A STUDY OF 137 CASES OF ANENCEPHALY

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In a survey of congenital defects in Dublin (Coffey and Jessop, 1955), it was noted that the predominant abnormality was anencephaly, which accounted for 29·5 per cent. of all major abnormal births. It also appeared that there were certain peculiarities regarding the distribution of this abnormality in the city. It was felt, therefore, that a more detailed inquiry into this condition would be of interest.

The present report is based on births which occurred between March 1, 1953, and April 30, 1955, in the three Dublin Maternity Hospitals (the Rotunda Hospital, the National Maternity Hospital, and the Coombe Hospital) which deal with 80 per cent. of the births in Dublin and the neighbourhood. In the period March 1, 1953, to May 1, 1954, the cases were those already included in the general survey of congenital defects. In the period May 1, 1954, to April 30, 1955, the cases were solely those obtained in the anencephaly study.

METHODS

The occurrence of a case of anencephaly was notified to the authors, usually within 24 hours of the birth. The mother was interviewed as soon as possible after this, using the same questionnaire as that employed in the previous survey.

At the time of the interview, the mother knew that the baby was dead but did not usually know the cause of death, and in completing the questionnaire no information was given to her about the baby's condition. It was felt that if she knew that the baby had been abnormal she might make a special effort to recall instances of other abnormal births in her family, and that consequently an error might be introduced in comparing the information given by her with that obtained for the controls.

A control group of 192 normal cases was taken at random from the same hospitals. When the mother of the abnormal baby had been interviewed, the Ward Sister was asked to indicate the mother in the same puerperal ward who had been delivered of the next normal (but not necessarily live born) baby, and this mother was then questioned. All the normal births included in the initial study of congenital deformities were retained, so that the control group is larger than the anencephaly group.

When the abnormal baby had been born prematurely, the mother was sometimes well enough to be discharged within 48 hours of delivery and before she had been interviewed. In such cases the author who visited the hospital obtained the available details from the hospital records and interviewed the mother of the control.

Haemoglobin was estimated by the acid haematin method, the "normal" being taken as 14·0 g. per 100 ml. Serum protein was estimated by the specific gravity method described by Phillips, Van Slyke, Dole, Emerson, Hamilton, and Archibald (1943). The Wasserman reaction was examined in every case.

RESULTS

INCIDENCE.—The total number of births recorded in the three Maternity Hospitals during the period March 1, 1953, to April 30, 1955, was 23,085. The distribution and incidence of anencephalics is shown in Table I.

TABLE I

INCIDENCE OF ANENCEPHALY IN DUBLIN MATERNITY HOSPITALS, 1953–55

Hospital	Total Births	Anencephalic Births	Incidence (per 1,000)
Rotunda	8,978	42	4·7
National Maternity ..	9,436	55	5·9
Coombe	4,671	40	8·6
Total	23,085	137	5·9

Difference between incidence in (a) Rotunda and National Maternity Hospitals taken together, and (b) Coombe Hospital = 2·64 × standard error (0·125); $P < 0.008$.

The figures support our earlier observations that the incidence is higher in Dublin than any so far reported from other centres, and that it is higher in one hospital (the Coombe) than in either of the other two.

SEX, CONDITION, AND STATE OF DEVELOPMENT OF FOETUS AND DURATION OF PREGNANCY.—In one case the sex was not recorded. There were 26 males and 110 females in the remaining 136, a ratio of 1 : 4·2.

Only 31 infants (22·6 per cent.) were born alive. Of the remainder some had clearly died at or shortly before birth and some had been dead long enough to show varying degrees of maceration. A number of foetuses which did not show obvious maceration were thought to have died perhaps a week or 10 days before delivery. The distribution of the cases according to the condition at birth and the state of development is shown in Table II. In order to allow for the weight of the brain, 10 per cent. was added to the observed weight of the foetus. Only fourteen foetuses (11·1 per cent.) weighed 2,500 g., the weight conventionally accepted as indicating maturity. The preponderance of females is less marked in this group, (nine females to five males) and it is entirely absent in those born alive or recently dead which weighed 2,000 g. and over.

