Anencephaly in France

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ANENCEPHALY is the most severe and most easily recognized malformation of the central nervous system. It is, therefore, a suitable characteristic for a survey of incidence, a study of geographical variations, and comparisons among different populations. Furthermore, such a study provides an opportunity to approach the fundamental problem of the etiology of congenital malformations.

Many valuable contributions on anencephaly are available as well as several comprehensive reviews and stimulating discussions (Penrose, 1946, 1957; Böök and Rayner, 1950; Record and McKeown, 1950; Record, 1961; MacMahon, Pugh, and Ingalls, 1953; Ingalls, Pugh and MacMahon, 1954; Coffey and Jessop, 1957; Edwards, 1958; Neel, 1958; Searle, 1959; Gittelsohn and Milham, 1962; Masterson, 1962; Hewitt, 1963).

This study is an attempt to ascertain the total incidence of anencephaly in France, as well as local variations, either secular or geographical. An attempt will be made to correlate these with factors of causal significance. Data also are presented on familial incidence and associated malformations.

ASCERTAINMENT OF MATERIAL

A brief form was designed which included two items: (1) total number of births for the period 1945 to 1955 inclusive and (2) number of anencephalic children per sex and year of birth. This form was sent to the obstetricians in public hospitals, excluding private hospitals and clinics, in 99 cities in France, each of at least 20,000 inhabitants. For Paris, we collected the data in seven maternity departments of public hospitals. Statistics were received from 84 cities, five of which were excluded later because of incomplete or inadequate data. From these 78 cities (86 maternity departments), a total of 746,276 births, including 402 anencephalic births, were recorded (Fig. 1).

The obstetricians in these 86 maternity departments then were requested to provide further information concerning the anencephalic births. In some instances, the physicians were able to make special inquiries, but in no case was it possible for us to interview the families of the propositi directly. We were requested by several physicians, for deontologic reasons, not to attempt such direct contact. At the completion of this survey, we were able to obtain adequate information about 299 patients.

To compare data, we used the general population statistics of the various districts (*départements*) of France for the period 1945 to 1954, the table of

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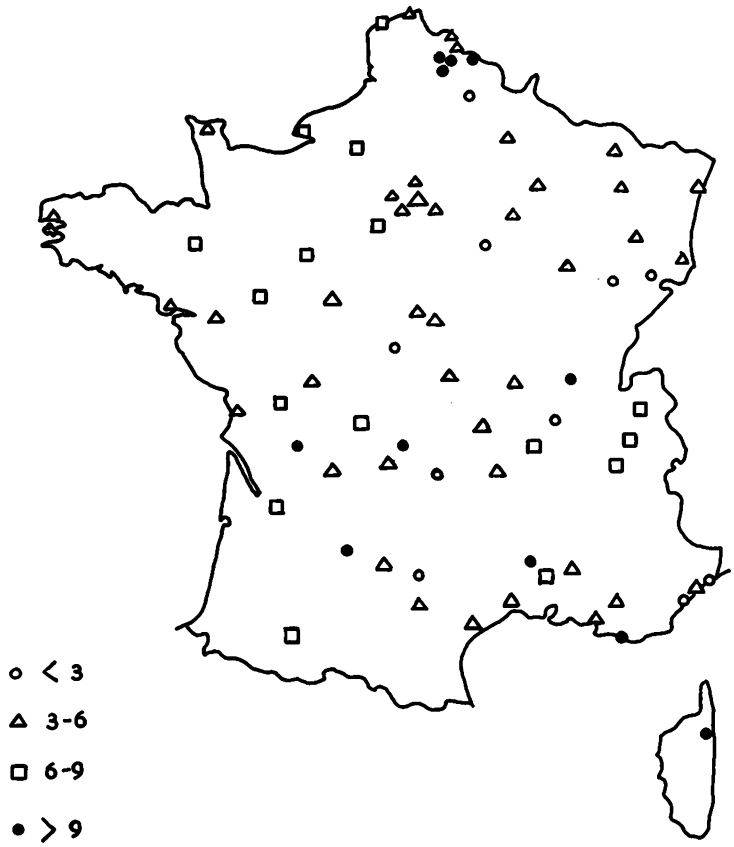

FIG. 1. Map of France showing location of cities included in survey of anencephaly.

mortality computed by Alison and Corone (1959), and the inbreeding coefficients calculated by Sutter and Goux (1964).

