CONGENITAL MALFORMATIONS OF THE CENTRAL NERVOUS SYSTEM IN SCOTLAND

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The reports of the Registrar General for Scotland provide information not available elsewhere on the causes of stillbirth as well as detailed reports on neonatal deaths. Data on the common causes of stillbirth have been available since 1939, by month of birth, maternal age, maternal parity, and legitimacy, and since 1950 by social class of father and place of birth also.

The present communication considers data relating to stillbirths due to anencephalus, spina bifida, and hydrocephalus, and to infant deaths due to spina bifida and hydrocephalus.

SOCIAL CLASS AND LEGITIMACY

The marked association of foetal defect with class was first advanced on adequate data in the report of the Registrar General for Scotland in 1950. An analysis of the incidence of stillbirths due to malformations of the central nervous system according to class and legitimacy is given in Table I and Fig. 1. The steep trend is striking. The association explains about a quarter of the social variation in stillbirth rate. That is to say, at least a quarter of the social variation in this rate is irrevocably determined by the time a woman attends an ante-natal clinic.

TABLE I

INCIDENCE (PER 1,000 TOTAL BIRTHS) OF MALFORMATIONS OF THE CENTRAL NERVOUS SYSTEM IN LEGITIMATE BIRTHS ACCORDING TO SOCIAL CLASS OF FATHER AND IN ILLEGITIMATE BIRTHS.
SCOTLAND, 1950-56 (Stillbirths only).

Type of Malformation	Social Class (Legitimate Births)					Illegitimate Births
	I	II	III	IV	V	
Anencephalus	0.89	1.74	2.74	2.97	3.60	2.75 (2.89)
Spina Bifida ..	0.17	0.23	0.29	0.33	0.31	0.3 (0.3)
Hydrocephalus	1.01	0.99	1.35	1.46	1.55	2.11 (1.40)
All	2.1	3.0	4.4	4.8	5.5	5.1 (4.6)

The figures in brackets are the incidences expected from the social class distribution of these illegitimate births for which data are available.

FIG. 1.—Incidence of stillbirths with malformations of the central nervous system in Scotland, 1950-56, by social class and legitimacy.

The incidence of anencephalus in illegitimate births is considerably lower than considerations of class and parity might suggest. In Birmingham, Record and McKeown (1949) found eight illegitimate anencephalics against an expectation, without standardizing for parity, of 15.3. In spina bifida the few cases in illegitimate stillbirths are not suggestive of any influence of illegitimacy, and agree, in this, with the Birmingham data. In hydrocephalus there is a considerably higher incidence in illegitimate births than in legitimate births in the years 1950-1956. A comparison of the numbers of illegitimate stillbirths with those expected, if the incidence was the same as in legitimate births in Scotland from 1939-1949 (Table II), confirms that anencephalus is less common in illegitimate births; however the apparent increase in risk in hydrocephalus cannot be confirmed in these years.

TABLE II

THE NUMBER OF ILLEGITIMATE STILLBIRTHS WITH MALFORMATIONS OF THE CENTRAL NERVOUS SYSTEM COMPARED WITH THOSE EXPECTED WITHOUT STANDARDIZATION FOR PRIMIPARITY OR CLASS. SCOTLAND 1939-49.

Type of Malformation	Observed (a)	Expected (b)	Ratio a : b
Anencephalus ..	165	176	0.94
Spina Bifida ..	31	30.3	1.0
Hydrocephalus ..	101	104	0.97

PARITY

The form in which the Scottish data are presented limits any independent analysis by maternal age and parity. We may, however, obtain a fairly precise estimate of the relative liability in first births compared with second births, since the mean interval between these births is small, so that maternal age, like class, has in these conditions only a slight and conservative bias. The ratio of numbers of first born to second born in the affected (Table III), divided by that ratio in the control population, gives this relative liability (Table IV).

TABLE III

RATIO OF NUMBERS OF FIRST TO SECOND BIRTHS

Type of Malformation	Scotland (Stillbirths) 1950-1956	Birmingham*	Rhode Island†
Anencephalus ..	1.85	2.03	2.18
Spina Bifida ..	1.94	2.06	2.16
Hydrocephalus ..	1.82	1.38	2.43
Control ..	1.34	1.14	1.41

*Record and McKeown (1949).

†Ingalls, Pugh, and MacMahon (1954).

TABLE IV

RATIO OF NUMBERS OF FIRST TO SECOND BIRTHS IN AFFECTED DIVIDED BY RATIO IN CONTROL POPULATION

Type of Malformation	Scotland	Birmingham	Rhode Island
Anencephalus ..	1.38	1.8	1.5
Spina Bifida ..	1.45	1.8	1.5
Hydrocephalus ..	1.36	1.3	1.7

This ratio, being based on stillbirths, will also reflect any variation with parity in the proportion of malformed foetuses surviving birth. In anencephalus this proportion is too slight to lead to more than a slight exaggeration of this ratio, but in the case of spina bifida and hydrocephalus the increased hazards of first births and the larger proportion surviving might be expected to considerably exaggerate this ratio. Data collected in Birmingham and Rhode Island, which are based on both stillbirths and infant deaths, are therefore shown alongside the Scottish figures. The consistency of the three series suggests that no gross bias is introduced by restricting attention to stillbirths. In Scotland there is clear evidence in each condition of a relative increase in risk to the foetuses of primiparae of almost a half.

