A Clinical and Genetical Study of Anencephaly[1]

J. A. BÖÖK[2] AND S. RAYNER

Department of Medical Genetics, Institute of Genetics, University of Lund, Sweden

INTRODUCTION

ANENCEPHALY, rhachischisis, cranioschisis, acrania, holoacrania, etc., constitute a series of brain anomalies having presumably a common origin. The basic developmental failure is a defective closure of the medullary plate. The deficiencies in skeletal and muscle development seem to be only secondary to this primary anomaly of the central nervous system. The different names given above therefore should correspond to different types of manifestation only.

There is no need here to go into morphological or developmental details. For an evaluation of the correctness of the above conclusion the reader is referred to the papers by Ernst (1909), Ströer and van der Zwan (1939), and Bonnevie (1940).

It is evident that studies of developmental anomalies in human embryos are extremely difficult to perform. The scarcity of facts forces us to devise working hypotheses on evidence from experimental studies on animals. No doubt the condition of pseudencephaly, thoroughly studied in the mouse by Bonnevie (1936), is closely related to anencephaly in man. As this study in many respects formed a starting point in the present investigation some of the facts may be mentioned briefly.

Pseudencephaly in the mouse is primarily connected with disturbances in the development of the two germ layers. Major disturbances lead to the death of the embryo at that stage. If the disturbances are less pronounced the embryo may survive but with a defective and arrested development of the chorda plate and the medullary tube. If the disturbances are very slight a restitution may follow and the embryo develops further. In some cases, however, the result will be an open defect of the medullary tube in the mesencephalic region. Owing to the strong flexion of the neural tube this part of the brain is turned inside out. Thus the typical picture of pseudencephaly (which closely corresponds to anencephaly in man) arises secondarily from purely mechanical factors.

The evidence brought forward by Bonnevie shows that pseudencephaly is a developmental anomaly which in most cases causes the death of the embryo at an early stage, followed by disintegration and absorption *in utero*. Then, if we make the assumption that this condition is the effect of a simple recessive gene, we should *a priori* not expect clear-cut mendelian ratios within the litters. Among embryos up to 6 mm. length Bonnevie found

Received January 15, 1950.

[1] Aided by a grant from *Reservationsanslaget for Främjandet av Medicinsk Forskning* at the University of Lund.

[2] Special Research Fellow of the U. S. Public Health Service during 1950–1951. Fellowship taken at the Dight Institute for Human Genetics of the University of Minnesota.

17.5 per cent abnormal and among older embryos only 8.3 per cent. Among 30 pseudencephalics studied by the same author, not one developed up to full term.

The theory of Bonnevie that pseudencephaly in her material arose after a spontaneous mutation and that the condition was transmitted as the effect of a recessive autosomal lethal gene seems very well founded.

The hereditary pseudencephaly of the mouse produced by Snell and coworkers (*cf.* Snell & Picken, 1935) in X-ray experiments shows the same morphological and developmental characteristics. However, in this case it is very likely that gross chromosomal abberations lie behind the defect, i.e., translocations or chromosome deficiencies.

We also want to stress the well known fact that conditions similar to or identical with pseudencephaly-anencephaly have repeatedly been induced in various embryos (e.g. frogs and mice) with the aid of external agents (e.g. by changing the osmotic pressure of salt solutions in which the embryos develop and by X-rays.) Inasmuch as these experiments do not involve genic or chromosomal changes, the resulting anomalies may be regarded as *phenocopies*. The production of such phenocopies is naturally not contradictory to the fact that in other cases the same condition may be hereditary.

Anencephaly in Man

Most anencephalics in man are stillborn or if born alive live only for a few hours. The pregnancies usually terminate before full term. Delivery is practically always spontaneous. According to Suabedissen (*op. cit.* Hiilesmaa, 1945) delivery in 80 per cent of the cases took place between the 191*st* and 270*th* menstruation day when the fetal weight was from 1,000 to 2,500 g. and its length varied between 24 and 48 cm.

Turning to the question of the frequency of anencephaly, we have to consider the fact that the available figures give only the obstetrician's point of view. The frequency with which anencephalics appear in obstetric departments may be easily measured, but this is of course only one side of the problem, as it tells us nothing about the occurrence of anencephaly in the early stages of pregnancies and especially among aborted embryos.

Malpas (1937) obtained a figure of 0.308 per cent anencephalics among 13,964 deliveries in Liverpool during the period 1923–32. Ballantyne (*op. cit.* Dunn & Salter, 1944) found 1 case of anencephaly in 1,460 deliveries (0.068 per cent). Hiilesmaa (1945) gives a frequency of 0.30 per cent among 11,425 deliveries in Viipuri and 0.03 per cent among 17,084 deliveries in Helsinki.

As for the etiology of anencephaly, highly different opinions are to be found in the literature. On the one hand, we find Mall's (1917) categoric declaration (p. 70): "It is perfectly clear that monsters are not due to germinal and hereditary causes but are produced from normal embryos by influences which are to be sought in the environment." A similar opinion was put forward by Ossenkopp (1932). On the other hand a number of authors have discussed heredity as a probable etiological factor, e.g. Hammer (1933), Josephson and Waller (1933), Malpas (1937), Schade (1939), Dunn and Salter (1944), and Penrose (1946). With the exception of the studies by Malpas and Penrose, these papers

concern highly selected cases wherein two or more cases of anencephaly were found in the same family, or, as in the paper by Josephson and Waller, in identical twins. These observations therefore cannot be used as definite evidence for or against heredity.

Malpas' (1937) communication deals with 13,964 deliveries among which 44 cases of anencephaly were found (0.308 per cent). He concluded that the age of the mother might be of importance as the percentage incidence of anencephaly was 10 times greater in the maternal age group 46–50 than in the age group 16–20. The family data were based on questionnaires sent to the parents. It was found that the percentage incidence of anencephaly among the other members of the fraternities which contained one anencephalic was 2.6 as compared with an incidence in the general population of 0.308. In no case were the parents first or second cousins. Most interesting is Malpas' observation that the mothers of the anencephalics had a higher incidence of abortions. He gives the figure of 12 per cent, against 6 per cent in the general population.

Penrose's report (1946) deals with a study of 21 cases of anencephaly belonging to 20 different sibships. In these fraternities a total of 55 pregnancies resulted in 7 abortions (12.7 per cent), 1 stillborn of unknown cause, 2 cases with spina bifida (3.6 per cent), 1 case of anencephaly (1.8 per cent) and 44 non-malformed babies. In one family the parents were first cousins. In this paper, anencephaly, spina bifida and congenital hydrocephalus were statistically treated as equivalents. The analysis led Penrose to the conclusion that his figures indicate "a slight but significant tendency for the conditions to be duplicated in the families" (p. 73). Furthermore his calculations indicate that advancing maternal age is significantly related to the incidence of this *group* of malformations.

The data so far available, presented by various authors, scanty as they are, may be summarized as follows:

1. No one has ever been able to demonstrate an exogeneous etiological factor in anencephaly.

2. The incidence of anencephaly among the sibs of anencephalic propositi is slightly but probably significantly raised.

3. There is no doubt a causal connection between anencephaly and spina bifida.

4. The higher incidence of abortions among offspring of mothers of anencephalic propositi seems to be significant.

5. There is a peculiar sex ratio, with excesses for the female sex, as will be discussed further in this paper.

6. Most cases of anencephaly obtained from obstetric departments are premature.

7. Not a single fact has been produced containing evidence definitely against a genetical etiology.

Sex Incidence in Anencephaly

It has long been recognized that most anencephalics coming to observation are of female sex. Table 1 shows a compilation from the available literature.