RESULTS

Incidence of Anencephaly

Frequency. For the period 1945 to 1955, the over-all incidence is 5.39 for 10,000 total births, a figure similar to that found in most places but definitely lower than that recorded in Northern Ireland, Scotland, and Birmingham (Southern England), or in white populations in some parts of the United States (Lamy and Frézal, 1960; McKeown and Record, 1960; Masterson, 1962; Penrose, 1957).

The sex ratio computed for 369 anencephalic births is 40% (148 males and 221 females), which is higher than in most statistics. Analysis according to birth rank shows no definite trend, contrary to the conclusions of McKeown (1960) and MacMahon, Pugh, and Ingalls (1953).

Secular variation. There are some fluctuations from year to year. The differences are not significant (χ^2 test for homogeneity = 10.8, corrected for continuity; df = 10; $P>0.10$). (See Table 1.) If the data are grouped by

TABLE 1. INCIDENCE OF ANENCEPHALY IN FRANCE

Years	Births	Anencephaly ♂	♀	?	Total	per 10^4 births
1945	37387	1	10	1	12	3.21
1946	50769	8	17	3	28	5.52
1947	53884	9	15	6	30	5.57
1948	54061	11	18	–	29	5.36
1949	60081	13	12	2	27	4.49
1950	68414	16	14	2	32	4.68
1951	69454	12	19	2	33	4.75
1952	73824	16	31	–	47	6.37
1953	77139	24	25	2	51	6.61
1954	81119	20	33	1	54	6.66
1955	81576	17	25	1	43	5.27
Total	707708	147	219	20	386	5.45
Years unknown	38568	1	2	13	16	4.15
Total	746276	148	221	33	402	5.39

triennia, there is a slight increase from 4.60 per 10^4 births in the postwar period to 5.95 in recent years. The same trend has been observed in Scotland and in Birmingham (Edwards, 1961; McKeown, 1960), where the incidence of the malformation is much higher (20–30 per 10^4). Nevertheless, for New York State, Gittelsohn and Milham (1962) found a rapid decline of over 50%, from 12.3 per 10^4 in 1946 to 6 per 10^4 in 1959. Adjustments for the changing proportion of first births and the varying maternal age has a minor effect and does not alter the pattern.

Seasonal variation. We compared the distribution of anencephalic births among the months of each year with the distribution of births in the general population (Table 2), and no significant difference was found. The same results appear if the data are grouped in the various trimesters of the year. Finally, Edwards's test (Edwards, 1961) for the recognition of cyclic trends does not indicate any significant trend ($d = 0.0338$; $\chi^2 = 2.62$, corrected for continuity; $df = 2$, $P > 0.10$). The results are at variance with those of Edwards (1958) and Record (1961) in Scotland and of McKeown (1960) in Birmingham, who record a higher incidence of the malformation in autumn and winter.

Distribution. There is a wide range of variation (maximum, 16 per 10^4 in Montauban [Lot et Garonne]; minimum, 2 per 10^4 in Lyon, Rhône) from town to town, even between towns near one another. We also noticed fluctuations between maternity clinics in Paris and Lyon. For the seven maternity hospitals in Paris and the four in the suburbs, the range is 5.3 (maximum, 8.4 per 10^4; mimimum, 3.1 per 10^4), which is not significant. For the three maternities in Lyon, the figures are 0.9, 1.9, and 4.4 per 10^4.

