ANENCEPHALUS, SPINA BIFIDA, AND HYDROCEPHALUS INCIDENCE RELATED TO SEX, RACE, AND SEASON OF BIRTH, AND INCIDENCE IN SIBLINGS*

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For the congenital malformations, as for many other non-communicable diseases and defects, the collection of epidemiological knowledge based on statistical procedures is just beginning. A comprehensive investigation of the incidence of malformations of the central nervous system in Birmingham, England, and the relationship of these malformations to certain epidemiological variables, has recently been reported by Record and McKeown (1949; 1950a,b; 1951) and McKeown and Record (1951). With the object of determining the applicability of these authors' results to areas other than England and Wales, a somewhat similar, retrospective investigation was undertaken in Rhode Island, U.S.A. This communication describes the findings of this investigation, with the exception of data relevant to the association with maternal age and parity, which is reported separately (Ingalls, Pugh, and MacMahon, 1953).

MATERIAL

The study is concerned with all cases of anencephalus, spina bifida, encephalocele, and hydrocephalus born in the five largest maternity units in the state of Rhode Island during the years 1936-52. For the years 1936-49 births in these hospitals constituted 67 per cent. of all births in the state. For the years 1950-52, the 1949 level of 74.4 per cent. was almost certainly maintained, but vital statistics are not yet available.

Information about the total population of births was obtained from monthly hospital reports and from a sample group assembled by taking every hundredth name

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from the delivery-room registers of the same hospitals. The registers list chronologically all births occurring in the hospital. For a fuller description of the comparison group, the reader is referred to the discussion of maternal age and birth rank (Ingalls and others, 1953).

INCIDENCE

The incidence for the three main diagnostic groups in 4-yearly periods is given in Table I. Anencephalus with spina bifida is included with "anencephalus", and spina bifida with hydrocephalus and also encephalocele is grouped under "spina bifida". The first grouping is adopted since, while no note may be made of the presence of spina bifida in an anencephalic baby, it seems less likely that a baby with both anencephalus and spina bifida will be diagnosed as spina bifida. It may well be that the incidence of spina bifida in patients with anencephalus is higher than that here recorded. Spina bifida with hydrocephalus is classified with spina bifida, since many subjects who will develop head enlargement do not exhibit it at birth. The diagnostic data recorded failed to distinguish clearly between encephalocele and cervical meningocele. Very few of these subjects underwent *post-mortem* examination.

For the group as a whole, incidence was highest in the period 1940-43 and lowest in the years 1948-52. Although the highest incidence for anencephalus and hydrocephalus occurred in the years 1944-47, as against 1940-43 for spina bifida, incidence is lowest in 1948-52 for each of the three malformation groups.

TABLE I
INCIDENCE (PER 1,000 TOTAL BIRTHS) OF CENTRAL NERVOUS MALFORMATIONS IN FIVE RHODE ISLAND
MATERNITY UNITS

Years	Total Number of Births	Incidence and Numbers of Malformations							
		Anencephalus		Spina Bifida		Hydrocephalus		Total	
		Number	Per mille	Number	Per mille	Number	Per mille	Number	Per mille
1936-39	32,375	47	2.01	59	2.52	22	0.94	128	5.47
1940-43	33,139	71	2.14	120	3.62	30	0.91	221	6.67
1944-47	47,030	107	2.28	116	2.47	52	1.11	275	5.85
1948-52	65,110	101	1.55	131	2.01	48	0.74	280	4.30
1936-52	168,654	326	1.93	426	2.53	152	0.90	904	5.36

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The Figure shows the data by single years, and demonstrates a more or less consistent decline from 1942, the peak year, to 1952. Remarkably similar data were presented for these same malformations in England by MacMahon, Record, and McKeown (1951). Minor differences between the trends noted in England and in Rhode Island include: an earlier peak of incidence in England (1940-41 as against 1942-43), a somewhat sharper fall in incidence in the British material, and absence of decline in incidence of hydrocephalus in Birmingham.

Figure.—Incidence of malformations of the central nervous system in Providence, Rhode Island, 1936-52.

SEX RATIO.—Sex ratios of individual malformations are given in Table II, which exhibits the well-established predominance of females in anencephalus and spina bifida and of males in hydrocephalus.