TABLE II

SEX, CONDITION, AND STATE OF DEVELOPMENT OF ANENCEPHALICS

Weight* (g.)	Number Born Alive or recently Dead		Number Macerated or Otherwise presumed Dead for Some Time Before Birth		Total
	Male	Female	Male	Female	
Under 1,250 ..	2	8	5	19	34
1,250–1,999 ..	1	19	6	28	54
2,000–2,499 ..	3	2	1	18	24
2,500 and Over	4	5	1	4	14
Total ..	10	34	13	69	126
Not Recorded					11

*10 per cent. of the observed weight has been added to allow for the weight of the brain.

Duration of pregnancy (reckoned from the date of onset of the last menstrual period) is shown in Table III. Fifty-two (38·2 per cent.) could be regarded as mature if a gestation of at least 37 weeks is accepted as the criterion of maturity. The preponderance of females is least in the most mature groups of those born alive or only recently dead, the male : female ratio being 5 : 8 at 40 weeks and over.

TABLE III

DISTRIBUTION OF ANENCEPHALICS ACCORDING TO DURATION OF PREGNANCY

Duration of Pregnancy (wks)	Number Born Alive or recently Dead		Number Macerated or Otherwise presumed Dead for Some Time before Birth		Total
	Male	Female	Male	Female	
Under 28 ..	–	4	1	10	15
29–36	6	16	10	37	69
37–39	1	7	1	13	22
40 and Over ..	5	8	2	15	30
Total ..	12	35	14	75	136
Not Recorded					1

Two of the anencephalics were twins and in each case the other twin was normal. One pair consisted of two males and the other of an anencephalic male and a normal female.

OTHER CONGENITAL ABNORMALITIES.—Twelve of the 137 anencephalics had an associated defect of the central nervous system, ten of them being cases of spina bifida and two of meningocoele. There were also four cases of exomphalus and two of talipes. During the earlier part of the study, such particulars were sometimes obtained from the clinical notes rather than from direct examination of the foetus and it is possible that some associated deformities were not recorded.

AGE AND CIVIL STATUS OF MOTHER.—The difference between the age distribution of the mothers who gave birth to anencephalic children and that of the controls is shown in Table IV.

TABLE IV

INCIDENCE OF ANENCEPHALICS ACCORDING TO MATERNAL AGE

Maternal Age (yrs)	Affected		Controls		Ratio of Percentage of Affected to Controls
	No.	Per cent.	No.	Per cent.	
Under 20 ..	3	2·2	8	4·2	0·52
20–24 ..	17	12·4	37	19·4	0·64
25–29 ..	27	19·7	70	36·6	0·54
30–34 ..	44	32·1	38	19·9	1·61
35–39 ..	33	24·1	26	13·6	1·77
40–44 ..	13	9·5	11	5·7	1·67
45 and Over ..	—	—	1	0·6	—
Total ..	137		191*		

*One not recorded
$\chi^2 = 22·2$ for $n = 5$; $P < 0·005$

The incidence of anencephalic births is significantly higher in mothers over 30 years of age.

Two (2·2 per cent.) of the mothers of anencephalics were unmarried as compared with five (2·6 per cent.) of the mothers of controls.

PARITY.—The distribution of affected foetuses and controls according to parity is indicated in Table V.

TABLE V

INCIDENCE OF ANENCEPHALICS ACCORDING TO PARITY

Parity	Affected		Controls		Ratio of Percentage of Affected to Controls
	No.	Per cent.	No.	Per cent.	
1	31	22·6	55	28·6	0·79
2	17	12·4	47	24·5	0·51
3	23	16·8	24	12·5	1·34
4	17	12·4	25	13·0	0·95
5	12	8·8	13	6·8	1·29
6	13	9·5	8	4·2	2·26
7	12	8·8	3	1·6	} 1·68
8	—		5	2·6	
9	3	2·2	4	2·1	
10 and Over	9	6·5	8	4·1	
Total ..	137		192		

$$\chi^2 = 15\cdot3 \text{ for } n = 6; P < 0\cdot025$$

Of the mothers who gave birth to anencephalic children 22·6 per cent. were primiparae as compared with 28·6 per cent. of the mothers of controls. This difference is of doubtful significance. When age is taken into account (Tables VI and VII), the association of anencephaly with multiparity is not significant.