It is likely that part of the observed variation is the consequence of random sampling, the low incidence of the malformation, and the relatively small numbers of births in many clinics. It could be related also to the relative

TABLE 2. RELATIONSHIP BETWEEN ANENCEPHALY AND MONTH OF BIRTH

Month of birth	Anencephalic births n	Anencephalic births %	General population %
January	27	9.38	8.62
February	27	9.38	8.09
March	21	7.29	8.98
April	27	9.38	8.70
May	30	10.42	8.83
June	25	8.68	8.37
July	26	9.03	8.63
August	22	7.64	8.30
September	16	5.56	8.02
October	23	7.97	7.85
November	20	6.94	7.57
December	24	8.33	8.04
	288	100.00	100.00

TABLE 3. DISTRIBUTION OF ANENCEPHALIC BIRTHS IN FRANCE

Region	Departments	Number of births	Anencephalic births n	Anencephalic births per 10^4
1	Aisne Nord Pas de Calais	53,312	53	9.9
2	Finistère Ille et Vilaine Loire Atlantique Manche	33,126	18	5.4
3	Eure et Loir Maine et Loire Sarthe Deux-Sèvres	34,858	29	8.3
4	Allier Cher Indre Indre et Loire Vienne	29,769	14	4.7
5	Aube Cote d'Or Marne Yonne	41,437	17	4.1
6	Meurthe et Moselle Moselle Vosges	51,203	24	4.7
7	Doubs Bas-Rhin Haut-Rhin Belfort	33,920	10	3.
8	Cantal Corrèze Loire Haute-Loire Puy de Dome Haute-Vienne	58,654	32	5.5
9	Hérault Lot et Garonne Tarn Tarn et Garonne	32,092	15	4.7
10	Rhone Alpes Maritimes Bouches du Rhone Corse	77,057	15	1.9
11	Gard Var Vaucluse Monaco	45,807	27	5.9
12	Charente Charente Maritime Dordogne Gironde Basses Pyrénées	37,791	26	6.9
13	Seine Seine et Oise	160,645	78	4.9
14	Ain Isère Savoie Haute Savoie	37,233	30	8.1
15	Seine Maritime	18,922	14	7.4
	Total	746,276	402	5.4

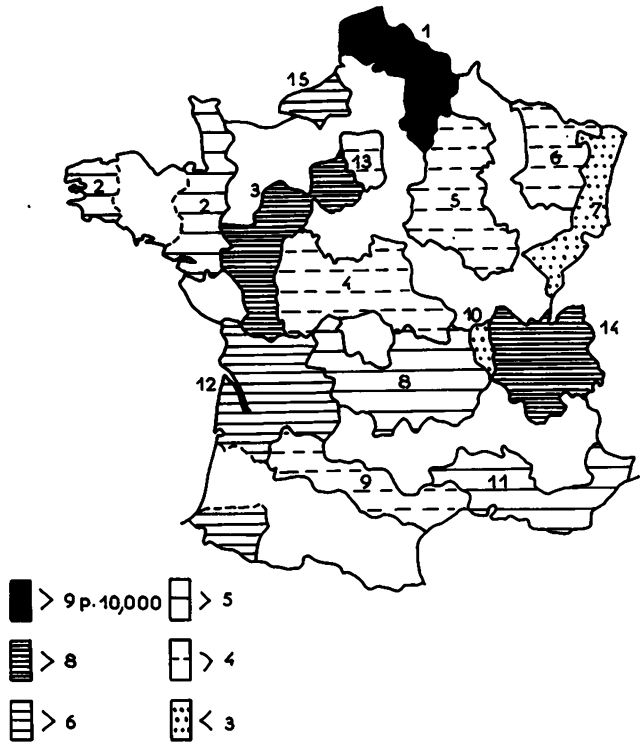

FIG. 2. Map of France showing grouping of data into 15 geographical regions.

efficiency with which anencephalics are recorded and located in hospital files. However, in reference to such an obvious and severe malformation, bias would be minimal. Some general trends do appear in several areas and, for further analysis, we have arranged the data in 15 groups corresponding to different geographical regions (Table 3, Fig. 2). This grouping retains a wide range of variation in the incidence of anencephaly, which varies by a factor of 5. The heterogeneity of the distribution is highly significant ($\chi^2 \cong 70$, corrected for continuity, df = 14, $P<0.001$) and remains so even if we exclude the low value for region 10 (Lyon, Rhône) ($\chi^2 \cong 25$, df = 13, $P<0.01$).