The sex ratio in this material is about 3 ♀ : 1 ♂. There are at the moment no data available which could explain these findings. It may be that the majority of the anencephalic male embryos die at a very early stage and are expelled or the cause may be sought in a relatively strong sex limitation in the manifestation of the trait.

TABLE 1

AUTHOR	FEMALE	MALE	UNKNOWN SEX
Ballantyne, 1904	30	10	6
Malpas, 1937	31	13	—
Murphy, 1936 (*op. cit.* Dunn & Salter, 1944)	74	27	—
Angevine, 1938	13	6	1
Hiilesmaa, 1945	34	5	—
Penrose, 1946	16	2	3
Total	198	63	10

TABLE 2

DIAGNOSIS	LENGTH OF EMBRYO *mm.*	AUTHOR	NOTES
Anencephaly + spina bifida	14	Mall, 1917	All these embryos were obtained as spontaneous abortions or after hysterectomies and were dead at the observation
Anencephaly	13.5		
Anencephaly	15		
Anencephaly	6		
Anencephaly + spina bifida	24		
Anencephaly + spina bifida	27		
Anencephaly + spina bifida	2.1		Obtained as above but still alive at the observation
Anencephaly	190	Mall, 1917	
Anencephaly + spina bifida	10	Harbeson, 1939	Spontaneous abortion
Anencephaly	16.5	Dodds & De Angelis, 1937	

Anencephaly in Early Pregnancy

The fact that anencephaly has been observed repeatedly in pregnancies which terminated at an early stage in the death of the embryo is of particular interest. It appears to show that anencephaly undoubtedly is a causal factor in spontaneous abortion or, more generally, in early intrauterine fetal death. Available data do not permit an estimation of the frequency with which fetal death due to anencephaly or allied disturbances occurs. Nevertheless, such deaths appear to be not too uncommon. In Mall's (1917) material of human embryos with localized anomalies almost 40 per cent belong to the cranio-rachischisis group. Table 2 shows a compilation of anencephalics diagnosed at an early stage.

THE PRESENT INVESTIGATION

The problem set forth in this study was to collect evidence for or against a genetical etiology in anencephaly. It is closely connected with the search for lethal genes in human populations. In such studies it does not seem to be correct to collect a number of malformations or monsters of highly different appearance which may be and probably are of an entirely different etiology. The correct method should be to concentrate in the first place on well recognized clinical or pathological entities one by one. As our experience in medical genetics tells us, this, of course, does not mean that there will be any guarantee of a biological relation between a clinical and a genotypical entity; nevertheless, this way of proceeding probably will give a better result.

This is the reason why we have started with anencephaly alone as an easily recognized pathological condition. At the outset of the study the following questions were raised:

1. Will the examinations of the mothers or their anamnestic data, particularly during pregnancy, reveal any condition which may have a bearing on the birth of an anencephalic child?

2. Is it possible to find data which point to a genetical etiology? For practical reasons the family research work was limited to parents and sibs.

The Present Material

Every case of anencephaly born at the Obstetric Department, University Clinic of Lund, from 1923 to 1945 and at the Obstetric Department, University Clinic of Malmö, from 1917 to 1947 has been registered by Dr. O. Benoni-Nilsson. For placing this material at our disposal we are indebted to him and to the heads of these clinics, Professors A. Sjövall, M.D., and S. Genell, M.D., respectively. Altogether 67 cases were registered as *propositi*. These cases belonged to 67 different families. A family record was made for each propositus and the addresses of parents and sibs were traced in the parish registers. The geographic distribution of the present material is limited to the southern part of Malmöhus Län (south-western Skåne, Sweden) as concerns the domiciles of the mothers at the time the anencephalic child was born (table 3).

Of these original 67 families we were able to visit and examine personally 46 families. The remaining 21 had to be excluded for one of the following reasons: 1) the mother was deceased, 2) the family had moved to distant parts of the country or abroad, or 3) the family refused to cooperate (12 families).

To secure a uniform judgment, these 46 families were visited and examined by us personally, and all hospital records were studied. As for the clinical examination and the anamnesis, the following data were considered important.

Anamnesis: Medical histories were secured, with special reference to 1) con-

sanguinity between the parents, 2) complete clinical history of every person, 3) the condition of the mothers during each pregnancy, with special reference to German measles and other virus diseases, 4) a history of syphilitic infection,

TABLE 3. DISTRIBUTION OF CASES OF ANENCEPHALY BY YEARS, AS OBSERVED AT THE OBSTETRICAL DEPARTMENTS OF THE UNIVERSITY CLINICS AT MALMÖ (1917–1947) AND AT LUND (1923–1945)

MALMÖ				LUND			
Year	Number of deliveries	Anencephalics		Year	Number of deliveries	Anencephalics	
		Number	Per Cent			Number	Per Cent
1917	1279	1	0.08	1917	—	—	—
1918	1081	0	0.00	1918	—	—	—
1919	1079	1	0.09	1919	—	—	—
1920	1508	2	0.13	1920	—	—	—
1921	1261	1	0.08	1921	—	—	—
1922	1195	0	0.00	1922	—	—	—
1923	1144	3	0.26	1923	1643	1	0.06
1924	1273	2	0.16	1924	1707	0	0.00
1925	1254	0	0.00	1925	1716	1	0.06
1926	1245	2	0.16	1926	1740	1	0.06
1927	1160	3	0.26	1927	1702	2	0.12
1928	1233	1	0.08	1928	1931	0	0.00
1929	1201	0	0.00	1929	1874	0	0.00
1930	1302	3	0.23	1930	2117	1	0.05
1931	1399	0	0.00	1931	2059	3	0.15
1932	1306	0	0.00	1932	2090	1	0.05
1933	1239	0	0.00	1933	1838	0	0.00
1934	1407	2	0.14	1934	1983	0	0.00
1935	1497	3	0.20	1935	1952	0	0.00
1936	1701	1	0.06	1936	2038	1	0.05
1937	1841	3	0.16	1937	2271	1	0.04
1938	2013	2	0.10	1938	2316	2	0.09
1939	2232	1	0.04	1939	2362	2	0.08
1940	2284	1	0.04	1940	2320	3	0.13
1941	2503	0	0.00	1941	2097	0	0.00
1942	2920	0	0.00	1942	2367	0	0.00
1943	3240	1	0.03	1943	2503	4	0.16
1944	3492	3	0.09	1944	2714	1	0.04
1945	3477	1	0.03	1945	2866	3	0.10
1946	3445	2	0.06	1946	—	—	—
1947	3422	1	0.03	1947	—	—	—
Total	56633	40	0.07 ±0.01		48179	27	0.06 ±0.01

5) any mechanical interference during pregnancy (e.g. attempt to provoke abortion), 6) a history of Rh-incompatibility.

Clinical examination: Every person showing signs or symptoms of disease

was examined physically and/or neurologically and/or mentally with the usual bedside equipment.

According to our original plan the mothers were tested for the Rh factor. For the serological examination we are indebted to Rune Grubb, M.D., Bacteriological Institute, Lund. However, when it was found that among the 10 first tested mothers 8 were Rh positive and only 2 Rh negative, this test was omitted as probably having nothing to do with the present problem.

The Wassermann test was performed in a few mothers not previously tested at the hospitals during pregnancy. They were all negative. We are indebted to Professor Arvid Lindau, M.D., for these tests.