TABLE II
SEX RATIO

Malformation	Sex			Total	Sex Ratio (Per cent. Male)
	Male	Female	Not Determined		
Anencephalus ..	69	159	2	230	30.3
Anencephalus with Spina Bifida	29	64	3	96	31.2
Spina Bifida ..	106	117	5	228	47.5
Spina Bifida with Hydrocephalus	69	91	—	160	43.1
Encephalocele ..	19	19	—	38	50.0
Hydrocephalus ..	83	68	1	152	55.0
Total	375	518	11	904	42.0

For anencephalus (including anencephalus with spina bifida) certain peculiarities of the sex ratio

noted by McKeown and Lowe (1951) and MacMahon and McKeown (1952) are also found in the present series (Table III). Sex ratio is low in first births and at short gestations. The increasing sex ratio with increasing length of gestation is most marked in first births.

TABLE III
SEX RATIO OF ANENCEPHALUS

Gestation* (wks)	Birth Order					
	1		2 and over		Total	
	No.	Sex Ratio Percent. Male	No.	Sex Ratio Percent. Male	No.	Sex Ratio Percent. Male
Under 33 ..	41	19.5	28	35.7	69	26.1
33-37 ..	55	23.6	75	29.3	130	26.9
38 and over	46	37.0	60	36.7	106	36.8
Total ..	142	26.8	163	33.1	305	30.2

*Excluded are five cases of unknown sex, fifteen of unknown gestation, and one of unknown birth rank.

Duration of gestation is also generally shorter for first than for later births (Table IV). These differences are not statistically significant, but they are consistent with significant trends noted in the somewhat larger Birmingham material.

TABLE IV
PERCENTAGE DISTRIBUTION OF ANENCEPHALICS
BY DURATION OF GESTATION

Birth Order	Gestation (wks)						Total	
	Under 33		33-37		38 and over			
	No.	%	No.	%	No.	%	No.	%
1 2 and over	41	28.9	55	38.7	46	32.4	142	100
	28	17.2	75	46.0	60	36.8	163	100

$$\chi^2 = 5.96, n = 2, p \approx 0.05$$

MacMahon and McKeown (1952) suggested the possibility that the change in sex ratio with increasing length of gestation is related to greater severity or earlier onset of hydramnios in female anencephalics although, in their material, the total incidence of hydramnios was the same in the two sexes. The fact that the overall incidence of hydramnios is also higher in females in this series (Table V) points in the same direction. Table V also shows an increasing

TABLE V
PERCENTAGE INCIDENCE OF HYDRAMNIOS IN
CASES OF ANENCEPHALUS

Birth Rank	Sex		Total
	Male	Female	
1	34.2	37.5	36.6
2	36.0	46.4	43.2
3	41.7	48.1	46.2
4+	29.4	65.4	51.2
Total ..	34.8	44.6	41.6

incidence of hydramnios with birth order, which suggests that hydramnios is not the explanation of the earlier onset of labour in firstborn anencephalics.

INCIDENCE RELATED TO COLOUR, RACE, AND RELIGION.—The great majority of births in Rhode Island are to white parents. According to central statistics, non-white births constitute only about two and a half per cent. of the total; the proportion of non-whites among hospital births is even lower, being only 1.98 per cent. in our comparison series. There are therefore too few non-whites in this series for adequate examination of incidence in whites and non-whites separately. We can however compare the number of non-whites in the comparison series with that in the malformation series.

Percentages of non-whites are given in Table VI; they are significantly fewer in the anencephalic group and more frequent in the hydrocephalic group than in the comparison series. The percentage is also low for spina bifida. If 1.98 per cent. is accepted as the true proportion of non-white births in these hospitals, the probability of finding no non-whites in 310 anencephalics by chance is $(0.9802)^{310}$, or approximately 1 in 500.

TABLE VI
FREQUENCIES OF NON-WHITE BIRTHS

Diagnosis	Number* of Known Colour	Non-White		Difference from Comparison Series
		Number	Percentage	
Comparison Series	1,563	31	1.98	—
Anencephalus ..	310	0	0	$-2.0 \pm 0.8 \dagger$
Spina Bifida ..	401	4	1.0	-1.0 ± 0.7
Hydrocephalus ..	140	7	5.0	$+3.0 \pm 1.3 \dagger$
All Malformations	851	11	1.29	-0.69 ± 0.56

*Colour was not recorded for 53 (5.9 per cent.) of 904 malformations and 107 (6.4 per cent.) of 1,670 in the comparison series.