The significance of these variations are not readily evident, and we have been careful to note the biases which could influence them. For instance, one can assume that a patient with anticipated complications would be more likely to be delivered in a hospital, so that births occurring in these hospitals would not be representative of births in the general population. In a few instances, cases have been selected because of anomalies of pregnancy and X-ray diagnosis of the malformation. Furthermore, we noted that hydramnios was present in 54% of the recorded cases.

The importance of these biases depends, to some extent, on the percentage of births occurring in maternity hospitals and clinics among the total numbers of births. If the percentage is low, there is a concentration effect (and

TABLE 4. STATISTICS ON BIRTHS IN GENERAL POPULATION

Region	Anencephaly per 10^4 births	Births in maternity hospitals and clinics %	Mother < 25 years of age in general population %	Birth ranks	Stillbirths/ total births × 1,000	Illegitimate/ total births × 1,000
1	9.94	7.35	37.05	2.61	26.02	6.02
2	5.43	7.56	27.47	2.60	24.91	3.51
3	8.32	12.70	34.37	2.79	22.66	5.12
4	4.70	12.10	38.30	2.57	24.80	6.11
5	4.10	19.50	34.41	2.61	24.13	7.26
6	4.69	19.06	32.59	2.61	25.15	6.26
7	2.95	14.74	29.87	2.56	24.92	7.01
8	5.46	18.78	32.04	2.47	24.68	4.41
9	4.67	17.77	35.51	2.32	23.40	5.49
10	1.94	52.07	31.96	2.36	21.58	7.09
11	5.89	12.28	33.53	2.24	26.71	7.44
12	6.88	10.44	36.23	2.43	22.17	6.84
13	4.86	17.15	34.09	2.09	25.88	11.96
14	8.06	16.74	35.26	2.65	23.68	4.74
15	7.40	10.93	34.70	2.77	28.78	8.21
Means	5.39	14.62	33.83	2.47	25.59	7.46

TABLE 5. MATERNAL AGE AND BIRTHS

Maternal age	Anencephalic births n	Anencephalic births %	General population 1945–1956 total %	General population 1945–1956 stillbirths %
< 20	17	6.72	4.17	3.83
20–24	96	37.94	29.44	23.20
25–29	64	25.30	31.48	27.44
30–34	39	15.42	18.45	19.07
35–39	25	9.88	11.50	16.15
40–44	11	4.74	4.97	10.31
> 44	1			
Total	253	100.00	100.01	100.00

	Mean age
Anencephalic children	27.42 ± 0.40
General population (total)	28.45 ± 0.002
Stillbirths	30.13 ± 0.016

Comparisons of the distribution

Anencephalic *vs.* general population: $P \cong 0.02$
Anencephalic *vs.* stillbirths: $P < 0.001$

vice versa). The correlation coefficient computed between the incidence of anencephaly and this percentage is $r = -0.63$ (15 df) and definitely significant, $P \cong 0.001$ (Table 4). We shall make allowance for this fact in further interpretation of the variation.