TABLE VI

DISTRIBUTION OF ANENCEPHALICS ACCORDING TO MATERNAL AGE AND PARITY

Parity	Maternal Age (yrs)						Total
	Under 20	20–24	25–29	30–34	35–39	40–44	
1	3	8	12	7	1	—	31
2	—	5	6	4	2	—	17
3	—	4	4	7	4	4	23
4	—	—	2	4	8	3	17
5	—	—	1	6	4	1	12
6	—	—	2	6	4	1	13
7	—	—	—	7	4	1	12
8	—	—	—	—	—	—	—
9	—	—	—	2	1	—	3
10 and Over	—	—	—	1	5	3	9
Total	3	17	27	44	33	13	137

TABLE VII

INCIDENCE OF ANENCEPHALICS ACCORDING TO PARITY WITH ADJUSTMENT FOR MATERNAL AGE

Parity	No. Affected		No. of Controls
	Actual	Adjusted for Effect of Age*	
1	31	45·5	55
2	17	22·6	47
3	23	22·8	24
4	17	12·7	25
5	12	8·6	13
6	13	10·4	8
7 and Over	24	14·4	20

$$\chi^2 = 6\cdot60 \text{ for } n = 6; P = 0\cdot50$$

* Parity distribution in this column calculated by using the age-parity relationship in Table II and taking the age distribution of the controls as a standard.

RELATION OF ANENCEPHALY TO BLOOD GROUP OF MOTHER.—The distribution of mothers according to blood groups is shown in Table VIII.

TABLE VIII

INCIDENCE OF ANENCEPHALICS ACCORDING TO BLOOD GROUP OF MOTHER

Maternal Blood Group	Mothers of Affected		Mothers of Controls	
	Number	Per cent.	Number	Per cent.
O	78	67·8	105	55·0
A	33	28·7	56	29·3
B	4	3·5	26	13·6
AB	—	0·0	4	2·1
Total	115	100	191	100
Not Recorded	22		1	

When Groups B and AB are taken together
$$\chi^2 = 11\cdot7 \text{ for } n = 2; P < 0\cdot005$$

68 per cent. of the 115 mothers of anencephalics whose blood was tested belonged to Group O. This is significantly higher than the figure for the mothers of controls (55 per cent.), which approximates closely to the estimate of 54 per cent. made by Dawson (1952) for the whole Dublin population. Of the seven mothers to whom a previous anencephalic infant had been born, five were members of Group O. We have no data on the blood group of either the father or the foetus.

NUTRITIONAL STATE OF THE MOTHER.—This was assessed clinically and by estimating the haemoglobin and plasma protein. (Tables IX and X, and Table XI, opposite.)

TABLE IX

INCIDENCE OF ANENCEPHALICS ACCORDING TO NUTRITIONAL STATE OF MOTHERS

Clinical Assessment of Mother's Nutritional State	Mothers of Affected		Mothers of Controls	
	Number	Per cent.	Number	Per cent.
Good	61	58·1	123	64·1
Fair	36	34·3	59	30·7
Poor	8	7·6	10	5·2
Total	105	100	192	100
Not Recorded ..	32			

$$\chi^2 = 1\cdot30 \text{ for } n = 2; P < 0\cdot55$$

TABLE X

INCIDENCE OF ANENCEPHALICS ACCORDING TO MATERNAL HAEMOGLOBIN

Haemoglobin (per cent.)	Mothers of Affected		Mothers of Controls	
	Number	Per cent.	Number	Per cent.
Under 70 ..	38	35·5	47	24·5
70 and Over ..	69	64·5	145	75·5
Total	107	100	192	100
Not Recorded ..	30			

$$\chi^2 = 4\cdot11 \text{ for } n = 1; P < 0\cdot05$$

TABLE XI

INCIDENCE OF ANENCEPHALICS ACCORDING TO
MATERNAL PLASMA PROTEIN

Plasma Protein (g. per 100 ml.)	Mothers of Affected		Mothers of Controls	
	Number	Per cent.	Number	Per cent.
Under 5·5	42	43·8	54	28·4
5·5 and Over ..	54	56·2	136	71·6
Total	96	100	190	100
Not Recorded ..	41		2	

$$\chi^2 = 6·72 \text{ for } n = 1; P < 0·01$$

The levels of haemoglobin and plasma protein show significant differences between the mothers of anencephalics and the mothers of controls. The clinical assessment shows a similar trend, but the difference is not significant.