†Difference exceeds twice its standard error.

Several writers have suggested that American Negroes experience a low incidence of malformations as a group, but the evidence has not been convincing.

A low incidence is suggested by centrally compiled birth and death certificate material (U.S. Public Health Service, 1949), but such material is undoubtedly subject to unequal ascertainment in the two groups. Other writers have demonstrated that deaths ascribed to malformation form a lower percentage of early deaths in Negroes than in whites (Clements, 1931; Murphy, 1936; Potter, 1940; Gruenwald, 1941), but this percentage is of course influenced by total still-birth and infant death rates, and is no indication of the relative frequencies of malformations in the total population of births. Murphy (1940) found the death rate from malformations to be 5.7 and 3.2 per thousand live births for whites and Negroes respectively, but the malformed infants were not derived solely from the general population on which the rates were based.

The suggestion in the present data that incidence of anencephalus and spina bifida is lower in non-whites than in whites, but that the incidence of hydrocephalus is higher offers further evidence that for race, as for other variables, examination of individual malformations is more profitable than consideration of malformations as a group.

The material in Table VII was collected to examine the relationship between religion and malformation, in view of known differences between religions in attitudes toward contraceptive practices and possibly to attempted abortion. No difference between Catholic and "Other" (almost entirely Protestant) religions is evident. However, somewhat surprisingly a low proportion of Jews is found in the malformation groups. This proportion is lowest for anencephalus and highest for hydrocephalus. If the percentage distribution of the comparison series is used to estimate the total number of Jewish births, the incidences of anencephalus, spina bifida, and hydrocephalus are 0.30, 0.60, and 0.30, respectively. These rates are equivalent to about one-seventh, one-quarter, and one-third of the corresponding figures for Gentiles. So far as we are aware, a low incidence

TABLE VII
PERCENTAGE DISTRIBUTIONS ACCORDING TO RELIGION

Religion*		Malformations								Comparison Series (b)		Difference (a) - (b)
		Anencephalus		Spina Bifida		Hydrocephalus		Total (a)				
		No.	%	No.	%	No.	%	No.	%	No.	%	
Catholic	..	227	70.28	310	73.99	104	68.42	641	71.70	1,123	69.28	+ 2.42 ± 1.91
Jewish	..	2	0.62	4	0.95	2	1.32	8	0.89	64	3.95	- 3.06 ± 0.69†
Other		94	29.10	105	25.06	46	30.26	245	27.40	434	26.77	+ 0.63 ± 1.85
Total		323	100	419	100	152	100	894	100	1,621	100	

*Religion was not stated for ten (1.1 per cent.) of 904 malformations and 49 (2.9 per cent.) of 1,670 comparison births.

†Difference exceeds twice its standard error.

of central nervous malformations in Jews has not been commented upon previously. Neither the low incidence in Jews nor that in non-whites can be accounted for by any unusual parity composition of these groups, since the differences in incidence are much larger than those between individual birth ranks.

RHESUS FACTOR AND ABO BLOOD GROUPING.—Distributions according to rhesus factor and blood group were examined in view of the possibility of their relevance to the different racial incidences noted above. A further indication for such an examination was the demonstration by Waterhouse and Hogben (1947) that matings between group O mothers and group A fathers produce a relative deficiency of group A children compared to other matings.

Results of blood examination were recorded more consistently, and for a longer period at the largest maternity hospital than at the four smaller institutions. The examination is therefore confined to propositi from this hospital, which contributed 480 (53.1 per cent.) of the malformations, and 868 (52.0 per cent.) of the comparison subjects. Blood group data were not available for the whole of the period surveyed, but were recorded for the mothers of 289 (60.2 per cent.) malformations and 542 (62.4 per cent.) comparison subjects. Rhesus status, but not ABO group, was available for an additional 31 mothers of malformations and for 37 in the comparison series.

The proportion of Rh-negative mothers is 11.7 per cent. (of 111) for anencephalus, 15.5 per cent. (of 148) for spina bifida, 11.5 per cent. (of 61) for hydrocephalus, and 13.4 per cent. (of 320) for all malformations combined, none of which percentages differs significantly from the corresponding value of 15.0 per cent. (of 579) in the comparison series.