Maternal age. Table 5 compares the percentage distribution of anencephalic births, total births, and stillbirths to maternal age. A definite excess of anencephalic births appears for the younger mothers, i.e., mothers less than 25 years of age. The χ^2 test, corrected for continuity, is significant at the

TABLE 6. COMPARISON OF BIRTH RANKS BETWEEN ANENCEPHALIC BIRTHS AND BIRTHS IN THE GENERAL POPULATION (LIVE- AND STILLBORN)

Birth ranks	Anencephalic births n	Anencephalic births %	General population total %	General population stillbirths %
1	101	39.76	35.46	40.85
2	61	24.02	27.33	21.25
3	36	14.17	16.23	13.84
4	26	10.24	8.62	7.95
5	12	4.72	4.71	5.21
6 and 7	11	4.33	4.46	5.69
> 7	7	2.76	3.19	5.20
Total	254	100.00	100.00	99.99
Mean birth ranks:	Anencephalic births (254)		2.45	
	General population			
	Total		2.56	
	Stillbirths		2.69	

2% level in the comparison with total births and highly significant if the comparison is restricted to stillbirths ($P<0.001$). The mean is lower for anencephalic births, and again the differences are significant ($P = 0.01$ for total births, $P<0.001$ for stillbirths).

There is some discrepancy between the findings made by several authors about the influence of maternal age on the incidence of anencephaly. Our data show some agreement in that respect with those of Ingalls, Pugh, and MacMahon (1954), Edwards (1958), and Record (1961), although, unlike those authors, we do not find a symmetrical excess of older mothers.

The percentage of mothers less than 25 years in the general population show a wide range of variation in the 15 previously defined regions (Table 4). The coefficient of correlation between the incidence of anencephaly and the percentage of mothers less than 25 years of age is 0.45 ($0.05<P<0.10$). Although not significant, it is fairly consistent with other findings about maternal age.

Parity. In computing birth ranks, multiple births are counted once and abortions and miscarriages are omitted. We do not find significant differences between the means for anencephalic births, legitimate total births, and legitimate stillbirths (general population 1945–1954). Furthermore, the three distributions do not display significant differences (Table 6), although there is a trend similar to that found by others (Penrose, 1946; MacMahon, Pugh, and Ingalls, 1953; Ingalls, Pugh, and MacMahon, 1954; Edwards, 1958; McKeown, 1960), that is, a higher proportion of firstborn among anencephalic births than in the general population (live- and stillbirths).

The mean birth rank (Table 4) and the numbers of firstborn for 100 total births in the 15 regions were correlated with the incidence of anencephaly. None was significant ($r \cong 0.35$, $P>0.10$).

Paternal age. No effect of paternal age is apparent from our data (Table 7).

TABLE 7. PATERNAL AGE

	Anencephalic births n	Anencephalic births %	General population %
20	1	0.76	0.42
20–24	23	17.42	14.10
25–29	40	30.30	29.94
30–34	24	18.18	21.48
35–39	22	16.67	19.21
40–44	19	14.39	10.33
45 &	3	2.27	4.52
Total	132	99.99	100.00

Means: Anencephalic children 31.74 ± 0.62
General population, 1945—52 32.26 ± 0.002

Stillbirths, illegitimate births, and consanguinity rate. We find no correlation between incidence of stillbirths, frequency of illegitimate births, or consanguinity rate computed for the 15 regions and for the incidence of anencephaly in these areas. The absence of correlation with consanguinity rate, although not conclusive, argues against the hypothesis favored by Polman (1950) and presumed by Hewitt (1963) to account for the east-west gradient observed in his survey in the United States.

We have no useable data on the social classes from which our patients are extracted. It is likely that deliveries in public hospitals tend to come from the lower classes, and, if the trend were consistent with that observed in other series, it should be a reasonable assumption that our estimate is probably higher than for the general population. This is suggested by the finding in Belfast (Coffey and Jessop, 1957), where the incidence is 6.71 and 3.7 per 1,000 among hospital births and total births, respectively. It is our opinion that the effect of this association on the observed influence would be negatively correlated with the percentage of registered births in public hospitals.

Further study of the association with maternal age. The association of anencephaly with maternal age was the only definite association in our data. An association with birth rank cannot be excluded. Other factors seem inconsequential. For the final interpretation, the bias introduced by selection of cases and negative correlation with percentage of births in maternity hospitals and clinics must be considered.