VOMITING DURING PREGNANCY.—The incidence of excessive vomiting was more than three times as frequent in the mothers of anencephalics as in the mothers of controls (Table XII).

TABLE XII

FREQUENCY OF VOMITING DURING PREGNANCY

History of Vomiting	Mothers of Affected		Mothers of Controls	
	Number	Per cent.	Number	Per cent.
Nil	39	37·5	96	50·0
"Normal"	34	32·7	79	41·1
Excessive	31	29·8	17	8·9
Total	104	100	192	100
Not Recorded ..	33			

There is no significant difference between the two groups in the frequency of vomiting during the earlier months, but there is a marked difference in the later months (Table XIII).

TABLE XIII

TIME OF ONSET OF EXCESSIVE VOMITING DURING
PREGNANCY

Time of Onset of Excessive Vomiting	Number of Mothers of	
	Affected	Controls
Up to 3rd Month	12	12
3rd, 4th, and 5th Months ..	7	1
6th Month and Later	12*	4

*Two cases had vomiting in both early and later pregnancy

This suggests either that the vomiting was the result rather than the cause of the abnormality, or that both abnormality and vomiting were due to some common factor. In about one-third of the cases of severe vomiting after the third month the disturbance lasted less than four weeks. Information was not obtained about the occurrence of vomiting in previous pregnancies.

ILLNESSES DURING PREGNANCY.—Each mother was questioned carefully about her general health during pregnancy, particular attention being paid to virus infections, including "influenza". Since laboratory confirmation was not available this latter term was used in the popular sense and probably embraced a number of types of severe upper respiratory tract infections.

A high proportion (about 80 per cent.) of the mothers had had no illness during pregnancy and this proportion was almost the same in the mothers of anencephalics and in mothers of controls. The Wasserman reaction was negative in all cases. Amongst the mothers who had suffered from illnesses, the incidence was the same in both groups, approximately one illness per mother. However, in the mothers of anencephalics, the illnesses had occurred predominantly in the first 3 months, while in the control group they had occurred generally at a later period. Of 28 mothers who gave a history of illness during the first 3 months of pregnancy, 21 were mothers of anencephalics and seven were mothers of controls. No mother gave a history of rubella during pregnancy.

PREVIOUS CONGENITAL ABNORMALITIES.—There were 98 multiparae in the anencephalic series who were interrogated, of whom 26 had previously given birth to a congenitally abnormal baby, seven of them to an anencephalic foetus. In one of the latter the present pregnancy had been the seventh and the mother had had two previous anencephalics, her fourth and sixth babies. Her other four children were normal. The control series contained 137 multiparae, nine of whom had had a malformed child. None of the mothers of controls had ever given birth to an anencephalic.

PREVIOUS OBSTETRIC HISTORY.—Of the 98 multiparae for whom data were available, 52 per cent. gave a history of miscarriages, abortions, or stillbirths, as compared with 28 per cent. of the mothers of controls. A small part of this difference, and of the difference mentioned in the preceding paragraph, can be explained by the fact that the mothers of anencephalics had had, on the whole, more pregnancies than the mothers of controls.

PREVIOUS MEDICAL HISTORY.—A careful clinical history was taken from each mother, but nothing of any significance was elicited; nor was there any significant difference between mothers of anencephalics and the mothers of controls in the proportion who had a satisfactory level of health.

TABLE XIV

CONGENITAL ABNORMALITIES IN MOTHER'S AND FATHER'S FAMILY

Affected Relative	Mothers				Fathers			
	Of Affected		Of Controls		Of Affected		Of Controls	
	Number	Per cent.	Number	Per cent.	Number	Per cent.	Number	Per cent.
None	86	82·7	184	96·8	96	92·3	180	97·3
Brother or Sister	8	7·7	5	2·6	5	4·8	4	2·2
Father, Mother, Uncle, or Aunt	5	4·8	—	—	1	1·0	1	0·5
Cousin	5	4·8	1	0·5	2	1·9	—	—
Total	104	100	190	100	104	100	185	100
Not Recorded	33		2		33		7	

$\chi^2 = 17·9$ for $n = 1$; $P < 0·005$ $\chi^2 = 3·8$ for $n = 1$; $P = 0·05$

FAMILY HISTORY OF CONGENITAL ABNORMALITIES.
—The frequency of a family history of congenital abnormalities on the maternal and paternal sides is indicated in Table XIV. The information was given by the mother and is, therefore, limited to abnormalities that were obvious on inspection.