Frequency of anencephaly in the present material. Our material comprises altogether 104,812 deliveries among which 67 cases of anencephaly were recorded. This gives a frequency of 0.064 per cent. As seen in table 3 the difference between the material obtained in Malmö and Lund is not significant. The difference between our figure and the figures given by previous authors (see p. 62) is probably accidental.

The Propositi

Some clinical data concerning the 67 propositi of the present material have been summarized in table 4.

Duration of pregnancy. In 64 cases sufficient data were obtained to form an estimate of the duration of the pregnancy. The mean value was 265.5 days counted from the end of the last menstruation. This is close to the normal average of 270 to 280 days. The duration of normal pregnancies, however, may vary within rather wide limits and is usually given as 230 to 330 days. As seen in table 4, most of the cases fall within these limits, but 15 of them or about 23 per cent were below 230 days. No doubt this allows the conclusion that there is a marked tendency to premature births in anencephalic pregnancies.

As length of pregnancy and clinical estimation of the development of the fetus will decide whether the patient goes to the obstetrical or to the gynecological department (the latter taking care of all cases considered to be abortions) the material is naturally biased for these two factors. In other words, the shortest pregnancies have been excluded. In spite of this the tendency is obvious.

Hydramnion. A conclusive hydramnion was recorded in 33 cases, i.e., in about 50 per cent. This only confirms previous observations that hydramnion is one of the commonest signs in anencephalic pregnancies as is also the case in other pregnancies with a malformed fetus. The possible etiological significance of hydramnion has been discussed at length in previous literature. The conception of today concerning malformations of the embryo is that an increase in the amount of liquor amnii beyond the normal limits cannot be claimed as an etiological factor, but may rather be considered as a consequence of the pathological condition of the fetus. Hydramnion in anencephaly suggests that a direct tran-

TABLE 4

FILE NO.	HYDRAMNION	DURATION OF PREGN.	DEAD BEFORE DELIVERY	BORN ALIVE AND DIED AFTER	WEIGHT (G.)	LENGTH (CM.)	SPINA BIFIDA	SEX
KKL								
91/23	+	264		55 min.	2760	46		♀
348/25		301		25 min.	3020	48		♂
1740/26		287		2 hours	1210	46		♀
824/27		244	+		1160	27	+	♀
1190/27		323	+		3520	51		♂
1772/30		288	+		2670	42	+	♀
1768/31	+	242		1 min.	1210	34	+	♀
2090/31	+	249	+		1560	41		♀
2121/31	+	227		10 min.	1150	32		♀
235/32		249		30 hours	3150	?		♂
1620/36	+	298	+		4070	56		♀
1676/37	+	330		3 hours	3300	45.5		♀
125/38		253	+		2030	45		♂
388/38	+	259	+		1740	39		♀
410/39	+	229	+		?	?		♂
2347/39	+	237		1 hour	1660	40		♀
513/40	+	313	+		4550	53		♂
1385/40		262	+		?	?		♂
2717/40		214	+		680	24		♀
2541/43	+	229	+		?	?		♀
3511/43	+	250	+		1400	39		♀
3793/43	+	311	+		4300	53.5		♂
4081/43		?	+		?	?		♂
2556/44	+	272		22 hours	2450	43		♂
1365/45		295	+		3000	49		♂
3318/45	+	211	+		1300	43		♂
4416/45	+	296	+		2300	44		♀
KKM								
645/17		260		27 hours	2900	47		♂
1134/19	+	272	+		2500	48		♀
661/20	+	257		2 hours	1830	?		♀
664/20		345	+		3560	52		♀
1088/21		256	+		1800	40		♀
788/23		330		20 hours	3400	46		♀
1014/23		225	+		1330	38		♀
1161/23	+	?	+		2150	48		♂
621/24		263	+		1400	?		♀
662/24		226		5 hours	1250	37		♂
7/26		276		3 hours	3860	51		♀
1667/26	+	284	+		1670	38		♀
278/27		254	+		860	28	+	♀
1205/27	+	232	+		2000	41		♂
1558/27	+	197	+		670	31		♀
1199/28		229	+		1020	26	+	♀
440/30	+	271	+		1320	39		♀
1292/30		297	+		3400	52		♂
1700/30		244	+		1045	38		♀

TABLE 4.—*Continued*

FILE NO.	HYDRAMNION	DURATION OF PREGN.	DEAD BEFORE DELIVERY	BORN ALIVE AND DIED AFTER	WEIGHT (G.)	LENGTH (CM.)	SPINA BIFIDA	SEX
1174/34	+	242	+		1630	32	+	♀
2042/34		208	+		700	34	+	♀
834/35	+	204	+		995	25	+	♀
851/35	+	234	+		1000	34	+	♂
1522/35	+	220	+		900	35	+	♀
128/36	+	349	+		1520	35		♀
1798/37	+	222	+		1330	41		♂
1823/37		?	+		?	26		?
2301/37		210	+		395	27		♂
769/38	+	251	+		1710	44		♂
2023/38		303		14 hours	3600	45		♀
1485/39	+	276		45 min.	1705	46		♀
2236/40		324	+		1370	42	+	♀
619/43		310	+		3200	53		♀
1173/44		308		6 hours	3300	53		♀
1999/44		234		10 min.	1320	36		♂
2275/44		297		1 min.	3350	52		♀
2032/45		334	+		3100	52		♀
962/46		266	+		1800	38	+	♀
1463/46	+	219	+		950	37		♂
3512/47	+	328		35 hours	3580	57		♂
Total.....	33		47				12	42♀:24♂:1Δ

sudation of fluid may occur from the exposed nervous structures which have the same epiblastic origin as the amniotic epithelium.

Anencephaly. The sex distribution in the present material was 42 females: 24 males: one case of unknown sex. This corresponds to a sex ratio of about 2♀ : 1♂. The excess for the female sex thus is a little less in our material but still pronounced (cf. table 1).

Forty-seven propositi died before or during delivery. The remaining lived only for a short period varying from a few minutes to 35 hours.

The weight at birth has been recorded in 62 cases, the mean value being 2090.5 g., which is considerably below normal. The total length was recorded in 60 cases, the mean value being 41.4 cm.

The diagnosis of anencephaly needs no further comment as the condition is easily recognized, and a discussion of the variability of its manifestation is out of the scope of this paper. We only want to stress the fact that in 12 cases the brain defect was connected with a spina bifida aperta. These findings, which are in complete agreement with previous communications, may point to a causal connection between the two conditions.

Prematurity. As outlined above, anencephaly has repeatedly been observed

as a cause of fetal death in early pregnancy. Therefore, it is of particular interest to see how many will show full term development in an obstetrical series like the present one. We accept the following conventional definitions and limits. Concerning weight, if this is less than 2,500 g. the child is considered premature. Concerning length, the upper limit for abortion is 35 cm.; for prematurity, 47 cm.; and over 47 cm. is considered full term development. These figures will account for all fetuses without gross malformations. In anencephaly the malformation inevitably causes a reduction of weight due to the lack of brain tissue and also a reduction of length due to the skull defect. In a comparison with the development of normal fetuses this should in some way be corrected for.