Accordingly, the multiple correlations between the incidence of anencephaly, the percentage of registered births, and the percentage of mothers less than 25 years old were computed (after Brownlee, 1953). Table 8 shows that the ratio of the variance of the regression term for maternal age to the residual is 3.197 with degrees of freedom 1 and 13, $0.01<P<0.05$, again a finding consistent with previous analysis.

Association with Other Conditions

Condition. There is a high proportion of livebirths among our anencephalic children (32%), with no significant difference between males and females.

TABLE 8. MULTIPLE CORRELATION BETWEEN THE FREQUENCY OF ANENCEPHALY (y), THE PERCENTAGE OF REGISTERED BIRTHS (x_r) AND THE PERCENTAGE OF MOTHERS LESS THAN 25 YEARS (x_a)

$b_{yx_r} = -0.113$, $b_{yx_a} = 0.266$

Source of variance	Sums of squares	Degrees of freedom	Mean squares
Variation explained by x_r	24.907	1	24.907
Increment explained by x_a	7.309	1	7.309
Total explained by x_r and x_a	32.216		
Residual	30.688	13	2.360
Total	62.904	15	

Variance ratio 7.309/2.360 = 3.097; $0.01 < P < 0.05$.

In most instances, the newborn lived only a few minutes. They were officially classified as stillborn, having died before the formal notification of birth, the third day. As in the study of McKeown and Record (1960), none was alive after the first week.

Gestation time varied widely, with a high proportion of premature births (53% before 255 days) and postmature births (14% after 300 days). These findings do not deserve further consideration. Furthermore, the mean birth weight is low and there is a strong positive correlation between gestation time and birth weight ($r = +0.715$).

Penrose (1957) states that in several series there is a definite excess of mothers belonging to blood group O. This is not apparent in our scanty data; 24 mothers out of 57 (42%) belong to group O.

Association with major defects. The association of multiple major defects with anencephaly has been noted by many investigators (see Neel, 1958). Assessing exact percentages of association is difficult in our survey because precise information was not always recorded. Unless explicitly recorded, it was provisionally assumed that there were no associated malformations. Our figures are thus conservative. Moreover, we have no knowledge of the percentage of necropsies in this sample, although it is certainly not uniform. It may be assumed reasonably to be low. With these reservations, there are four associations in our study which are in agreement with results from others.

1. Spina bifida was frequently associated with anencephaly (17%).

2. There were five cases of talipes (1.7%), a finding which agrees with the data of McKeown and Record (1960); there were two cases of polydactyly; and in nine other instances there were limb defects (either cases of aplasia or unspecified).

3. Harelip and/or cleft palate was found in six patients (2%). In three patients this was associated with other defects. For purposes of comparison, the frequency of harelip among all associated defects (excluding spina bifida) was calculated, considering each recognized defect as a sepa-

TABLE 9. TWIN BIRTHS

Sex of the anencephalus	Sex of the twin	Type of twinning	Condition of twin	Maternal age	Birth rank
♂	♂	monochorial	930 g, died after birth	30	2
		monochorial monoamniotic	750 g, died after birth	25	3
		?	normal, alive	?	2
	♀		born alive, apparently normal, deceased from hyperbilirubinemia	26	2
	?	?	alive, apparently normal	32	?
♀	♀	monochorial diamniotic	alive, apparently normal	26	2
		?	alive, apparently normal	27	2

rate entity, even though more than one might be present in a single patient. This yielded a total of 36 defects, of which six (17%) were harelip, a figure higher but comparable to that from McKeown (13%) as noted by Neel (1958). Other defects in the digestive system were one case of atresia and two cases in which the exact nature of the defect was not given.

4. There was a rather high proportion of exomphalos (omphalocele) in our series, five of the 36 associated defects (14%). In McKeown's survey, it was 24%. The difference is of dubious significance. Be that as it may, the trends are similar to those in the two surveys quoted by Neel.