The proportion in which there was no history of an abnormal relative was smaller in the anencephalic series than in the control series, on both the mother's and the father's side.

Abortions and miscarriages were not included, since it was felt that information was not likely to be reliable. One case, however, was of such interest that a special inquiry was made. The mother was one of a pair of twins which she believed to be identical. Before her present pregnancy she had had two abortions and two abnormal babies, one hydrocephalic and one anencephalic. The present was her fifth pregnancy and had resulted in a second anencephalic. Her twin sister had had four full-term children and three miscarriages about which no further information was available. In twelve pregnancies, these twin sisters had produced three abnormal babies, five abortions or miscarriages, and four normal children.

No case was noted in which the father was one of twins.

RELATION OF ANENCEPHALY TO OCCUPATION OF PARENTS.—The occupation of the parents was used as a rough indication of their social class and possibly of their nutritional state (Tables XV and XVI). The finding of greatest interest is that nearly 10 per cent. of the fathers of anencephalics were unemployed whereas none of the fathers in the control series was out of work. The mothers of the two series show no obvious differences.

TABLE XV

INCIDENCE OF ANENCEPHALICS ACCORDING TO FATHER'S OCCUPATION

Father's Occupation	Fathers of Affected		Fathers of Controls	
	Number	Per cent.	Number	Per cent.
Manual (regular) ..	81	66·4	133	71·5
Manual (casual) ..	4	3·3	23	12·4
Non-Manual	25	20·6	30	16·1
Unemployed ..	12	9·7	—	—
Total	122	100	186	100
Not Recorded ..	15		6	

TABLE XVI

INCIDENCE OF ANENCEPHALICS ACCORDING TO MOTHER'S OCCUPATION

Mother's Occupation	Mothers of Affected		Mothers of Controls	
	Number	Per cent.	Number	Per cent.
Housewife	18	17·8	29	15·2
Manual	58	57·4	114	59·7
Non-Manual ..	25	24·8	48	25·1
Total	101	100	191	100
Not Recorded ..	36		1	

DISCUSSION

The incidence of anencephaly recorded in this survey (5·9 per 1,000) is higher than any so far reported. Previous workers have found incidences per 1,000 varying from 0.64 (Böök and Rayner, 1950) to 3·15 (Malpas, 1937). In our material, the incidence in one hospital reached 8·6.

The preponderance of females has been noted by all the workers who have studied this problem (*e.g.* Malpas, 1937; Angevine, 1938; Penrose, 1946; Record and McKeown, 1949; Böök and Rayner, 1950; Carter, 1950), but no satisfactory explanation has yet been put forward. All workers also agree

that a high proportion of anencephalics are born prematurely. It has been noted that the proportion of males increases with increasing length of gestation (MacMahon and McKeown, 1952) and the same trend can be demonstrated in the data of Böök and Rayner (1950) and in the results of the present investigation.

The findings in this paper agree also with those of other workers in suggesting a familial element in the incidence of anencephaly. Difficulties in interpretation arise from the fact that information is not available at present about the composition of complete families in which an anencephalic birth has occurred. The suggestion of Böök and Rayner (1950) that anencephaly could be caused by a recessive "anencephalic" gene would require an excessively high mutation rate. Neither in our material nor in that reported by others could any definite conclusion be drawn regarding the association with consanguinity.

Of special interest in relation to familial incidence is the occurrence of a high incidence of abortions and malformations in the families of two sisters who were identical twins. No record of a similar case has been found in the literature of anencephaly.