In Table VIII the percentage distributions by ABO groups are compared, and again there are no significant differences between mothers of malformed and those of normal babies. We have

examined these distributions for the period 1948–52 when information was available for 86.4 per cent. and 93.2 per cent. of the two groups, and, also, the percentage distributions by ABO group separately for Rh-positive and Rh-negative mothers. No noteworthy differences between malformations and comparison subjects were evident.

Wiener (1946) noted six families in which spina bifida and erythroblastosis had both appeared, and suggested that at least one type of spina bifida may be produced by Rh-sensitization. In the present material there were also at least six families in which a malformation was followed by the birth of an infant with erythroblastosis. Record and McKeown (1950a) suggested that such families are the result of the fortuitous coincidence of two conditions neither of which is uncommon. Our data support this view, but the detection of sensitization effects occurring in a small proportion of families would require information on other members besides the mother. However, it does not seem likely that sensitization to the Rh or ABO groups is an aetiological factor in any appreciable proportion of malformations of the central nervous system.

SEASON OF BIRTH.—Table IX (opposite) shows incidence of malformations in 3-monthly periods. The standard quarters are used, since analysis by months did not suggest any more profitable grouping. That no seasonal variation in incidence of anencephalus was found is surprising in view of the report of McKeown and Record (1951), who noted among 158,307 births in Birmingham a significant excess of anencephalics born in the half-year October to March, although no seasonal change in incidence was evident for spina bifida or hydrocephalus. This high incidence of anencephalus in the winter months was independent of seasonal fluctuations in the proportions of births of various birth ranks. The large material on still births (based on 763,788 total births) published by the Registrar-General for Scotland showed similar relationships.

TABLE VIII
PERCENTAGE DISTRIBUTIONS BY BLOOD GROUP*

Blood Group	Malformations								Comparison Series (b)		Difference (a) – (b)
	Anencephalus		Spina Bifida		Hydrocephalus		Total (a)				
	No.	%	No.	%	No.	%	No.	%	No.	%	
O	51	49.0	64	48.5	25	47.2	140	48.44	242	44.65	+ 3.79 ± 3.63
A	39	37.5	48	36.4	18	34.0	105	36.33	223	41.14	- 4.81 ± 3.56
B	9	8.7	16	12.1	8	15.1	33	11.42	62	11.44	- 0.02 ± 2.32
AB	5	4.8	4	3.0	2	3.8	11	3.81	15	2.77	+ 1.04 ± 1.27
Total	104	100	132	100	53	100	289	100	542	100	

*This Table is based on malformations and comparison births in one hospital only. Blood group is unknown for 191 (39.8 per cent.) of 480 malformations and 326 (37.6 per cent.) of 868 comparison births.

TABLE IX
INCIDENCE OF MALFORMATIONS BY SEASON OF BIRTH

Quarter	Total Births	Malformations							
		Anencephalus		Spina Bifida		Hydrocephalus		Total	
		Number	Per mille	Number	Per mille	Number	Per mille	Number	Per mille
Jan.-March ..	40,638	77	1.89	106	2.61	34	0.84	217	5.34
April-June ..	41,387	79	1.91	101	2.44	36	0.87	216	5.22
July-Sept. ..	44,324	87	1.96	109	2.46	38	0.86	234	5.28
Oct.-Dec. ..	42,305	83	1.96	110	2.60	44	1.04	237	5.60
Total	168,654	326	1.93	426	2.53	152	0.90	904	5.36

We have examined our material from various aspects in an unsuccessful attempt to explain the absence of seasonal influence in the Rhode Island series. Restriction of the examination to propositi born in the period 1940-47 (the years covered by the Birmingham inquiry) was unfruitful. In Table X, percentage distributions by quarter-year are given for first-born anencephalics and comparison subjects, since the seasonal difference seemed to be most marked in first births in Birmingham. The percentage of anencephalics is high in the quarter October-December, but not significantly so, and the percentage in the first quarter is by contrast low. Examination according to month of last menstrual period also revealed no difference between anencephalics and normal births.