MATERNAL AGE

In anencephalus and hydrocephalus, but not in spina bifida, there is a U-shaped distribution of incidence with maternal age, the incidence falling until about 25 years, and then rising fairly steeply. The proportion of first births is, of course, much higher in young women, and, if we make the assumption that the relative increase in liability due to primogeniture is constant by age and class, we may eliminate this bias by weighting the controls to contain the appropriate excess of primiparae and the appropriate proportion of each social class. An examination of the Birmingham series showed that age did not appear to influence the primogeniture effect in anencephaly, spina bifida, or hydrocephalus.

The relative liabilities at each maternal age are given in Table V and Fig. 2 (opposite). Because of the small effects of standardizing for class, and the almost equal primogeniture effect in each condition, the standardization has not appreciably influenced the comparative effects of maternal age on the three conditions. Each shows a steeply rising trend with maternal age, the relative liability at age 40-44, compared with that at 20-24, being doubled in

TABLE V

RELATIVE INCIDENCE OF STILLBIRTHS BY CENTRAL NERVOUS MALFORMATION ACCORDING TO MATERNAL AGE, STANDARDIZED TO REMOVE VARIATION DUE TO SOCIAL CLASS AND PRIMIPARITY

Type of Malformation	Maternal Age (yrs)						
	Under 20	20—	25—	30—	35—	40—	45 and Over
Anencephalus	1.40	1.00	0.97	1.12	1.49	1.81	0.98
Spina Bifida	0.5	1.00	1.33	1.94	2.36	3.40	13.4
Hydrocephalus	1.47	1.00	1.22	1.67	2.02	2.27	4.37

Rates based on less than ten cases are shown in italics.

anencephalus and hydrocephalus and trebled in spina bifida.

However, it is not possible to distinguish between the contribution due primarily to maternal age and that consequent on parity; it is possible that the maternal age effect is largely due to the incidence increasing with parity, independently of social class and to the close association of maternal age and parity.

Since the data are restricted to stillbirths, and only about one-fifth of cases of spina bifida, and two-thirds of hydrocephalics, are stillborn, the increasing incidence with maternal age may to some extent reflect an increasing proportion of cases being stillborn at higher maternal ages. The trends are smooth, and it does not appear likely from the Figure that the relatively high rates of anencephalus and hydrocephalus in women under 20 are sampling effects. It may, however, be due to the primogeniture effect being more marked in very young women. Attempted abortion is unlikely to predispose to anencephalus very frequently as it is no commoner among illegitimate births. There is also direct evidence confirming this (Whitehouse and McKeown, 1956).

REGIONAL VARIATION

The incidence of each malformation shows distinct geographical variation (Table VI and Fig. 3, overleaf).

In each the range in incidence varies by a factor of at least two. In general, the incidence in the Lowlands exceeds that in the Highlands, but there is no particular association with the great industrial areas which show for each condition an incidence similar to that of the surrounding country. Direct inspection shows a greater concordance between spina bifida and anencephalus than between either

FIG. 2.—Relative liability to stillbirth from malformations of the central nervous system, by maternal age. Corrected for primiparity and class, but not for parity.

FIG. 3.—Incidence of malformations of the central nervous system in Scotland, 1950-56, per thousand births (see key to each diagram).

TABLE VI
INCIDENCE OF MALFORMATIONS OF THE CENTRAL NERVOUS SYSTEM BY REGION. SCOTLAND 1950-56

Region	Anencephalus (Stillbirths)	Spina Bifida (Stillbirths and Infant Deaths)	Hydrocephalus (Stillbirths)
Aberdeen Burgh			
Remainder Aberdeen Co.	1.62	0.90	0.72
Kincardine County			
Arbroath Burgh			
Dundee Burgh	2.81	1.76	1.26
Remainder Angus Co.			
Argyll County			
Inverness Burgh	1.44	0.92	1.10
Remainder Inverness			
Ayr Burgh			
Kilmarnock	2.90	1.92	1.32
Remainder Ayr Co.			
Banff County			
Moray County	2.55	1.77	1.49
Nairn County			
Berwick Co.			
East Lothian Co.	3.46	2.12	2.57
Caithness County			
Ross and Cromarty Co.	1.53	0.93	1.44
Sutherland Co.			
Clackmannan County			
Kinross County			1.42
Perth Burgh	2.63	1.92	
Remainder Perth Co.			
Dumfries Burgh			
Remainder Dumfries Co.	2.94	3.10	1.55
Kircudbright County			
Wigtown County			
Clydebank Burgh			2.44
Dumbarton Burgh			1.85
Remainder Dumbarton County			1.59
Dunfermline Burgh			
Kirkcaldy Burgh	2.73	1.75	1.84
Remainder Fife Co.			
Glasgow Burgh	3.01	1.81	1.37
Airdrie Burgh			
Coatbridge Burgh	3.10	2.17	2.01
Hamilton Burgh			
Motherwell and Wishaw Burgh	2.76	1.07	1.51
Rutherglen Burgh			
Remainder Lanark Co.	3.09	2.45	1.59
Edinburgh	2.69	1.41	1.06
Remainder Midlothian	3.81	1.59	1.39
Roxburgh County			
Peebles County	1.71	1.48	1.82
Selkirk County			
Paisley Burgh	2.21	2.13	1.56
Port of Glasgow Burgh	3.85	2.52	1.13
Greenock Burgh			
Remainder Renfrew Co.	2.44	1.56	1.00
Stirling Burgh			
Falkirk Burgh	2.53	2.16	1.47
Remainder Stirling Co.			
West Lothian County	3.27	1.92	1.36

Areas in heavy type represented by rectangles on maps (Fig. 3).
Figures in italics based on less than 25 cases.

of these and hydrocephalus, and this is confirmed by rank correlations for the 23 areas (Table VII).