The weight of the brain in the newborn is about 10 per cent of the total body weight. In anencephaly not all of the nervous tissue is lacking, but, on the other hand, the skull is defective. Presumably about 5 cm. of the length is lost in a full term anencephalic child due to the defect of the skull and the shortened

TABLE 5. DEVELOPMENT OF THE ANENCEPHALICS OF THE PRESENT MATERIAL ACCORDING TO THE WEIGHT AND LENGTH OF THE FETUS

Weight (grams):

250–750	750–1,250	1,250–1,750	1,750–2,250	2,250–2,750	2,750–3,250	3,250–3,750	over 3,750	Total
4	11	17	6	4	7	9	4	62

Length (centimeters):

20–25	25–30	30–35	35–40	40–45	45–50	50–55	over 55	Total
1	6	6	12	11	12	10	2	60

neck. Therefore it seems reasonable to estimate that about 10 per cent of the weight and 10 per cent of the length are lost due to the malformation. The limit between premature and full term development has to be lowered correspondingly. From table 5 it can easily be seen how many fetuses may be considered premature according to any chosen limit. We think it justified to judge fetuses below 2,250 g. in weight or below 40 cm. in length as not fully developed. This would give a figure of about 40 to 60 per cent premature anencephalics in this material. Even if we lower the limit to 1,750 g. and 35 cm., this will still give a figure of 20 to 50 per cent unquestionably premature fetuses. There is thus even in obstetrical material a strong tendency toward premature birth in anencephaly.

The Mothers of Anencephalics

Anamnestic data. Complete anamnestic data have been obtained for the 46 mothers who have been visited and examined by us. An analysis of these data has not given the slightest indication that any special clinical or pathological condition of the mother may have a connection with the birth of the anence-

phalic child. 31 mothers claimed that they always had been perfectly healthy up to the time when the anencephalic was born.

Condition during anencephalic pregnancy. According to the 67 clinical records, of which 46 cases were completed by personal inquiry, 51 mothers had no disorders whatsoever during pregnancy. In the remaining 16 cases the following conditions, apparently without significance as for the etiology of anencephaly, have been recorded:

Albuminuria, 3 cases
Diabetes mellitus, 1 case
Periodic vomiting + swollen legs, 1 case
Edema of the legs + slight albuminuria, 1 case
Arterial hypertension, 1 case
Medium anemia, 3 cases
Edema of the legs without albuminuria, 2 cases
Visual disturbances + edema of the legs + albuminuria, 1 case
Cystopyelitis, 1 case
Thrombosis of left leg, 1 case
Oophoritis, 1 case.

All of these are conditions often met with in pregnancies which terminate with the birth of a normal baby, and we do not think they represent anything of significance.

No evidence of syphilitic infection has been obtained in any case. A special inquiry as to infection with German measles during early pregnancy gave a completely negative result. As mentioned above, a search for Rh-incompatibility as a possible etiological factor gave a negative result too.

Maternal age. Maternal age has often been claimed as a factor in human congenital malformations (Penrose, 1946, and others). As far as we know, it has hitherto been clearly demonstrated beyond doubt only in mongoloid idiocy, for we cannot accept calculations based upon a collection of different malformations which may have a quite different etiology.

For the following statistical analysis we are indebted to Professor C. E. Quensel, F. D., and to Mr. H. Ambjörn, F. K., who helped calculate tables 7–10.

The age distribution of the mothers of the propositi has been compared with the normal distribution during 1916–1945 in the same area (Malmöhus Län) as that from which the propositi were collected. Children born in and out of wedlock have been treated separately.

The actual age distribution on which the analysis was based is shown in tables 6–9. The results of the statistical analysis appear in tables 10 and 11.

We have reached the conclusion that maternal age is undoubtedly *not* of significance in anencephaly. As for illegitimate anencephalics the material is too small to allow a chi-square calculation but the correspondence between observed and expected figures is nevertheless good.

The distribution of the anencephalics of married and unmarried women is likewise in good correspondence with the expected figures (cf. table 11).

The Sibships of the Anencephalic Probosili

Suppose that anencephaly were caused by a single recessive gene (point mutation or chromosome deficiency) with complete manifestation and that this

TABLE 6. MATERNAL AGE OF ANENCEPHALIC CHILDREN BORN INTRAMATRIMONIALLY (3 CASES HAVE BEEN EXCLUDED AS OFFICIAL STATISTICAL FIGURES FOR COMPARISON LATER THAN 1945 ARE NOT AVAILABLE)

AGE OF MOTHERS, (YRS.)	DISTRIBUTION OF ANENCEPHALICS ACCORDING TO 5 YEAR PERIODS 1916–20	1921–25	1926–30	1931–35	1936–40	1941–45	TOTALS
15–20	—	—	—	1	—	—	1
20–25	1	1	2	3	2	3	12
25–30	1	1	3	1	4	3	13
30–35	1	4	1	2	4	1	13
35–40	1	1	2	—	3	3	10
40–45	—	—	—	—	2	1	3
Totals.....	4	7	8	7	15	11	52

TABLE 7. MATERNAL AGE OF ALL CHILDREN BORN INTRAMATRIMONIALLY IN MALMÖHUS LÄN, SWEDEN (THE INVESTIGATION AREA). ACCORDING TO SWEDISH OFFICIAL STATISTICS

AGE OF MOTHERS, (YRS.)	DISTRIBUTION OF CHILDREN ACCORDING TO 5 YEAR PERIODS 1916–20	1921–25	1926–30	1931–35	1936–40	1941–45	TOTALS
-20	474	633	658	643	855	1158	4421
20–25	7411	7316	6808	6203	7301	9715	44754
25–30	12011	11148	9538	9077	10548	13751	66073
30–35	9687	9282	7774	6790	8211	11404	53148
35–40	7287	6535	4996	4179	4360	6189	33546
40–45	3199	2796	2181	1624	1492	1682	12974
45–50	247	248	214	140	132	125	1106
50–55	—	—	—	—	1	—	1
Totals.....	40316	37958	32169	28658	32900	44024	216023

gene did not cause an interruption of the pregnancy before full term. Then we should expect to find about 25 per cent anencephalic children among the sibs. Evidently it is not as simple as that. Anencephaly is repeated in the sibships with a very low frequency in the neighborhood of 1 per cent (cf. Penrose, 1946). However, if we consider a gene having a lethal effect mainly at an early stage during embryonal development, any percentage between 0 and 25 may be found. Thus the fact that a congenital defect is repeated in the sibships with

a very low frequency is by itself no conclusive evidence against a genetical etiology.

In the foregoing we have been trying to show that anencephaly very often causes the interruption of the pregnancy before term and that many anencephalic pregnancies end with early abortions. Thus, assuming a simple recessive gene, a frequency of 25 per cent is not to be expected. On the other hand, we should expect a relatively high frequency of abortions in the sibships of the propositi.

TABLE 8. MATERNAL AGE OF ANENCEPHALIC CHILDREN BORN EXTRAMATRIMONIALLY

AGE OF MOTHERS, (YRS.)	DISTRIBUTION OF ANENCEPHALICS ACCORDING TO 5 YEAR PERIODS 1916–20	1921–25	1926–30	1931–35	1936–40	1941–45	TOTALS
15–20	—	—	1	—	1	—	2
20–25	—	—	3	2	—	2	7
25–30	—	1	—	—	1	—	2
30–35	—	—	1	—	—	—	1
Totals.....	0	1	5	2	2	2	12

TABLE 9. MATERNAL AGE OF ALL CHILDREN BORN EXTRAMATRIMONIALLY IN MALMÖHUS LÄN, SWEDEN (THE INVESTIGATION AREA). ACCORDING TO SWEDISH OFFICIAL STATISTICS

AGE OF MOTHERS, (YRS.)	DISTRIBUTION OF CHILDREN ACCORDING TO 5 YEAR PERIODS 1916–20	1921–25	1926–30	1931–35	1936–40	1941–45	TOTALS
-20	1484	1694	1866	1655	1602	1494	9795
20–25	3571	3494	3390	2791	2258	2053	17557
25–30	1660	1474	1300	1040	821	829	7124
30–35	817	655	509	409	409	435	3234
35–40	455	394	279	217	213	256	1814
40–45	162	152	112	85	70	86	667
45–50	11	13	9	4	4	4	45
Totals.....	8160	7876	7465	6201	5377	5157	40236

Calculations According to the Propositus Method of Weinberg

In 4 families there are twin pairs and in 3 cases one of the twins was an anencephalic. Since conclusive evidence about these pairs being mono- or dizygotic is lacking in every case, we think it better to exclude these families from the calculations.