TABLE X
PERCENTAGE DISTRIBUTION BY QUARTER-YEARS OF FIRST-BORN ANENCEPHALICS AND COMPARISON SUBJECTS

Quarter	Anencephalics		Comparison Series		Difference
	No.	%	No.	%	
Jan.-March	33	22.0	171	24.5	-2.5 ± 3.8
April-June	33	22.0	169	24.2	-2.2 ± 3.8
July-Sept.	40	26.7	186	26.6	+0.1 ± 4.0
Oct.-Dec.	44	29.3	173	24.7	+4.6 ± 3.9
Total	150	100	699	100	

It would be unwise to conclude from this data that the seasonal variation in incidence of anencephalus noted in Birmingham and Scotland is not present in the United States, and that this is a major difference in the epidemiological behaviour of anencephalus in the two countries. We have elsewhere found that the selective features entailed in limitation of observations to hospital material may influence appreciably the magnitude of demonstrated associations (Ingalls and others, 1953), and it is possible that some such mechanism is operating in the present instance. Were the presence of such a difference in seasonal influence between the two countries confirmed, however, it would be of considerable interest.

INCIDENCE OF MALFORMATIONS OF THE CENTRAL NERVOUS SYSTEM IN SIBLINGS.—Since the mothers of the propositi were not interviewed in the present inquiry, our information on siblings is limited to:

- (1) such data on previous siblings as was recorded in the obstetric case records;
- (2) malformed siblings who were propositi by reason of birth in one or other of the study hospitals;
- (3) all subsequent siblings, malformed and normal, born in Providence Lying-In Hospital after propositi born in that hospital.

This hospital maintains a unit record system which enables records to be readily inspected for all births of the same mother occurring in the hospital. Our estimate of risk to subsequent siblings is derived from this source. Fraternities containing two malformed members are listed in the Appendix to this paper.

The incidence of malformations of the central nervous system in siblings born subsequent to the first propositus in Providence Lying-In Hospital is shown in Table XI. 463 mothers gave birth to 480 propositi in this hospital and to one affected sibling who was not a propositus. The total incidence in subsequent siblings (5.3 per cent.) is rather higher than the estimate of 2.8 per cent. given by Record and McKeown (1950b). Penrose (1946) found seven (1.5 per cent.) affected in 471 siblings. Hindse-Nielsen (1938) found 28 (5.1 per cent.) affected among 548 sibs of patients with spina bifida.

TABLE XI
INCIDENCE OF MALFORMATIONS OF THE CENTRAL NERVOUS SYSTEM IN SIBLINGS BORN AFTER THE FIRST PROPOSITUS IN PROVIDENCE LYING-IN HOSPITAL

Type of First Malformation	Number of Fraternities	Number of Subsequent Siblings	Central Nervous Malformations	
			No.	%
Anencephalus	162	119	6	5.0
Spina Bifida	215	166	11	6.6
Hydrocephalus	86	54	1	1.9
Total	463	339	18	5.3

The number of sibs following hydrocephalic propositi in the present material is too small for calculation of rates, but the limited data agree with the observation of Penrose (1946) and of Record and McKeown (1950a) that recurrence of malformation is less frequent after hydrocephalus than after anencephalus or spina bifida. This is contrary to the material presented by Murphy (1940), but the discrepancy may be accounted for by the fact that in Murphy's data spina bifida with hydrocephalus appears to have been classified as hydrocephalus.

It is of both practical and theoretical interest to know the relative risk of recurrence of the same or different malformations. For this purpose we have combined our own material with that of Record and McKeown (1950a) in Table XII.

TABLE XII
RISK OF RECURRENCE OF THE SAME AND OF DIFFERENT
MALFORMATIONS OF THE CENTRAL NERVOUS SYSTEM*

Diagnosis in First Propositus ..		Anen- cephalus	Spina Bifida	Hydro- cephalus
Number of Subsequent Siblings ..		330	384	116
Number of Sub- sequent Sib- lings affected	Anencephalus	1	7	—
	Spina Bifida	5	12	1
Percentage Inci- dence of Sub- sequent Sib- lings affected	Hydrocephalus	1	—	1
	Anencephalus	1.2	1.8	—
	Spina Bifida	1.5	3.1	0.9
Percentage Incidence in all Births†	Hydrocephalus	0.3	—	0.9
Percentage Incidence in all Births†		0.21	0.25	0.09

*The Table is based on a combination of the present data with that of Record and McKeown (1950a). Only malformations subsequent to the first propositus are included.

†Obtained by combining the estimates of the two series.