TABLE VII

REGIONAL RANK CORRELATIONS BETWEEN INCIDENCES OF ANENCEPHALUS, SPINA BIFIDA, AND HYDROCEPHALUS

Malformation	Anencephalus	Spina Bifida	Hydrocephalus
Spina Bifida ..	+0.57		
Hydrocephalus..	+0.18	+0.40	
Post Neonatal Death Rate ..	+0.35	+0.37	+0.31

These positive correlations are to some extent due to the association between the incidence of each condition and social class; this probably explains the correlation with post-neonatal death rates.

It is convenient to explore urban/rural variations of incidence in the larger towns and smaller cities, as the two main cities, having large ports, are likely to be partly populated by seaborne immigration and not genetically comparable to their surrounding country. Analysis shows a considerable and consistent increase in risk of spina bifida attributable to urbanity, but no association between urbanity and anencephalus or hydrocephalus (Table VIII). The method of analysis is described in Appendix A.

LONG-TERM SECULAR TRENDS

The proportion of all births resulting in each of the three common malformations of the central nervous system varies considerably from year to year (Fig. 4, overleaf), and there appears to be little concordance between any pair (Table IX).

TABLE IX

RANK CORRELATIONS IN THE INCIDENCE OF MALFORMATIONS OF THE CENTRAL NERVOUS SYSTEM, 1939-56.

Anencephalus and Spina Bifida	..	..	..	..	+0.09
Anencephalus and Hydrocephalus	..	..	..	..	+0.24
Spina Bifida and Hydrocephalus	..	..	..	..	-0.18

It is remarkable that the war years show no special feature, and that, although improved social conditions have led to a great reduction in most other causes of stillbirth and neonatal death, these malformations which are much commoner in association with low social class, have shown no sustained decrease. Although there is no suggestion of any trend, there are considerable annual variations which are too great to be explained by varying parity distributions. In the case of spina bifida and hydrocephalus the small numbers of stillbirths do not allow any more detailed breakdown. In anencephalus, however, we may attempt to define some features of this extra-ordinary variation in terms of various subgroups.

TABLE VIII

COMPARISON OF URBAN AND RURAL INCIDENCE OF MALFORMATIONS OF THE CENTRAL NERVOUS SYSTEM

Regions		Anencephaly			Spina Bifida			Hydrocephalus		
Urban	Rural	Urban/Rural Ratio	Natural log of Ratio	<i>i</i>	Urban/Rural Ratio	Natural log of Ratio	<i>i</i>	Urban/Rural Ratio	Natural log of Ratio	<i>i</i>
Aberdeen Burgh	Remainder of Aberdeen County	1.14	+0.131	17.3	1.50	+0.405	8.3	0.83	-0.185	8.0
Dundee Burgh	Remainder of Angus County	1.18	+0.167	17.6	1.93	+0.657	8.4	0.72	0.324	10.0
Arbroath Burgh										
Ayr Burgh	Remainder of Ayr County	0.84	-0.174	21.6	1.68	+0.519	19.0	0.84	-0.171	10.0
Kilmarnock Burgh										
Dumfries Burgh	Remainder of Dumfries County	1.11	+0.110	6.6	1.98	+0.683	5.7	1.70	+0.531	4.4
Dunfermline Burgh	Remainder of Fife County	1.07	+0.068	23.3	1.12	+0.113	15.4	1.25	+0.223	6.9
Kircaldy Burgh										
Inverness Burgh	Inverness County	0.69	-0.371	11.5	2.59	+0.952	2.9	2.00	+0.693	4.7
Perth Burgh	Remainder of Perth County	1.11	+0.110	7.5	0.82	-0.198	6.2	0.55	-0.605	3.8
Falkirk Burgh	Remainder of Stirling County	0.87	-0.139	12.9	0.83	-0.186	1.1	0.78	-0.247	7.4
Stirling Burgh										
Weighted Mean ..	.. .. .	1.0	-0.013 ±	0.092	1.5	+0.390 ±	0.121	1.0	-0.018 ±	0.124

Numbers in italics are based on ratios involving less than ten observations.

FIG. 4.—Incidence of malformations of the central nervous system in Scotland, 1939 to 1956, per year, per thousand births.

FIG. 5.—Incidence of anencephalus in first and later births in Scotland, 1936 to 1956, per year, per thousand births.

If we consider the incidence in first and in all other birth ranks separately (Fig. 5), it is clear that the greater part of the variation is due to a varying incidence in first births, and that the incidence in these births appears to vary independently of that in later births, which it does not always exceed (Fig. 6).

FIG. 6.—Incidence of anencephalus in first and later births. Parallel lines represent approximate 95 per cent. range expected if the variation were entirely due to chance.