Several studies have been published on the association of anencephaly with maternal age and parity. Malpas (1937) and Penrose (1946) concluded that the incidence of anencephaly was greater in the older age groups, but Record and McKeown (1949), Carter (1950), and Böök and Rayner (1950) considered that maternal age had little or no bearing in incidence. Our findings indicate a sharp increase in incidence at maternal ages over 30. The effect of parity is less clear because of its correlation with maternal age. Record and McKeown (1949) found that anencephaly was more likely to occur in first births and in births from the sixth onwards, and Ingalls, Pugh and MacMahon (1954) are in general agreement with this. On the other hand, Böök and Rayner (1950) concluded that anencephaly was distributed at random through the different birth ranks. In our material, when allowance has been made for maternal age, the association between anencephaly and parity is not significant. The higher incidence of primiparae among our control mothers in a hospital population may explain the discrepancy between our results and those of Record and McKeown (1949).

The fact that the patients in our series were interviewed made it possible to obtain information that would not have been available from hospital or other records, and since this interview took place shortly after the birth, the information is the more likely to be reliable. It is noteworthy that the occurrence of illness during the first 3 months of pregnancy was much more frequent in the mothers of anencephalics than in the control group, even though no particular illness seemed to be of special importance.

Since we were able to support a clinical assessment with objective tests, the results bearing on nutritional state are of interest. There would seem to be a definite association between anencephaly and defective nutrition. Of the other workers who have considered this question, or the related question of the association of severe congenital defects with social class, only Walker (1954) noted a similar tendency. The relation of nutrition to the occurrence of congenital deformities has been reviewed by Hogan (1953).

Evidence of nutritional defects in our series was to some extent unexpected because of a previous finding (Irish National Nutrition Survey, 1948; Jessop, 1950) that the average intake of most nutrients was high in the great majority of the population. However, in the lower income groups in Dublin and other towns, the average intake according to the Survey was below the recommended allowance in the case of calcium, vitamin A, riboflavin, and vitamin C. Furthermore, the finding of a satisfactory average intake in a group of people is no guarantee that all members of the group are adequately nourished.

Moreover, it must be remembered that malnutrition is only one aspect of a general low standard of living. The incidence in one of the hospitals from which our material was derived was very much higher than in either of the other two hospitals. This hospital is situated in a very poor part of the city and its patients come partly from the surrounding area and partly from a new housing estate in which most of the inhabitants are carrying the heavy burden of furnishing a house in addition to bringing up a young family. This peculiarity of distribution requires further investigation and a direct inquiry into the relation of living conditions to the occurrence of anencephaly in Dublin has been planned.

SUMMARY

(1) The results of a study of 137 cases of anencephaly that occurred in three Dublin maternity hospitals between March 1, 1953, and April 30, 1955, are presented. Information about familial and environmental factors was obtained from the mothers at the time of the birth, and the results were compared with those of a control group.

(2) The incidence (per 1,000 hospital births) was 5·9; in one of the three hospitals it was 8·6. The

ratio of males to females was 1 : 4·2. The preponderance of females was less in the more mature groups and was absent in those born alive or recently dead and weighing 2,000 g. or more. A high proportion of foetuses were immature, judged either by weight or by period of gestation.

(3) Other congenital deformities were present in about 13 per cent. of anencephalics; the majority involved the central nervous system.

(4) The incidence of anencephaly was significantly higher in the babies of mothers over 30 years of age. Allowing for the influence of maternal age, differences between affected and controls in relation to parity were not significant.

(5) The proportion of mothers of blood group O was significantly higher for anencephalics than for controls or for the general population.

(6) The mothers of anencephalics had significantly lower haemoglobin and plasma protein levels than the controls. There was also some indication that the state of nutrition assessed clinically was lower in the mothers of anencephalics, and 10 per cent. of the husbands of these women were unemployed.

(7) Excessive vomiting during pregnancy did not appear to bear any clear relation to anencephaly, but there was some evidence that mothers of anencephalics experienced more illness during the first 3 months of pregnancy than the mothers of the controls.

(8) The incidence of congenital deformities in previous births to mothers of anencephalics was four times higher than in those to mothers of controls; the incidence of abortions and miscarriages was almost double.

(9) Congenital abnormalities had occurred more frequently in the families of the fathers and mothers of anencephalics than in those of the parents of the controls.

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