Twin births. Seven of the anencephalic newborn were twins (Table 9). There is strong evidence in favor of monozygosity in three instances; two other pairs are like-sexed; and only one pair is stated as unlike-sexed. We can, therefore, assume that these twin births are predominantly monozygotic. There is not concordance for anencephaly, a finding already noted by Record and McKeown (1950) and Penrose (1957). Three of the twins died very soon after birth. Although the probable cause of death was premature birth, there is the possibility of nonapparent gross malformations.

Sibships of anencephalic children. There are 254 sibships with 677 children and 423 sibs; 374 of them were born before the propositus, 49 after. The mode of selection, from maternity files, accounts for such a distribution and does not permit the derivation of recurrence risk figures. Furthermore, as the sample of children born after the propositus should be more biased than the subgroup of previous births, further computations refer only to the latter.

The several anomalies noticed in the sibships (before and after the anencephalic birth) are listed in Table 10. They are summarized in Table 11 and compared with data from the population of maternity hospital births for anencephaly and from the general population for stillbirths.

The total percentage of stillbirths (in the sense of the French regulations

TABLE 10. SIBSHIPS OF ANENCEPHALIC CHILDREN

Size and number of sibships	Anencephaly		Stillbirths		Malformations	Twin births	
	before	after	before	after	before	before	after
2 (57)	1		1 ♀ premature		1 clubfoot 1 deaf-mute		
3 (45)	1 ♂		1 ♀ premature 1 1 1 ♂ malformed				
4 (25)	1 ♀		1 1 ♀ hydrocephaly 2 (1 malformed) 1 2 ♂ (1 hydrocephaly + spina bifida) 1		1 spastic	1	
5 (17)			2 ♂, ♂ 3 ♀, ♂, ♀ 2 ♂ ♂			1 1 ♀♀ 1 ♂♂ 1 ♂♀	1 ♂♂
6 (7)	1		1 ♀ 1 spina bifida	1 hydrocephalus + spina bifida			
7 (7)	1 ♂		1		1 harelip + cleft palate		
8 (3)							
9 (2)							
10 (1)							
11 (1)							
	5		23	1	4	5	1

Before (after) refers to before (or after) the birth of the affected child.

as previously stated) is 7.5, i.e., 2.9 times more than in the control general population. Among the 28 stillbirths, eight displayed a major defect of the central nervous system (2.1%) and five of the siblings (1.3%) were anencephalics. Therefore, there is beyond any doubt a strong familial concentration of the malformation, as previously stressed by others. Actually, the increase amounts to a factor of 25—a figure fairly consistent with that estimated by Penrose (1957). It is likely that the factor is somewhat smaller for other malformations of the central nervous system, but it cannot be computed from our data. Although the statistical significance of the findings is difficult to assess, both spina bifida and hydrocephaly seem to occur more frequently in these families.

In addition to the 374 term or near-term previous births, there were 34 (8.3%) spontaneous abortions recorded in the files as having occurred

TABLE 11. SIBSHIPS OF ANENCEPHALIC CHILDREN (PREVIOUS BIRTHS)

153 sibships 874 previous births	Number	%	Ratio sipships/ general population
Anencephaly	5	1.34	24.8
Stillbirths	23	6.15	
Total	28	7.49	2.9
Malformations in livebirths	4	1.07	

before the birth of the propositus, and three (8%) afterward. We have no control group to test the significance of these percentages; however, in Neel's series (1958), the corresponding figures are 6.6% in the sibships of anencephalic propositi and 8.1% for propositi with other defects.

The increased frequency of lethal outcome in the other pregnancies of mothers who have given birth to children with anencephaly or spina bifida has been stressed by Masterson (1962). In that respect, Record (1961) found a total abortion and stillbirth incidence of 14.4%, all known malformations of the central nervous system being excluded. Our corresponding figures are 13.2% (54/408) for the previous pregnancies and 12.4% for all the pregnancies. They are in fairly good agreement with the preceeding estimates.