The recent rise and fall in incidence between 1950 and 1956 is almost entirely confined to first births. Unfortunately we cannot identify the first births by maternal age, place, season, or social class, and in attempting to invent the body of

any contingency table by inferences based in the margins it is all too easy, as in the tobacco-air pollution controversy, to make inferences which can be shown to be formally irrelevant to the data. The most economical explanation however, confirms the suggestion of MacMahon, Pugh, and Ingalls (1953) that the extra risk to first births may be considerably influenced by the environment of the mother. In addition it may be worth pointing out that in Social Class V the numbers of cases of anencephalus in 1950, 1951, and 1952 was 24, 39, and 49 respectively in an almost constant number of births.

In view of the known seasonal variation in anencephalus (McKeown and Record, 1951), we may also break down the secular pattern into winter and summer births, taking the last quarter of one year and the first quarter of the next as winter, and the middle quarters of the year as summer. Fig. 7 (overleaf) shows the winter and summer incidences separately.

Although of doubtful meaning except as comparative indices, it may be of interest to present the rank correlation coefficients between various incidences and ratios (Table X, overleaf).

Each coefficient has a standard error of sampling of about 0.25.

The variation in incidence in winter births is considerably greater than in summer births, the fluctuations of which hardly exceed those to be expected from chance. This suggests that the variations in incidence are largely due to some very variable influence acting on some pregnancies in the summer months. Attempts to associate these variations with notifiable diseases have not been successful. The absence of any association, of

FIG. 7.—Incidence of anencephalus in winter and summer in Scotland, 1939 to 1956, per year, per thousand births.

TABLE X	
RANK CORRELATIONS IN ANENCEPHALUS, 1939-56	
Male proportion and Winter*/Summer ratio	- 0.45
First born/Later born ratio and Winter*/Summer ratio	0.04
Male proportion and First born/Later born ratio .. .	0.24
Incidence in first births and Incidence in later births..	- 0.04
Summer incidence and Incidence in preceding winter†	+ 0.18
Summer incidence and Incidence in following winter†	+ 0.53
Mean summer temperature and Incidence in following winter†	- 0.05

*Winter defined as first and last quarters of same year.
†Winter defined as last and first quarters of successive years.

winter incidence with the mean temperature of the preceding summer is not suggestive of any direct climatic effect.

The fact that variations in incidence appear to be dominated both by first births and by winter births suggests that the influence of season is more marked on first births, as MacMahon and others (1953) have suggested with reference both to the data from Birmingham (McKeown and Record, 1951) and to their data from Rhode Island. However, if a harmonic curve is fitted to the data on first and other births in Birmingham, the

difference in seasonal variation is found to be very slight (± 28 per cent. for first born and ± 26 per cent. for later born). The seasonal swing in Birmingham was somewhat more marked than that in Scotland (± 15 per cent.). The method is described in Appendix B.

The sex ratio in anencephalus shows variation from year to year, and MacMahon and McKeown (1952) showed, at a formally significant level, that the proportion of males was considerably lower in first births than in later births. The negative rank correlations found between the proportion of first births and the proportion of males confirms this (Table X), but the rather larger negative correlation between the male proportion and the winter/summer ratio suggests, once again, that part of this variability is due to a varying risk to first pregnancies conceived in spring and summer. The rank correlation coefficient between the first born/later born ratio and the winter/summer ratio is close to zero: however, it has a large standard error (0.25), and it involves the unsatisfactory definition of winter as the first and last quarters of the same year.

Finally, we may present a comparison of the infant death rates for Scotland and for England

FIG. 8.—Infant deaths from spina bifida and hydrocephalus in Scotland and in England and Wales, 1939 to 1956, per thousand live births.

and Wales in the years 1939–1956 for spina bifida and hydrocephalus (Fig. 8). It is remarkable that while the variations in spina bifida were very similar, the variations in hydrocephalus appear to be almost independent, and with the exception of the three obvious outliers, which represent the years 1940, 1941, 1942, the figures for the remaining years appear quite unrelated. The incidence of infant death from hydrocephalus is about three times as high in Scotland as in England and Wales. It appears that the majority of cases of spina bifida are conditioned by some environmental agent varying concordantly on both sides of the border.

SEASONAL VARIATION

A pronounced seasonal variation in the incidence of anencephalus, the winter incidence being about a third as great again as the summer incidence, has already been demonstrated on the Scottish data in confirmation of a similar variation observed in Birmingham (McKeown and Record, 1951). Analysis of the data for Scotland since published shows an identical trend, and confirms the absence of any seasonal variation in incidence in spina bifida or hydrocephalus.

A more exacting analysis may be made by fitting a harmonic curve to the monthly incidence for

each year: in view of the nature of the variation it is appropriate to take the year starting in July and ending in June. The estimated parameters of the fitted curve of relative incidence for the years between July, 1939, and June, 1956, are shown in Fig. 9. The sector in which a point lies represents the month of maximum incidence, and its distance from the centre its seasonal fluctuation in percentage of the mean.

Fig. 9.—Intensity and direction of seasonal variation in anencephalus in Scotland in the period July, 1939, to June, 1956.