The examination is limited to the risk following the first propositus and even in this combined material the numbers are small. The Table compares the risk of each malformation in subsequent siblings with that in the general population, and the results indicate that:

(1) Following anencephalus, the risk of both anencephalus and spina bifida is considerably raised, being about six times that in the general population. The risks of anencephalus or spina bifida are approximately equal. Hydrocephalus in a subsequent sib was observed only once.

(2) Following spina bifida, there is a similar relation ship, although spina bifida is somewhat more frequent in subsequent siblings than anencephalus; the risk of anencephalus is about seven times and that of spina bifida about twelve times greater than in the general population. Hydrocephalus was not observed in these fraternities.

(3) The number of subsequent sibs following hydrocephalus is small, but the limited data suggest that hydrocephalus is more common in subsequent siblings than anencephalus and/or spina bifida.

The tendency of anencephalus and spina bifida to recur or alternate in the same fraternity is confirmed by a wider examination of the literature. 74 fraternities in which two or more malformations of the central nervous system occurred may be assembled as follows:

- 35 from the present series (Appendices A and B);
- 26 from Record and McKeown (1950a, Appendix A, Groups I and II);
- 7 from Penrose (1946);
- 5 from Worcester, Stevenson, and Rice (1950);
- 1 from Böök and Rayner (1950).

These fraternities are unselected in so far as they are not derived from isolated reports of affected families. For reasons already given, the fraternities reported by Murphy (1940) are excluded.

In 24 of these fraternities in which the first malformation was anencephalus, subsequent malformations were anencephalus 12, spina bifida 10, hydrocephalus 2.

In 44 fraternities in which the first malformation was spina bifida, subsequent malformations were anencephalus 19, spina bifida 25, hydrocephalus 1.

Following hydrocephalus (six fraternities) anencephalus occurred twice, spina bifida once, and hydrocephalus three times.

The implication is clear that the factors responsible for the increased incidence in certain fraternities operate on anencephalus and spina bifida as one unit, and hydrocephalus as another distinct entity.

OTHER MALFORMATIONS IN SIBLINGS.—The index cases (first propositi) had 307 previous and 321 subsequent siblings (total 628), excluding suspected or confirmed cases of central nervous malformation and twins of propositi; seven of these exhibited a variety of malformations other than those of the central nervous system, details of which are given in Appendix D. The incidence of other malformations in siblings (1.1 per cent.) is approximately the same as that of non-nervous system malformations in the general population.

DISCUSSION

Evidence is accumulating that anencephalus and spina bifida share common aetiological factors. McKeown and Record (1951) summarized certain common characteristics and other features of similarity have become apparent in the present inquiry:

- (1) Females predominate in both, although more in anencephalus than in spina bifida;
- (2) Both have shown a declining incidence in the post-war years in Birmingham and in Rhode Island;
- (3) Both exhibit a low incidence in second births and a high incidence in first births and those of higher rank;

- (4) In both, association with maternal age is relatively small compared to the association with birth order;
- (5) Both show a low incidence in Jews as compared with Gentiles, and in American non-whites as compared with whites;
- (6) Both recur or alternate in affected fraternities.

Seasonal variation in the incidence of anencephalus, but not in that of spina bifida, was observed in Birmingham and Scotland, but not in the present inquiry. Taken in conjunction with the inferred similarity in embryological development of anencephalus and spina bifida, this epidemiological behaviour suggests that it is reasonable for the present to regard these malformations as aetiologically related.

Hydrocephalus when not accompanying spina bifida, on the other hand, exhibits certain distinguishing features of behaviour:

- (1) Greater frequency in males;
- (2) Association with maternal age rather than with birth order;
- (3) Higher incidence in non-whites;
- (4) Tendency to repeat in affected fraternities;
- (5) Comparative infrequency in fraternities containing members with anencephalus or spina bifida.

Hydrocephalus thus appears to be aetiologically distinct from the anencephalus-spina bifida group.

With the possible exception of the association with birth order and the decline in incidence in the post-war years, none of the associations yet demonstrated for anencephalus and spina bifida can be explained only in terms of either genetic or environmental factors. We have shown elsewhere that in Rhode Island the high incidence in first births as compared with later births was limited to the years of high incidence, 1940-47 (Ingalls and others, 1953). This is very suggestive of the influence of factors in the external environment of the mother. However, it cannot be determined whether these factors influence the incidence of the malformations or merely the proportion which are carried to term and diagnosed.