There remain 42 families. After the usual exclusion of the propositi we find here 86 children born alive and without any malformation, 1 stillborn of unknown cause (no malformation), 1 child with rachischisis (stillborn) and 22 spontaneous abortions. Thus, if we consider craniorachischisis as an entity,

this condition was found in the sibships with a frequency of 0.9 per cent. However, the frequency of spontaneous abortions among the mothers of anencephalic propositi is 20 per cent. As for the craniorachischisis group, the empirical risk figure found here is lower than that given by Penrose (1946), but considering that we are forced to deal with small numbers we may for practical purposes preliminarily state:

If a woman has borne a child with anencephaly the mean risk figure that any subsequent pregnancy will result in another full-term or nearly full-term baby with a craniorachischisis malformation is about 1 per cent. However, the risk that such a pregnancy will end with spontaneous abortion is about 20 per cent.

TABLE 10. STATISTICAL ANALYSIS OF MATERNAL AGE OF ANENCEPHALICS AS COMPARED WITH THE TOTAL POPULATION OF BIRTHS FROM TABLES 7 AND 9

BORN INTRAMATRIMONIALLY			BORN EXTRAMATRIMONIALLY		
Age of mother (years)	Observed	Expected	Age of Mother (years)	Observed	Expected
15–25	13	11.84	15–20	2	2.92
25–30	13	15.90	20–25	7	5.24
30–35	13	12.79	25–30	2	2.12
35–45	13	11.20	30–35	1	0.96

$\chi^2 = 1.20$, D.F. = 3.

TABLE 11. ANENCEPHALICS BORN INTRAMATRIMONIALLY AND EXTRAMATRIMONIALLY COMPARED WITH THE TOTAL POPULATION OF BIRTHS

	EXTRAMATRIMONIAL	INTRAMATRIMONIAL	TOTAL
Anencephalics	12	52	64
Total births	40,236	216,023	256,259

$\chi^2 = 0.45$, D.F. = 1.

SOME GENETICAL CONSIDERATIONS

As we have some reason to suspect that the aborted embryos produced by the mothers of anencephalic full term babies really contain anencephalic embryos it may be justified to add a genetical analysis based on this hypothesis. Furthermore, we assume that we are dealing with a simple recessive lethal gene. The material, i.e. the 46 completely examined sibships used here, will be found in table 12. The expected number of affected individuals (by which is meant here the abortions too) for every different sibship size can be calculated from the expansion of $(a + 3b)^n$ and omitting sibships expected to have only normal members. These latter would naturally never appear in any sample of this kind. For the principles of this calculation the reader is referred to Macklin

(1938). The analysis, summarized in table 13, appears to show that the distribution is such as might be expected in simple recessive inheritance.

TABLE 12. SYNOPSIS OF THE 46 COMPLETELY EXAMINED SIBSHIPS

Legend:

N*m* Male, no malformation.
N*f* Female, no malformation.
A*m*, A*f* Anencephalus, male, female respectively.
A*u* Anencephalus, unknown sex.
As*m*, As*f* Anencephalus with spina bifida, male, female respectively.
S*m* Spina bifida, male.
D*m*, D*f* Stillborn, cause unknown, male and female respectively.
M Spontaneous abortion.
F*m*, F*f* Feebleminded male and female respectively.
E*m* Epilepsy, male.
Propositus in brackets. A dash between two individuals means twins.

File No. KKL		*File No.* KKM	
91/23	N*f* F*m* (Af)	1134/19	N*f* (A*f*)
348/25	N*f* (A*m*) N*f* N*f* N*f*	661/20	N*f*-(A*f*) N*m* N*m*
1740/26	N*f* N*m* (A*f*) N*m* N*m*	788/23	N*m* N*f* (A*f*)
824/27	(As*f*) N*f*	621/24	(A*f*) N*f* N*m* N*f*
1772/30	(As*f*) N*f* M M M M	662/24	(A*m*)-D*m*
2121/31	(A*f*)	278/27	(As*f*) E*m* N*f* N*f*
1620/36	N*f* N*m* N*m* (A*f*)	1205/27	N*m* N*f* (A*m*) N*f* N*f*
1676/37	N*f* N*f* F*m* N*f* (A*f*)	1558/27	(A*f*)
338/38	N*m* N*f* N*m* N*f* N*m* (A*f*)	440/30	(A*f*) M N*m* N*f* N*m* N*m* M M
410/39	N*f* N*f* N*m* N*f* N*f* N*m*-(A*m*) N*f*	1292/30	N*f* M M N*m* N*m* (A*m*) N*m*
513/40	N*f* N*m* N*m* N*f* N*f* M M (A*m*) N*f*	1174/34	(As*f*) N*f*
1385/40	(A*m*) N*f* N*f*	2042/34	(As*f*) N*m* N*f*
2717/40	(A*f*) N*m*	834/35	S*m* (As*f*) N*m* N*m* N*m*
2541/43	N*f* M M (A*f*) N*m*	1522/35	(As*f*)
3511/43	M M (A*f*) N*m*	128/36	(A*f*) N*f* N*m* M M
3793/43	(A*m*) M N*m*	1823/37	N*m*-D*m* (A*u*)
4080/43	D*m* (A*m*) F*f* N*f*	2301/37	(A*m*) N*m* N*m* N*f*
2556/44	N*m* (A*m*) N*f*	2023/38	(A*f*) N*m*
1365/45	M M (A*m*) N*m*	1485/39	(A*f*) M N*m*
4416/45	M (A*f*)	2236/40	(As*f*) N*m* N*m*
		1173/44	(A*f*) D*m* N*m*
		2275/44	N*m* N*f* (As*f*)
		2032/45	N*m* (A*f*)
		962/46	(As*f*)
		1463/46	(A*m*) N*f*
		3512/47	N*m* N*m* (A*m*)

A test according to Macklin's (1938) Percentage Affected Method is shown in table 14. The correspondence between observed and expected figures is very

good. However, it is more reasonable to assume that not all abortions have the same etiology. The slight tendency of an increase of the abortion rate in the larger sibships seen in table 14, and the slight accumulation on the last birth ranks (cf. table 19) may indicate that the etiology is not the same in all cases.

Suppose that only half the abortions are caused by the "anencephalic gene."

TABLE 13. DISTRIBUTION OF AFFECTED INDIVIDUALS (ASSUMING THAT ALL ABORTIONS RECORDED ARE ANENCEPHALICS) IN SIBSHIPS OF VARYING SIZE. EXPECTED FREQUENCIES ARE BASED ON THE EXPANSION OF $(a + 3b)^n$ (CF. MACKLIN, 1938).