SHORT-TERM SECULAR TRENDS

We may examine the short-term distribution of cases with a view to detecting any tendency to "clumping". If any epidemic disorder predisposed to an appreciable proportion of malformations as in rubella and congenital blindness, cases would tend to occur in short bursts, although the combination of many small epidemics might conceal this. On the other hand, any sufficient determinant of a genetic nature, or a predisposition related to some constant environmental feature or to some endemic infection, would be expected to lead to a random distribution of cases in time. The seasonal variation in incidence of anencephalus is consistent with its being related to some epidemic commoner in the spring and summer months, but there is no notifiable disease with a seasonal distribution consistent with this. The principle of the analysis following may be evident if we consider a hypothetical example. Suppose we have data on the

number of cases of some malformation in some area with a constant number of births over a period of years. If we consider the mean and variance of the numbers per year, the expected values of the mean and variance would be equal if there were no association between individual cases, but, in the presence of any determinants of an epidemic nature, the expected value of the variance would exceed that of the mean.

The result of this test is not suggestive of any clumping of cases. Analysis of the space-time matrix for cases of anencephalus in the regions of Scotland over the 7-year period 1950–1956, ignoring the areas with very low frequencies, leads to the result $\chi^2 = 283$ for 282 degrees of freedom.

However, visual examination of the figures appears suggestive of erratic variation beyond chance expectation. In Banff, for example, the series:

2, 1, 1, 8, 1, 1, 0

occurs, and suggests that there might be an occasional predisposing infection in addition to a fairly constant basic incidence. A form of analysis more appropriate to occasional epidemic disturbances is to consider the extent by which the largest number of cases exceeds the average during the period of observation. We may make a provisional investigation on the raw figures, assuming a constant number of births per year. If we represent the series in ascending order

$n_1, n_2, \dots, n_r$

then, in the absence of any epidemic disturbance, the square roots of these numbers (or, for a more exact approximation, the transformation $\sqrt{n + \frac{3}{8}}$) will be distributed as random samples from a normally distributed population with variance $\frac{1}{4}$.

If we take x_m as $\sqrt{n_r}$, where n_r is the largest number, and $\bar{x}$ as $\frac{1}{r}(\sqrt{n_1} + \sqrt{n_2} + \dots + \sqrt{n_r})$, we may make use of tables of the distribution of the studentized extreme deviate (Nair, 1948), which gives the tails of the probability distribution

$$\frac{\bar{x} - x_m}{\sigma}$$

A use of this test shows no suggestion of clumping; out of 45 areas in which more than ten cases occurred, in only one area was the result highly significant (Banff) and only in one other area was it significant. Although we should be cautious in assuming the superiority of such tests over unaided judgment, it appears reasonable to suppose that any infectious non-endemic condition relative to the areas and times studied is unlikely to be a determinant of any considerable proportion of cases.

Similar analyses for spina bifida showed only one area to be significant, and for hydrocephalus, none. In each case, because of the smaller numbers, even greater caution is necessary in taking absence of statistical significance as evidence against any clumping.

DISCUSSION

We may first summarize, in diagrammatic form, the sources of variation in incidence considered above (Fig. 10). These must be regarded as based on the margins of a multidimensional contingency table. The extent to which such studies allow inferences to be made about the body of the table is questionable as there is no unique body for any set of marginal totals. Multiple regression methods are sometimes recommended in these situations but their use is only justifiable if sufficient is known to justify the extensive assumptions on which they are based.

In all three malformations, the influence of the environment is so great that it is reasonable to doubt whether the disorders are genetically determined except in the essentially trivial sense that in such a fragile situation as the developing embryo the initial composition of the zygote will obviously be of importance. The available data on these malformations do not allow any inference that they are genetically determined in the sense that not more than a small proportion could be prevented by changing the environment within the framework of its present variation.

While it is becoming usual to regard an unexplained disease with a familial incidence as genetically determined, such conventions as monogamy and non-communal feeding do not allow the inference that familial disorders are decided at conception. At the present time the evidence for genetic determinants of the major congenital malformations is considerably less than the evidence which could have been advanced 50 years ago purporting to show that rickets was genetically determined.

SOCIAL CLASS.—The most remarkable variations relate to social class. Environmental variations of this magnitude must be suspected as an adequate cause of the familial tendencies of these conditions in the absence of any other evidence of genetic predisposition. The very low incidence in wives of men whose occupation allows them the status of Social Class I, in conjunction with the considerable variation in the immediate and past environment

FIG. 10.—Summary of certain environmental influences of the relative liability of still-birth from malformations of the nervous system.

of such women, suggests that a group of women might be specified in relation to their environment who had very low risks of producing a malformed child and almost no risk of an anencephalic. The relatively high maternal age and the high proportion of first births typical of this class make the advantages this environment confers even more remarkable, and any genetic predisposition to these malformations appears to be of the same order of controllability as predispositions to rickets or obesity.

Coffey and Jessop (1957) have shown that in Dublin it is possible to define groups by such criteria as a low haemoglobin, a low plasma protein level, or an unemployed husband, in which the risk of an anencephalic birth exceeds 1 per cent. In Aberdeen, Anderson, Baird, and Thomson (1958) have shown on small numbers that anencephalus may be as common as this in short women of Social Class V.