Explanations of either a genetic or environmental nature might be offered to explain the low incidence of these malformations in Negroes and in Jews. It is difficult to think of particular environments which are common to Negroes and Jews in the United States; it would perhaps be easier to attribute these differences to genetic influences, but it would be just as difficult to provide specific suggestions regarding the genetic mechanism involved.

Similarly, the high incidence in siblings as compared with the general population may be attributed

to the genetic constitution of the parents or the continuation of particular environments within the fraternity. The observation of Record and McKeown (1950a) that the abortion rate in affected fraternities is especially high in the pregnancy immediately preceding the malformed individual is particularly interesting. If it were confirmed that the risk within the fraternity is localized to particular time periods, it would indicate that environmental factors were largely responsible for the high incidence of these malformations in siblings.

Since the operation of genetic or environmental factors has not been determined with certainty, it is hardly surprising that no specific genetic mechanism or environment has been ascertained. On the assumption that the excess of abortions in anencephalic fraternities is due to early anencephalus, Böök and Rayner (1950) concluded that the condition was the result of a lethal genotypical factor, possibly a simple recessive. A similar view was expressed by Polman (1950). Such statements are however purely speculative. The high mutation rate necessarily assumed in such an hypothesis is a major difficulty.

Nor can it be said that any limited environment is incriminated. Association with birth rank, secular change, and race could all indicate a variety of associated environmental factors.

Interpretation of the epidemiological data so far collected on hydrocephalus is difficult, since the nature of the material permits consideration of the malformation only as a single entity. Pathological differences between types of hydrocephalus and differences in age at onset make it certain that markedly different aetiological factors are responsible for individual types of the malformation. This may also of course be true for anencephalus and spina bifida, but it has not been shown to be so, and there is no choice but to regard them, for the present, as being of uniform aetiology. However where such differences are known to be present, as in hydrocephalus, examination of material which takes account of them is likely to be most profitable. It seems unlikely therefore that any considerable advance in knowledge of this malformation will be made by statistical or genetic investigation without coincident pathological examination of the material.

SUMMARY

From the obstetric case records of the five largest maternity units in the State of Rhode Island, information was abstracted on the mothers of 904 infants with anencephalus, spina bifida, hydrocephalus, or encephalocele, and those of 1,670 infants selected at random (comparison series). Births in these

hospitals accounted for over 67 per cent, of those in the whole state, and are believed to be representative of all births occurring in the central and northern sections of the state.

Incidences of anencephalus, spina bifida, and hydrocephalus were 1.93, 2.53, and 0.90 per thousand total births respectively. The incidence of all three malformations was highest in the war years and declined during the post-war period. Certain associations of the sex ratio of anencephalus are recorded.

The percentage of non-whites was lower for anencephalus and spina bifida than for the comparison series (significantly so for anencephalus), and for hydrocephalus it was significantly higher. No difference in incidence of malformations was evident among the progeny of Catholic and Protestant mothers, but significantly fewer malformations than expected were found among Jews. Incidences of the three malformations in Jews were one-seventh, one quarter, and one-third of the corresponding rates for Gentiles. No differences between mothers of malformed infants and those in the comparison series were noted in respect of percentage distribution by Rh factor or ABO blood group. No significant seasonal variations in incidence were found.

The incidence of malformations of the central nervous system in siblings born subsequent to a propositus was 5·3 per cent., the risk being highest after spina bifida and lowest after hydrocephalus. Anencephalus and spina bifida appear to alternate freely in fraternities in which one such malformation has occurred. Hydrocephalus is relatively infrequent after anencephalus or spina bifida, but is the most common malformation following a hydrocephalic propositus.

Seven of 628 siblings of probands (1.1 per cent.) had malformations other than those here considered. This incidence is approximately the same as that of non-nervous system malformations in the general population.

Reasons are given for the belief that anencephalus and spina bifida are closely related aetiologically as well as embryologically, whereas hydrocephalus appears to be aetiologically distinct.

We are indebted to the administrative and obstetric staffs of the Providence Lying-In, Roger Williams General, St. Josephs, Pawtucket Memorial, and Woonsocket General Hospitals, who kindly gave access to their records.