As far as we can judge from the small number of cases, it does not seem that the expectancy for the occurrence of other malformations is raised in the sibships of anencephalics.

DISCUSSION

Our findings agree with those previously reported by other investigators with, as expected from such a survey, discrepancies on some points. The most noticeable difference is the lack of effect of primogeniture in our sample and the marked effect of young maternal age.

On the whole, the incidence of anencephaly in France is definitely lower than in the United Kingdom or in some places in the United States (Boston or Rhode Island) but higher than figures generally given for non-whites in Africa and America (Penrose, 1957). There are suggestive variations from part to part of the country, which are assumed to be related to maternal age, at least to some extent. There is no evidence of a correlation with consanguinity rates.

The familial tendency of the malformation is demonstrated as well as the probable relationship to spina bifida and hydrocephaly. The lethal outcome of other pregnancies in the sibships seems to be increased. Finally, all seven twin pairs were discordant for anencephaly.

There are several hypotheses concerning the etiology of anencephaly. One, derived from the experiments of Snell et al. and quoted by Penrose (1957), has received no support and can be rejected. Karyotypes of anencephalic newborn and their mothers have always been found to be normal, even in cases in which the familial pattern was suggestive of the mechanism operating in Snell's experiment, i.e., a mother with an anencephalic sib and an an-

encephalic child (Ruffié, personal communication). Fresh mutation of a dominant gene seems also unlikely (Penrose, 1957).

Fitting the data with the single recessive gene hypothesis proposed by Polman (1950) again causes considerable difficulty. Parental consanguinity higher than in the general population has not been demonstrated. If the gene frequency were high enough, these findings could be inconclusive. However, we found a correlation (significant at the 5% level) between consanguinity and frequency of dizygotic twinning, a much more common phenomenon than anencephaly (Lamy and Frézal, 1959). The proportion of affected sibs is significantly lower than the expected 25%, even if all the stillbirths (either with or without central nervous system malformations) are included, a somewhat arbitrary procedure. Moreover, this hypothesis is difficult to reconcile with the nonconcordance of twin pairs. The three lethals among our cases were thought to be environmental and likely due to prematurity.

Differences in the incidence among populations as well as differences observed in polytypic populations (Searle, 1959) give support to the hypothesis of a complex genetical background producing a state of susceptibility, as discussed by Penrose and by Neel in their illuminating papers.

We have to be aware that such a hypothesis implies the necessary intervention of environmental agents, deleterious or favorable, to explain the occurrence of the malformation in a predisposed child. Maternal age, birth rank, social class, or seasonal and secular variations may influence the likelihood of anencephaly. There is little evidence that viral infections could be responsible (Record, 1961). Nutritional factors and subtle deficiencies in minerals or vitamins rather more than gross malnutrition deserve further consideration. For instance, Penrose claims that the excessive purity of water deprived of calcium may be a precipitating cause of developmental defects. From that point of view, it seems very remarkable that folic acid deficiency as well as other teratogens in pregnant animals provoke a series of defects comparable with anencephaly. This has been demonstrated in rats (Nelson, 1960) and in cats and mice. The human counterpart has been observed in pregnant women treated by antifolics (Giroud and Tuchmann-Duplessis, 1962; Warkany, Beaudry, and Hornstein, 1959). We should like to add that the seasonal or secular variations could as well be explained by nutritional factors through the supply of food than by infections or climatic agents. At this time, it is difficult to draw any precise inferences from these observations.

SUMMARY AND CONCLUSIONS

The distribution of anencephaly has been studied in different parts of France for the period 1945 through 1955. There are suggestive variations of incidence which could be related to maternal age, the risk of occurrence being higher in mothers less than 25 years old. No definite effect of birth rank has been observed. Other factors, i.e., consanguinity, seem to be of no consequence in this series.

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