NUMBER AFFECTED	SIBSHIP SIZE, n								TOTAL SIBSHIPS		$(O - c)^2/c$
	2	3	4	5	6	7	8	9	Observed O	Expected c	
1	8	10	6	4	1	0	1	0	30	27.09	0.31
2	1	2	0	1	0	0	0	0	4	11.18	
3	—	0	2	2	0	1	0	1	6	2.90	
4	—	—	0	0	0	0	1	0	1	0.65	
5	—	—	—	0	1	0	0	0	1	0.13	
6	—	—	—	—	0	0	0	0	0	0.02	0.57
7	—	—	—	—	—	0	0	0	0	0.00	
8	—	—	—	—	—	—	0	0	0	0.00	
9	—	—	—	—	—	—	—	0	0	0.00	
Total no. sibships.....	9	12	8	7	2	1	2	1	42	41.97	0.88

$\chi^2 = 0.88$, D.F. = 1, $P = 0.35$.

TABLE 14. SINGLE RECESSIVE TEST ACCORDING TO MACKLIN'S "PERCENTAGE AFFECTED METHOD." IT IS ASSUMED THAT ALL ABORTIONS IN THESE SIBSHIPS ARE GENETICALLY ANENCEPHALIC

NUMBER OF PREGNANCIES IN FAMILY	TOTAL NUMBER OF PREGNANCIES	AFFECTED CHILDREN		NORMAL CHILDREN		$\Sigma(O - c)^2/c$.
		Observed O	Expected c	Observed O	Expected c	
2	18	10	10.26	8	7.74	0.015
3	36	14	15.48	12	10.52	0.350
4	32	12	11.84	20	20.16	0.003
5	35	12	11.55	23	23.45	0.026
6–9	44	17	12.54	27	31.46	2.219
Total.....	165	65	61.67	90	93.33	2.613

$\chi^2 = 2.613$, D.F. = 5, $0.70 < P < 0.80$.

If we add these to the anencephalics and the spina bifida case, presumably being of the same origin, we would have 58 affected individuals out of a total of 169, or 34 per cent. This is still not far from what one might expect for a simple recessive lethal for an average family size of 3.7 children.

The possible mutation rate, assuming that the Hardy-Weinberg formula

would hold for this fairly common gene, would be 6.4×10^{-4} chromosome per generation, according to the frequency determined earlier in this paper. This would mean that one person out of every 770 had a mutation from the normal to the "anencephalic gene" (This does not include any abortions).

However, as presumed above, the manifestation of this gene would in most cases occur as spontaneous abortion. Considering the spina bifida case of this material as genetically anencephalic, only one case was recognized among a total of 110 from presumably **Aa** × **Aa** matings (cf. p. 73 and table 15). On the other hand, 22 abortions were found. Thus, taking the other extreme and considering all abortions as genetically anencephalic, the condition could be diagnosed only in one case out of 23 presumably **aa** lethals, or in other words there would be 23 times as many pregnancies with a genetically anencephalic embryo as appears from the apparent frequency in an obstetrical material.

TABLE 15. LETHAL OUTCOME OF PREGNANCIES FOR MOTHERS OF ANENCEPHALIC PROPOSITI IN THE PRESENT MATERIAL, COMPARED WITH PREGNANCIES OF 1400 MOTHERS OF NORMAL PROPOSITI SELECTED BY FILE NUMBER COVERING THE PERIOD 1925 TO 1945 AT THE OBSTETRIC DEPARTMENT, UNIVERSITY CLINIC OF LUND

PREGNANCIES WITH KNOWN OUTCOME	ABORTIONS & STILLBIRTHS (LETHAL)	BORN ALIVE (NON-LETHAL)	TOTAL
Anencephalic propositus	24	86	110
Normal propositus	265	3289	3554
Total	289	3375	3654

$\chi^2 = 30.3$, D.F. = 1, $P < 0.001$.

Now a minimum estimate of the rate of spontaneous abortions in the Swedish population is 10 per cent. Thus the 104,812 deliveries of this material would at least correspond to 116,458 pregnancies. The 67 anencephalics should all come from **Aa** × **Aa** matings, but some matings of the same type would produce a number of **aa** genotypes all of which result in abortions, and naturally some would produce **AA** and **Aa** genotypes only. We would expect in this sample 1474 (22 × 67) pregnancies with an anencephalic embryo which terminate with abortions. Thus among the total of 116,458 pregnancies, 1541 (1474 + 67) could be considered genetically anencephalic embryos. The frequency of **aa** lethal genotypes would be 1541/116,458 or about 1.3 per cent. This would mean a very high mutation rate of 1.3×10^{-2} chromosome per generation or one person out of every 40 would have a mutation. However, this does not necessarily imply the rate of mutation at a special locus. The nervous structures are very sensitive during early embryonic stages, and point mutations or chromosome deficiencies which occur at different loci may have the same effect on the development of the brain and spinal cord. In other words, anencephaly and

allied disturbances may result from single recessives at different loci. The mutation rate discussed here (6.4×10^{-4} to 1.3×10^{-2}) thus may be considered more as a collected rate for mutations at different gene loci affecting the development of the brain and spinal cord and producing a more or less similar pathological picture.

The estimate of about 11,646 spontaneous abortions belonging to the present sample of 104,812 pregnancies furthermore would mean that 1474/11,646 or about 12% of all spontaneous abortions would be caused by lethal mutations affecting the nervous system.

The considerations under this heading are obviously very speculative but it seems very important to stress such interpretations which may be checked by further research. Abortions and stillbirths may be caused by lethal factors

TABLE 16. LETHAL OUTCOME OF PREGNANCIES FOR MOTHERS OF ANENCEPHALIC PROPOSITI IN THE PRESENT MATERIAL, COMPARED WITH PREGNANCIES OF 59 MOTHERS OF NORMAL RECRUIT PROPOSITI SELECTED FOR STUDIES OF DENTAL CARIES

PREGNANCIES WITH KNOWN OUTCOME	ABORTIONS & STILLBIRTHS (LETHAL)	BORN ALIVE (NON-LETHAL)	TOTAL
Anencephalic propositus	24	86	110
Recruit propositus	27	205	232
Total	51	291	342

$\chi^2 = 6.3$, D.F. = 1, $P = 0.012$.

to a much greater extent than most obstetricians and gynecologists today are inclined to think.

The Frequency of Abortions

The figure of 20 per cent in the present material has to be compared with a normal material in order to decide if the deviation is significant. The situation is that among a number of women selected under the conditions given above, which includes that they are women capable of giving birth to normal children, the frequency is 20 per cent. This figure cannot be compared with the general frequency of abortion obtained by random selection of a number of women, as then also women not able to produce full term babies (i.e. cases with habitual abortions only) will be included.

To obtain a suitable control material we have selected by file number from 1925 to 1945, 100 mothers of normal babies for each year an anencephalic was born at the Obstetrical Department, Lund. This material was treated according to the propositus method, too. All abortions and stillborns had been carefully noted in the files.

In this comparison we have included all pregnancies with lethal (abortions

and stillborns) as well as non-lethal outcome. As is seen in table 15, the difference is statistically highly significant. In the control material the mean frequency of lethal outcome of pregnancies for women who have had at least one normal baby is 7.5 per cent.

As some error may arise from taking a control material in this way due to the fact that abortions may accumulate at the end of the fertile period (7.5 per cent is in fact abortions previous to the last normal child) we have also made a comparison with another control material of women who were beyond the reproductive period.