The nature of this environmental influence is not clear. In view of the low incidence of anencephalus in France (Penrose, 1957) and the relatively high incidence in Rhode Island, U.S.A., some explanation other than generalized impairment in nutrition seems necessary. In Birmingham, an extremely detailed survey of the maternal environment in relation to work during pregnancy in six categories, occupation of husband by fourteen categories, and of rent by ten categories (Record and McKeown, 1949) was not suggestive of even the mildest association of these indices of class with malformation of the central nervous system taken together.

LEGITIMACY.—While the data are not suggestive of any considerable and consistent difference in risk in spina bifida or hydrocephalus, there is strongly suggestive evidence that anencephalus is relatively less frequent in illegitimate births particularly if allowance is made for class and parity. The interpretation of the relative hazards of illegitimacy is difficult; mothers of illegitimate babies include a majority of young primiparae spread among all social classes, and a minority of women whose age and parity status do not differ grossly from those of married women, and whose living conditions tend to be bad. The high proportion of primiparae of the former, and the poor circumstances of the latter, might be expected to lead to a high incidence of all three types of malformations. From these data it appears that ineffectual attempts at abortion could not be responsible for more than a very small proportion of C.N.S. abnormalities of the central nervous system.

PARITY.—The only safe inference which can be made from the Scottish data relate to the relative risk of primogeniture, and this is considerable in all three malformations. In anencephalus the various features of the secular trends in first and other births suggest that this increased risk in primogeniture may be in part due to a distinct condition, with a lower sex-ratio, to which spring and summer conceptions of primiparae are peculiarly but erratically predisposed. The data for spina bifida and hydrocephalus are too limited to allow any breakdown.

This primogeniture effect can only be interpreted as implying that the uterine environment in the few weeks after fertilization differs sufficiently between first and second pregnancies to reduce the risk of the zygote maturing with a malformation of the central nervous system by about one-third.

MATERNAL AGE.—In spina bifida and hydrocephalus, the considerable proportions surviving birth, and the probability that they are influenced by maternal age, prohibits any accurate assessment from data restricted to stillbirths of the increased risks associated with maternal age. While the increased hazards of birth with increasing maternal age must exaggerate these trends they can hardly be sufficient to explain them.

In anencephalus, although the infrequency of surviving birth makes this a trivial source of bias, it remains a possibility that, if the body of the age-parity table were known, the apparent influence of maternal age would merely reflect a parity effect.

The data for maternal age also give the sex of the stillbirth: an efficient test for trend was not suggestive of any tendency for the sex-ratio to be influenced by maternal age. In view of the sampling errors involved (if we assume a hypothetical infinite universe), this is not inconsistent with the lower proportion of males in firstborn anencephalics in Birmingham (MacMahon and McKeown, 1952).

REGIONAL VARIATION.—The way in which a study of the regional variations of congenital disorders may assist in understanding their aetiology is most easily considered by analysing the variations expected on certain assumptions.

First, in a disease the incidence of which varies if the same genotypic group is exposed to various environments, as in silicosis or typhoid, a study of those areas where the disease is very common and very rare may enable relevant differences in the environment to be inferred. In addition, high correlation between various groups of diseases, as

between chronic bronchitis and carcinoma of the stomach (Stocks, 1947), gives strong evidence that there are some environmental hazards common to both conditions.

Secondly, in a disease peculiarly common in certain genotypic groups, a study of the regional range may suggest some racial proclivity not completely blurred by intermarriage. For example, a subgroup of invaders, colonists, or immigrants may be peculiarly susceptible to some disorder, as Cypriots to thalassaemia, and areas of high incidence may merely reflect a disproportionate ancestry from these sources. While it is difficult to unravel the past, a variable and uncorrelated proportion of different disorders by area is inconsistent with any two of these disorders being strongly predisposed to as a result of the same genetically determined proclivity.

The regional pattern shows that an area with a high incidence of any one of the three major malformations of the central nervous system tends to have a high incidence of both the others, and that the association between anencephaly and spina bifida is particularly high. These associations reflect those found if the scale of the map is increased so that the single family becomes the unit (Penrose, 1946; Record and McKeown, 1950; MacMahon and others, 1953).

In neither case is it permissible to assume that these various deformities are end-results of similar initial disturbances, as they may result from independently acting agencies which are correlated. The independence of the secular variations in these conditions very strongly suggests that they are largely determined by distinct influences.

The only inferences which can be made from the regional data are that the very considerable variations in the incidence of malformations are to some extent correlated with circumstances predisposing to a high post-neonatal death rate and that in Scotland urbanity does not appreciably influence the incidence of anencephalus or hydrocephalus, but considerably and consistently increases the risk of spina bifida.

SECULAR VARIATION.—The main implications of the secular variation have been discussed above, and may be summarized briefly:

(1) There are considerable variations in annual incidence in all three conditions. These variations are almost independent. In anencephalus, in which the large numbers and high proportion of stillbirths allow a more detailed breakdown, a large part of this variability is due to first births and to

winter births: most of this variation could arise from a greatly varying risk to the spring and summer conceptions of nulliparous women.

(2) In anencephalus, but not in spina bifida or hydrocephalus, there is a seasonal trend, the mid-winter rate being about 30 per cent higher than the mid-summer rate.