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APPENDIX

APPENDIX A

FRATERNITIES CONTAINING AN INDEX PROPOSITUS AND A SUBSEQUENT PROPOSITUS OR AFFECTED SIBLING, BOTH BORN IN PROVIDENCE LYING-IN HOSPITAL

[illegible]

KEY

- (1) Sex is shown by M, F, ?.
 (2) Malformed individuals are in bold type, normal in italics.
 (3) The diagnosis of defects of the central nervous system is indicated by numerals as follows:

1. Anencephalus
2. Anencephalus with Spina Bifida
3. Spina Bifida
4. Spina Bifida with Hydrocephalus
5. Encephalocele
6. Hydrocephalus.

- (4) Other diagnoses are given in the notes at the end (†).
 (5) * propositus.
 (6) † miscarriage.
 (7) Individuals not born in Providence Lying-In Hospital are shown in brackets.

APPENDIX B

OTHER FRATERNITIES CONTAINING TWO AFFECTED MEMBERS BORN IN STUDY HOSPITALS

Reference Number	Siblings in order of Birth							
	1	2	3	4	5	6	7	8
442	(F)	(M)	M.3	M.4*				
443	F.4	M	F	F.1*	M			
444	†	†	†(M.2)*	M.1*				
445	(?)	(M.3)*	F	M	M.1*	F		
446	F	(M.2)*	F.4*					
447	(M)	(F.2)*	F.4*					
464	(?)	(F.1)*	(F.4)*					
465	(M)	(F.4)*	(F.2)*					
466	(M.3)*	(?)	(?)	(?)	(F.1)*			
467	(M.3)*	(F.3)*						
468	(F.3)*	(F)	(F.3)*					
469	(M)	(F.5)*	(F.3)*	†				
470	(?)	(M.4)*	(F.4)*					
471	(?)	(?)	(M)	(M.2)*	†	(F.3)*		
472	(?)	(?)	(?)	(F.2)*	(?)	(?)	(?)	(F.2)*
473	†	(F.2)*	(F.1)*					
474	(M)	(F.1)*	(M)	(F.1)*	(F)	†	(M)	

APPENDIX C

FRATERNITIES CONTAINING A PROPOSITUS FROM P.L.I. HOSPITAL AND A PREVIOUSLY MALFORMED SIBLING NOT BORN IN A STUDY HOSPITAL (DIAGNOSIS THEREFORE UNCONFIRMED)

Reference Number	Siblings in Order of Birth										
	1	2	3	4	5	6	7	8	9	10	11
448	M	(? 6)	(M)	(M)	(M.3)	F.1*					
449	(? 3)	†	F.1*								
450	(F)	(F.6)	(F)	(M)	(M)	M.3*					
451	(F.3)	(M.3)	†	†	(M)	†(F)	†	(F)	†(?)	(? 3)	M.4*
452	(M.3)	†M.4*									
453	F	(F)	(?.1)	F.6*	F	F	F	M			

APPENDIX D

FRATERNITIES CONTAINING A PROPOSITUS FROM P.L.I. HOSPITAL AND A SIBLING WITH A MALFORMATION OTHER THAN ONE OF THE CENTRAL NERVOUS SYSTEM

Reference Number	Siblings in Order of Birth				
	1	2	3	4	5
454	F.3*	M	M	†M	
455	†?	†F.3*	M	F	
456	†M	M.3*			
457	M	F.4*	†M		
458	†(?)	†M.4*			
459	†M	M.1*	F	M	M
460	†M	F.1*	F	M	M
463	M	†M	{ F.1* F		

Reference Number of Fraternity	Birth Rank	(†)Diagnostic Notes
425	11	Propositus; rudimentary external genitalia
430	1	Propositus; harelip
438	4	Propositus; omphalocele
440	6	Propositus; microcephalus; large umbilical hernia
441	3	Suspected congenital heart disease
444	4	Also extrophy of the heart
451	6,9	Congenital anomaly, unspecified
452	2	Propositus; oxycephaly
454	4	Right talipes equino-varus
	1	Omphalocele
455	2	Propositus; extrophy of bladder; primitive cloaca
456	1	Enlarged heart; ? congenital cystic kidney
457	3	Congenital duodenal stenosis
	1	"Abnormal infant"
458	2	Propositus; enlarged liver and spleen
459	1	Tumour in neck
460	1	Scaphocephaly
463	2	Spinal deformity