In another investigation carried out at our institute on dental caries, 59

TABLE 17. BIRTH RANKS OF ANENCEPHALIC PROPOSITI OF THE PRESENT MATERIAL. ABORTIONS ARE INCLUDED IN THIS CALCULATION

TOTAL NUMBER OF SIBS	NUMBER OF ANENCEPHALICS WITH BIRTH RANK 1	2	3	4	5	6	7	8	9	EXPECTED NUMBER EACH RANK	CORRECTED OBSERVED NUMBER FIRSTBORN	CORRECTED EXPECTED NUMBER EACH RANK	CORRECTED OBSERVED NUMBER LASTBORN
1	3	—	—	—	—	—	—	—	—	—	—	—	—
2	6	3	—	—	—	—	—	—	—	4.5	6.0	4.5	3.0
3	6	1	5	—	—	—	—	—	—	4.0	9.0	6.0	7.5
4	3	2	3	1	—	—	—	—	—	2.3	6.0	4.6	2.0
5	1	2	—	2	2	—	—	—	—	1.4	2.5	3.5	5.0
6	1	—	—	—	—	1	—	—	—	0.3	3.0	0.9	3.0
7	—	—	—	—	—	1	2	—	—	0.4		1.4	7.0
8	1	—	—	—	—	—	—	—	—	0.1	4.0	0.4	
9	—	—	—	—	—	—	—	1	—	0.1		0.5	
Totals.....	18 = *firstborn*							*lastborn* = 14		13.1	30.5	21.7	27.5

mothers of recruit propositi were thoroughly interviewed about their pregnancies. Lethal outcome was found in 11.6 per cent. The difference in comparison with the present material is still significant (cf. table 16).

We may thus state with considerable certainty that lethal outcome of pregnancies is more frequent in women who have had an anencephalic child.

The Birth Ranks of Anencephalics

When a trait is caused exclusively by genotypical factors it should be evenly distributed for all birth ranks, the first, second, third, etc., child having exactly the same chance to be affected. If, for instance, the first child is more often affected, birth trauma may be a factor; if it is the last, the age of the mother may have something to do with the condition.

The distribution of different birth ranks was tested according to the method of Weinberg and Schulz (cf. Schulz, 1936). When sibships with a different

number of siblings are summarized the sums of the expected figures for the different birth ranks should be compared with the corresponding sums of the observed figures. In this calculation we have only one anencephalic (the propositus) in each sibship. Children without sibs must be left out of consideration. The expected frequency for any birth rank is $\Sigma(a_n)/n$, where a_n is the observed number of affected individuals included in sibships of n members. By this it is assumed that each individual has the same chance for any particular birth position. Starting with the left half of table 17 the following expected figures have been calculated:

TOTAL NUMBER OF SIBS n	EXPECTED NUMBER OF ANANCEPHALICS WITH BIRTH RANK 1	2	3	4	5	6	7	8	9
1	—								
2	4.5	4.5							
3	4.0	4.0	4.0						
4	2.3	2.3	2.3	2.3					
5	1.4	1.4	1.4	1.4	1.4				
6	0.3	0.3	0.3	0.3	0 3	0.3			
7	0.4	0.4	0.4	0.4	0.4	0.4	0.4		
8	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	
9	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Total expected:	13.1	13.1	8.6	4.6	2.3	0.9	0.6	0.2	0.1
Total observed:	18	8	8	3	2	2	2	1	0

A chi-square test may be applied as follows:

BIRTH RANK	O	c	$(O-c)^2/c$
1	18	13.1	1.83
2	8	13.1	1.99
3	8	8.6	0.04
4–9	10	8.7	0.19
Totals	44	43.5	4.05

$\chi^2 = 4.05$, D.F. $= 3$, $0.20 < P < 0.30$

Consequently there is no objection to the assumption of a random distribution on the different birth numbers.

This calculation may be accepted as a reasonable estimation. However, it is affected with a minor incorrectness. If we want to score primogeniture against ultimogeniture the fact that the distance between the firstborn and the lastborn is a function of the number of siblings of each sibship must be taken into consideration. Thus, for instance, the difference between the firstborn and the lastborn must have a greater significance in a sibship of ten members than in a sibship of two only.

If we examine further especially the frequency of firstborn anencephalics as compared with lastborn the following correction may be applied (according to

Weinberg-Schulz). The significance of a four member sibship is two times greater than that of a two member, that of a six member sibship three times greater, etc. Obviously 3, 5, 7, member sibships have to be multiplied by 3/2,

TABLE 18. BIRTH RANKS OF ANENCEPHALIC PROPOSITI OF THE PRESENT MATERIAL. ABORTIONS ARE NOT INCLUDED IN THIS CALCULATION

TOTAL NUMBER OF SIBS	NUMBER OF ANENCEPHALICS WITH BIRTH RANK 1	2	3	4	5	6	7	8	9	EXPECTED NUMBER EACH RANK	CORRECTED OBSERVED NUMBER FIRSTBORN	CORRECTED EXPECTED NUMBER EACH RANK	CORRECTED OBSERVED NUMBER LASTBORN
1	4	—	—	—	—	—	—	—	—	—	—	—	—
2	11	2	—	—	—	—	—	—	—	6.5	11.0	6.5	2.0
3	5	2	5	—	—	—	—	—	—	4.0	7.5	6.0	7.5
4	3	2	1	1	—	—	—	—	—	1.8	6.0	3.6	2.0
5	1	2	—	1	3	—	—	—	—	1.4	2.5	3.5	7.5
6	—	—	—	—	—	1	—	—	—	0.2	—	0.6	3.0
7	—	—	—	—	—	1	2	—	—	0.4	—	1.4	7.0
8	—	—	—	—	—	—	—	—	—	—	—	—	—
9	—	—	—	—	—	—	—	—	—	—	—	—	—
Totals.....	20 = *firstborn*								*lastborn* = 14	14.3	27.0	21.6	29.0

TABLE 19. BIRTH RANKS OF SPONTANEOUS ABORTIONS OF THE PRESENT MATERIAL. ALL PREGNANCIES WITH KNOWN OUTCOME ARE INCLUDED

TOTAL NUMBER OF SIBS	NUMBER OF ABORTIONS WITH BIRTH RANK 1	2	3	4	5	6	7	8	9	EXPECTED NUMBER EACH RANK	CORRECTED OBSERVED NUMBER FIRSTBORN	CORRECTED EXPECTED NUMBER EACH RANK	CORRECTED OBSERVED NUMBER LASTBORN
1	—	—	—	—	—	—	—	—	—	—	—	—	—
2	1	—	—	—	—	—	—	—	—	0.5	1.0	0.5	—
3	—	2	—	—	—	—	—	—	—	0.7	—	1.2	—
4	2	2	—	—	—	—	—	—	—	1.0	4.0	2.0	—
5	—	1	1	1	1	—	—	—	—	0.8	—	2.0	2.5
6	—	—	1	1	1	1	—	—	—	0.7	—	2.1	3.0
7	—	1	1	—	—	—	—	—	—	0.3	—	1.1	—
8	—	1	—	—	—	—	1	1	—	0.4	—	1.6	4.0
9	—	—	—	—	—	—	1	1	—	0.2	—	0.9	—
Totals.....	3 = *firstborn*								*lastborn* = 3	4.6	5.0	11.4	9.5

5/2, 7/2, etc. The corrected observed and expected figures in tables 17, 18 and 19 have been calculated according to this principle. When comparing these corrected figures no apparent deviation was found. So our conclusion is that primogeniture or ultimogeniture apparently cannot be claimed as having a connection with anencephaly.