(3) There is reason to doubt whether any of the three conditions are appreciably influenced by any infections of an epidemic nature. However, statistical methods based on large areas should not necessarily be regarded as superior to intuitive judgments on small areas. An epidemic is only relative to the deme, and a disease can be endemic on a county scale, but epidemic on a village scale. All that can be said of the Scottish data is that, if an infection is involved, it is not epidemic in relation to units of county, large town, or city size.

POSSIBLE ENVIRONMENTAL INFLUENCES.—Penrose (1957) suggested eight groups of environmental influences as most worthy of consideration in anencephalus, and this survey of the Scottish data may be concluded by considering these:

(1) *Infection.*—The absence of any pronounced tendency to clumping in the time sequence of cases of each malformation, and the absence of any seasonal trend in spina bifida and hydrocephalus, probably excludes epidemic infections as a major cause. Endemic infections cannot be excluded on these grounds. In anencephalus, in which the class gradient makes this explanation attractive, the seasonal trend of greatest risk for early summer conceptions seems an unlikely consequence of an endemic infection in Scotland.

An increased incidence of febrile infections early in pregnancy resulting in anencephalus has been recorded on retrospective inquiry by Coffey and Jessop (1957).

Prospective inquiries relating to pregnancies resulting in any malformation have also shown this (*Bull. Inst. nat. Hyg., Paris*, 1956; MacDonald, 1958). In view of the higher incidence of febrile illness in winter, the absence of any seasonal trend in spina bifida or hydrocephalus, and the relative immunity of winter conceptions to anencephalus, it seems possible that an increased incidence of infection may merely reflect the very poor and overcrowded environments which predispose to these abnormalities.

(2) *Malnutrition.*—This, if used to denote inadequate intake, seems an unlikely factor in Scotland since 1945. There has been no tendency

to a decreasing incidence of malformations of the central nervous system in the last 18 years and there is a very much higher incidence of anencephalus in Great Britain and in Rhode Island than in most of Europe. In addition the class differences are relatively slight between Social Classes III, IV, and V, but considerable between I, II, and III, in contrast with those to be expected from inadequate nutrition.

(3) *Chemical Poisons*.—These appear worthy of serious consideration, particularly in view of the increasing number of preservatives, dyes, and bleaches in common use, and the increasing contamination of foodstuffs with antibiotics, weed-killers, insecticides, and synthetic oestrogens. We may mention some of the more obvious possibilities.

Alcohol can probably be excluded as an important cause because of the nature of the social class gradient, and, in the case of anencephalus, the remarkably low incidence in Stockholm (0.6 per thousand), Paris (0.5 per thousand), and Lyons (0.1 per thousand) (Penrose, 1957).

Tobacco appears to be largely excluded as a major factor by the erratic secular variation. It is not, however, unreasonable to suspect a vaso-constrictor and oxytocic substance as a contributory cause.

Preservatives, Dyes, and "Improvers" in Foodstuffs, which are widely used with no recommendation other than that of being toxic to bacteria or colourful or producing a white frothy bread, are so widespread that, if any were to cause embryonic damage, it would be extremely difficult to detect. The recent history of carcinoma of the lung shows how easily a lethal habit can become adopted, and how, although at least 80 per cent. of cases could be prevented by not smoking, there are remarkable regional variations in incidence due to various interactions. It seems probable that the failure of a quantitative improvement in nutrition to reduce the incidence of foetal deformity is due to independently increasing environmental hazards. Among factory-produced foodstuffs with a class gradient in intake, may be mentioned the colouring matter in margarine, the large number of mixtures which are supplied as dehydrated cakes and pastries, and ice cream. An aversion to foods processed on an industrial scale and a relative conservatism towards some modern farming techniques are possible reasons for the relatively low incidence of anencephalus on the European continent compared with

that in such relatively well-fed regions as Great Britain and Rhode Island.

(4) *Hormones*.—The variation in hormone levels is hardly likely to vary so widely by place, time, or social class as the abnormalities of the central nervous system, and it is unlikely that this aspect of the uterine environment could explain more than a small fraction of the variation in incidence. Recently a hormone preparation which disturbs the empty uterus sufficiently to induce menstruation has been widely advertised as a method of diagnosing pregnancy. Although this has not been in use long enough to be relevant to the differences in the years up to 1956, it is the type of insult which is likely to cause foetal malformations, and would often be administered at a stage in pregnancy when it might initiate malformations of the central nervous system.

(5) *Mechanical Trauma in utero*.—Anencephalus and spina bifida are probably determined in the first few weeks of embryonic life. Attempted abortion is unlikely to be a predisposing cause in anencephalus which is less common among illegitimate births. The data on spina bifida are hardly adequate to assess any effects of illegitimacy, but there is nothing to suggest any considerable influence. In hydrocephalus the stage at which the abnormality usually becomes irreversible is unknown: while the available data for 1950–1956 are consistent with an appreciable proportion of hydrocephalics being consequent on attempted abortion, this interpretation is not supported by the more extensive data for the years 1939–1949. Mechanical effects from coitus in the first weeks of pregnancy are hardly likely as an important cause of an abnormality which is almost as common in illegitimate births, and in which the incidence increases with maternal age.

