OF HYDRAMNIOS IN BIRMINGHAM ANENCEPHALIC GESTATIONS TERMINATING IN 1940–47

(The month when each birth was due was estimated as in Table I)

Occurrence		Births due in December to May	Births due in June to November
Onset of Labour	Number induced	54	47
	Number not induced ..	105	56
	Number unknown.. ..	59	42
	Percentage induced (among those of known onset) ..	34·0	45·6
Hydramnios	Number affected	73	61
	Number not affected ..	31	27
	Number unknown.. ..	114	57
	Percentage affected (among those of known status)..	70·2	69·3

DISCUSSION

Anencephalus has been produced in many ways in laboratory animals (Giroud, 1960), but apart from aminopterin no specific causal agent has yet been found to account for this malformation in man. The high frequency of discordance in monozygotic twins is strong evidence against a purely genetic aetiology. But it also suggests that the environmental influence or influences are peculiarly localized, leading to anencephaly in one embryo while the development of its twin usually proceeds normally. This is remarkable in view of the fact that the two embryos are genetically identical, are at the same stage of development when the influence operates, and are attached to the same part of the uterine wall.

The view that the environment is of aetiological importance has been encouraged by epidemiological studies in which the incidence of anencephalus has been shown to fluctuate with age and parity of the mother, social class, and season of birth. But before accepting these findings as evidence of environmental aetiology, we have to consider two other suggested explanations. The first is that variation in incidence may be due to genetic differences between the populations compared, since there can be little doubt that the influences which determine an individual's social class and reproductive history are in part genetic. For example, even a defect which is wholly genetic in origin would show a seasonal variation in incidence if the parents had an unusual seasonal pattern of reproduction. Our results, however, indicate that the parents of anencephalics do not behave in this way: their other children show no evidence of seasonal fluctuation when distributed according to month of birth (Table III).

The second alternative to accepting that the environment is of aetiological importance is to suggest that the variation in incidence of anencephalus at birth is due to differential loss of affected foetuses earlier in pregnancy. There is indirect evidence both for and against this explanation. It is supported by the finding that during the months when the incidence of anencephalus is low, the mean gestation period of those affected is longer than at times of high incidence (Fig. 9 and Table IV). This would be consistent with the view that anencephalics vary in their ability to survive in the uterus and that some influence with a seasonal rhythm removes the weaker ones at an early stage. In these circumstances, the anencephalics born after exposure to this seasonal influence might show a longer mean gestation than those born at other times, since the latter group would still include a proportion of weak ones.

The evidence against the suggestion that the seasonal variation can be explained by differential loss in early pregnancy is perhaps more convincing. It is known that anencephalus tends to recur in fraternities and that mothers of anencephalics have a raised abortion rate. It seems likely that at least some of the aborted foetuses are anencephalic. If loss of these foetuses were responsible for the seasonal variation they would be expected to have a seasonal pattern opposite to that shown by recognized anencephalics. Our observations, however, suggest that the two patterns are similar (Table III).

The effect of season on incidence is therefore more likely to be due to an aetiological influence than to variation in abortion rate. Speculations as to the nature of this influence have included the suggestion that it is a dietary factor; this might be either the presence in the food of some teratogenic substance, or the absence of some nutrient essential for the early development of the brain. Another view is that the seasonal peak is the result of some infectious disease affecting the mother at an early stage of pregnancy. No convincing evidence in support of either hypothesis has yet been produced, but the close correlation between the intensity of the seasonal influence and the hours of daylight (Record, 1961) seems to be more in accord with a dietary explanation.

The change in the seasonal fluctuation which has occurred in Birmingham since 1955 and in Scotland since 1958 indicates some modification of the influence responsible for the pattern previously observed. It is possible that there was an extension of the influence to the rest of the year rather than a reduction of its activity, since in both Scotland and Birmingham the change was brought about by a rise in incidence among summer births (Figs 4 and 8). During the most recent years for which data are available, the seasonal fluctuation seems to have returned, both in Scotland (Fig. 4) and in England and Wales (Fig. 5).

It is of some interest that, in the Birmingham series, the change in seasonal incidence since 1955 seems to have been associated with disappearance of the seasonal variation in gestation length (Fig. 9 and Table IV). A possible explanation is that the seasonal influence produced anencephalics which tended to be born earlier than those caused in other ways. But this tendency to early birth was not due to the presence of other deformities (Table II), obstetric interference (Tables IV and V), or hydramnios (Table V).

Summary

The incidence of anencephalus showed a fairly consistent seasonal variation (a winter peak and a summer trough) in Scotland until 1958. Since then much of the fluctuation has been obliterated by an increase in incidence among summer births. A similar disturbance of the usual pattern began in Birmingham in 1955 and was shown equally by anencephalus alone, by craniorrhachischisis, and by anencephalus with other defects.

Birmingham anencephalics born since 1940 were used to investigate aetiological aspects of the seasonal variation. The viable sibs of anencephalics showed no evidence of a seasonal pattern and the aborted sibs showed the same variation as the anencephalics themselves. This suggests that the seasonal variation in the incidence of anencephalus cannot be explained by fluctuation either in conception rate of mothers or in abortion of affected embryos.

During the years when there was a seasonal variation in incidence, anencephalics conceived in March to August (which produced the high winter incidence) had a shorter mean duration of gestation and a lower mean birth weight than those conceived in September to February. But after 1955 (when the change in seasonal incidence occurred) there was little difference in gestation and birth weight between the two groups.

The Birmingham data were made available by Dr E. L. M. Millar (Medical Officer of Health, Birmingham) and his staff, and analysed with the help of Mrs Eileen Armstrong, Miss Gillian Davis, Miss Ida Giles, and Mrs Betty Mann. We are greatly indebted to all these people for their ready co-operation.

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