DISCUSSION

Even if we cannot reject fully the idea of anencephaly being caused by some exogeneous factor, no evidence whatsoever has been found in favor of such a conception. On the other hand, the interpretation of the genetical analysis is hampered by the fact that practically nothing is known about the abortion produced by the mothers of anencephalic propositi. On the whole our knowledge about the condition of aborted embryos is very deficient and still remains a gap to be filled by future research.

It is reasonable to assume that the relatively high abortion rate of the mothers in the present material has some connection with anencephaly. The fact that cranio-rachischisis often has been found in early aborted embryos points in this direction. Thus there seems to be a relationship between this condition in man and pseudencephaly in the mouse (cf. Bonnevie, 1936). The conception of a genetical etiology is also supported or is not contradicted by the fact that no systematic deviation is found when the position in the birth rank or the age of the mothers was tested.

As anencephaly occurs with an apparent frequency of about 0.1 per cent, a raised frequency of consanguineous marriages among the parents might be expected, i.e. if caused by a simple recessive lethal with complete manifestation. However, considering that most anencephalic embryos may abort in early pregnancy, and thus are not recognized, the true frequency should be much higher. Furthermore anencephaly and spina bifida might be different manifestation types of the same biological entity, which should increase the apparent frequency to about 0.2 per cent at least. Under such circumstances only a slight increase in the frequency of consanguineous marriages is to be expected, and a very large material would be necessary to make this apparent. This consideration, of course, would imply that cranio-rachischisis was thought of as a genotypical entity.

Actually the very high mutation rate (see p. 77) which would be the consequence of such an assumption forms an objection to this view. However, this estimated high mutation rate might, as indicated on p. 78, represent a sum for two or several different recessive genes. As each one of these genes would have a lower frequency this would work in the opposite direction, i.e. increase the proportion of cases which might be expected to arise from consanguineous matings. It still, however, would be quite small, unless there were a large number of different loci involved.

We think that the theory of anencephaly in man as caused by a lethal genotypical factor (not necessarily meaning one and the same genotypical entity) seems well founded as a working hypothesis to be tested by further research. By that we admit that from a critical point of view the proof of a genetical

etiology has so far not been adduced, although the available data are highly suggestive of such an explanation.

From a practical point of view it is very important to know to what extent abortions and stillbirths in human populations are caused by genotypical factors. For instance, a treatment to retain the embryo in the uterus in threatening abortion when the condition is caused by genotypical factors which have a lethal or semilethal effect is naturally not indicated. There is every reason to believe that such factors are common in human populations just as in natural populations of different animals and plants.

SUMMARY

1. The present study concerns 67 cases of anencephaly belonging to 67 different sibships covering all cases delivered at the Obstetric Departments of Lund and Malmö during 1923–45 and 1917–47 respectively.

2. The incidence of anencephaly in the present material is 0.064 per cent (67 cases out of 104,812 deliveries).

3. The sex distribution was 42 females: 24 males: 1 case of unknown sex.

4. It is estimated that only about 50 per cent of the anencephalics reached a full term development. At least 10 per cent could be classified as late abortions and the rest as premature.

5. Forty-six families (parent-sibships) have been visited and examined by the present authors. No special diseases of the parents and especially of the mothers during pregnancy which could reasonably have a connection with the present malformation have been found.

6. Among the sibs of the anencephalic propositi no further cases of anencephaly were found, but one case of stillbirth with spina bifida was observed.

7. The frequency of abortions among the mothers of anencephalic propositi is significantly increased as compared with a suitable control material of our own.

8. In the present material there is one marriage between first cousins and one between second cousins out of 67 families. Thus a slight increase may be possible, but the material is too small for a proper evaluation.

9. The age of the mothers when the anencephalic children were born corresponds to that expected on the basis of random distribution.

10. Anencephalic children are probably distributed at random throughout the different birth ranks. A special test for primogeniture or ultimogeniture gave a negative result.

11. On the basis of the evidence of this study and in the literature we think that the theory of anencephaly in man as caused by a lethal genotypical factor seems well founded as a working hypothesis. It is then assumed that most anencephalic embryos will abort at an early stage and pass away as undiagnosed

abortions and that full term development (or easily recognized anencephaly) is exceptional.

REFERENCES

ANGEVINE, D. M. 1938. Pathologic anatomy of hypophysis and adrenals in anencephaly. *Arch. Path.*, Chic. 26: 507–518.

BALLANTYNE, J. W. 1904. *Manual of Antenatal Pathology and Hygiene;* Vol. II. *The Embryo.* Edinburgh: Wm. Green & Sons. Pp. 332–350.

BONNEVIE, K. 1936. Pseudencephalie als spontane recessive Mutation bei der Hausmaus. *Skr. Norske Vidensk. Akad.*, Oslo. 1. Mat.-Nat.-vid. Klasse, No. 9.

BONNEVIE, K. 1940. Tatsachen der genetischen Entwicklungsphysiologie. *Handbuch der Erbbiologie des Menschen.* Bd. I. Berlin: J. Springer. pp. 73–180.

DODDS, & DE ANGELIS, E. 1937. An anencephalic human embryo 16.5 mm. long. *Anat. Rec.* 67: 499–505.

DUNN, H. G., & SALTER, J. G. 1944. Recurrent anencephaly. *J. Obst. Gyn. Brit. Empire,* 51: 529–536.

ERNST, P. 1909. *Missbildungen des Nervensystems.* In Schwalbe's: *Die Morphologie der Missbildungen des Menschen und der Tiere.* Jena: Fischer. Teil 3, Abt. 2, Kap. 2.

HAMMER, E. 1933. Zur Aetiologie der Spaltbildungen am Neuralrohr. *Zbl. allg. Path.* 56: 289–295.

HARBESON, A. E. 1939. Anencephaly in human embryo ten millimeters long. *Am. J. Obst.* 38: 167–168.

HIILESMAA, V. 1945. A study of anencephalus and hydrocephalus deliveries. *Acta. obst. gyn. scand.* 25: (Supp. 1): 27–50.

JOSEPHSON, J. E., & WALLER, K. B. 1933. Anencephaly in identical twins. *Canad. M. Ass. J.* (new ser.) 29: 34–37.

MACKLIN, M. T. 1938. Methods of correcting pedigree data. *J. Hered.* 29: 295–303.

MALL, F. P. 1917. On the frequency of localized anomalies in human embryos and infants at birth. *Am. J. Anat.* 22: 49–73.

MALPAS, P. 1937. The incidence of human malformations and the significance of changes in the maternal environment in their causation. *J. Obst. Gyn. Brit. Empire,* 44: 434–454.

OSSENKOPP, G. 1932. Die Entstehung der hirnlosen Missgeburten. *J. Psychol. Neur.*, Lpz. 44: 613–638.

PENROSE, L. S. 1946. Familial data on 144 cases of anencephaly, spina bifida and congenital hydrocephaly. *Ann. Eugen.*, Cambr. 13: 73–99.

SCHADE, H. 1939. Beitrag zur Erblichkeit der Anencephalie. *Erbarzt,* 7: 116–120.

SNELL, G. D., & PICKEN, D. I. 1935. Abnormal development in the mouse caused by chromosome unbalance. *J. Genet.*, Cambr. 31: 213–235.

STRÖER, W. F. H., & VAN DER ZWAN. 1939. Anencephaly and rachischisis posterior with the description of a human hemicephalus of 18 mm. *J. Anat.*, Lond. 73: 441–450.