(6) *Radiation Trauma* from diagnostic procedures can clearly be ruled out as a common cause in view of the probable time of the foetal insult. Nevertheless it is of interest to note that, if an *ad hoc* inquiry based on a comparison of malformations of the central nervous system with a randomly ascertained collection of controls were made, the combined influences of primiparity, maternal age, and in the case of spina bifida, of urbanity, might conspire to produce a spurious association with pelvimetry. The association of a small pelvis with low social class might considerably increase the intensity of such an apparent association.

(7) *Foetal Anoxia* is capable of producing many malformations, including those of the central nervous system, in rodents. The common causes of relative maternal anoxia in man are flying in pressurized airliners, winter sports, and general anaesthesia, particularly when casually administered for minor operations. Flying and winter sports could hardly be related to more than a very small proportion of cases, even if they induced sufficient anoxia to be harmful. Anaesthesia in pregnancy is not uncommon because the free dental treatment of adults is restricted to expectant mothers; dental anaesthesia, though brief, is notoriously anoxic. Though this might initiate hydrocephalus and some other malformations, it is usually administered too late in pregnancy to influence the development of either anencephalus or spina bifida.

(8) *Climatic Anomalies* appear unlikely to have much influence. The incidence of anencephalus seems to be higher in the moderate climate of Scotland than in Scandinavia or central Europe. Spina bifida and hydrocephalus show no seasonal variation.

SUMMARY

The epidemiology of the common malformations of the central nervous system (anencephalus, spina bifida, and hydrocephalus) is discussed on the data of the Registrar General for Scotland.

It is concluded that:

(1) In all these conditions there is a marked association with social class.

(2) Anencephalus is relatively uncommon in illegitimate pregnancies: the incidence of spina bifida and hydrocephalus shows no consistent relationship to legitimacy.

(3) All three conditions are about 40 per cent. more common in first births than in second births.

(4) All three conditions become commoner with increasing maternal age. This may however merely reflect an association with parity. Anencephalus and hydrocephalus also appear relatively commoner in the pregnancies of women under 20 years of age.

(5) Each condition shows marked regional variation. Spina bifida, but not anencephalus or

hydrocephalus, is consistently and considerably predisposed to by urbanity.

(6) Each condition shows marked, but largely independent, year to year variations. In anencephalus these variations are largely due to the changing incidence in first births, and in winter births. In spina bifida, but not in hydrocephalus, the incidence in Scotland varies concordantly with that in England and Wales.

(7) There is a marked seasonal variation in the incidence of anencephalus but not of spina bifida or hydrocephalus, the peak incidence falling between late October and late February every winter from 1939–1940 to 1955–1956.

(8) There is no evidence of any tendency to “clumping” of cases. This implies that epidemic disorders do not make any important contribution to the incidence of these malformations.

(9) The marked environmental influences cast doubt on the necessity of advancing genetic causes to explain familial concentrations of cases.

(10) The fact that, although the malformations of the central nervous system are more common in less favourable social circumstances, their incidence has not declined during a period when nutrition has improved, suggests other environmental influences have become increasingly important.

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APPENDIX A

Suppose that we have data in the following form for several sets of towns and their surroundings:

	Town	Country
Anencephalic Births	a	b
All Other Births	c	d

Then the relevant estimator of the urbanity effect is of course

$$\frac{a}{a+c} \bigg/ \frac{b}{b+d}.$$

It is convenient to use the natural logarithm of this term which has the easily calculated sampling variance (Haldane, 1957):

$$\frac{1}{a} - \frac{1}{a+c} + \frac{1}{b} - \frac{1}{b+d}.$$

By weighting the estimate for each set by the inverse of its variance (i) we should obtain an efficient estimate of this urbanity factor if it were constant from area to area. The estimators:

$$\log_e \frac{a + \frac{1}{2}}{a + c + \frac{3}{2}} \bigg/ \frac{b + \frac{1}{2}}{b + d + \frac{3}{2}}, \text{ with variance}$$

$$\frac{1}{a+1} - \frac{1}{a+c+1} + \frac{1}{b+1} - \frac{1}{b+d+1},$$

have been used in Table VIII in an attempt to reduce bias.

Because of variations from place to place, the direct estimation of the incidence in groups of towns, and of their surroundings, would be fallacious.

APPENDIX B

In the case of the simple harmonic cyclic trend

$$1 + \alpha \sin(\theta + \varphi)$$

where θ specifies the time of the year, and φ the time of the year of maximum incidence, a simple, approximate, but very efficient method of estimating α and φ , when α is small, is to take the square root of the number of cases arising each month and to take moments about the centre; to a very close approximation we may take θ as 15° , 45° , 75° , etc., for Jan., Feb., March, etc., and assume a constant number of births per month.

It will be shown elsewhere that, given the numbers of events per months as $n_1, n_2, n_3 \dots n_{12}$, and taking $\theta_1, \theta_2, \theta_3$ as $15^\circ, 45^\circ, 75^\circ$, etc., then

$$N = \sum_{1}^{12} n_i$$

$$W = \sum_{1}^{12} \sqrt{n_i}$$

$$S = \sum_{1}^{12} \sqrt{n_i} \cdot \sin \theta_i$$

$$C = \sum_{1}^{12} \sqrt{n_i} \cdot \cos \theta_i$$

$$d = \frac{\sqrt{S^2 + C^2}}{W}, \quad \alpha \simeq 4d$$

$$\varphi \simeq \tan^{-1} \frac{S}{C}$$