Neural tube defects in New South Wales, Australia

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SUMMARY Cases of spina bifida cystica, encephalocele, and anencephaly occurring over a 9-year period, 1965 to 1973, in New South Wales, Australia, were identified. A low frequency of 1.1 for spina bifida and encephalocele (SB) and 0.9 for anencephaly (A) was found.

Secular trends parallel to those observed in the northern hemisphere were noted.

Detailed analysis of 1575 cases showed an excess of births in spring, corresponding with conception in the summer months, after correction for shorter gestation in anencephalus, which varies from the peak of spring conceptions observed in British studies.

An excess of female cases for each abnormality and a social class effect with a deficit of cases in classes I and II and an excess in classes IV and V and ex-nuptial births were apparent. The first birth rank for younger mothers did not show a significantly increased risk; however, the effect of high birth rank and older maternal age was more significant. Migration studies showed that in migrating from areas of high incidence these parents maintain a higher risk than the Australian population.

The highest risk group was that in which both parents were born in the UK, and the next highest that in which an English-born mother was married to an Australian father.

Mothers from Malta, and either or both parents from Lebanon, Egypt, and Austria were also at high risk.

Part-aboriginal children had a higher risk rate for ASB than white Australian children.

The proportion of older sibs affected was 4.12% of sibs of both sexes of an index case of spina bifida, and 3.19% of an index case of anencephaly. The abnormalities alternate or recur in families. An increased perinatal mortality rate in sibs was shown.

Twin studies showed a higher concordance rate for monozygotic pairs.

A sequential interaction in an excess of opposite sex sib before an index case was apparent.

The results of this study support a multifactorial aetiology for ASB resulting from genetic environmental interaction.

New South Wales is the eastern coastal state of Australia, with an area of 309 433 square miles and a population of 4 640 800 at the 1971 Census. The continent is geographically isolated with a large migrant population, seasonal reversal, and a hot climate.

Methods

There were 712 cases of anencephalus identified from stillbirth and neonatal death registrations at the NSW Registrar General's Department International Classification of Disease (ICD) 7409. Cases registered as 'monster' and 'multiple congenital abnormalities' were excluded unless definite anatomical evidence of neural tube malformation could be confirmed.

Records for 1965 to 1967 were incomplete; further cases were identified by examination of labour ward registers in obstetric hospitals and by letter to country centres.

One hundred and forty-two cases of encephalocele (ICD 7430), and 721 of meningomyelocele (7410, 7419), stillborn, and registered as perinatal deaths or deaths aged 1 month to 9 years from 1 January 1965 to 30 December 1975, were obtained from the Bureau of Census and Statistics and the Registrar General's Department.

Table 1 Sources of case identification

	Registrar General's records			Hospital records		
	Stillbirth	Neonatal death	Death	Obstetric stillbirth	Livebirth	Paediatric neonatal death
Anencephalus	387	207	—	106	—	12
Spina bifida	109	127	7	—	620	—

Table 2 Yearly incidence of neural tube closure defects in New South Wales

	1965	1966	1967	1968	1969	1970	1971	1972	1973	Total
Meningomyelocele cases	63	67	72	65	94	104	93	86	77	712
Rate	0.79	0.85	0.90	0.78	1.07	1.16	0.93	0.88	0.87	0.92
Encephalocele cases	15	15	14	13	16	16	18	17	18	142
Rate	0.18	0.19	0.17	0.15	0.18	0.17	0.18	0.17	0.17	0.17
Anencephalus cases	58	59	68	73	76	93	77	107	101	712
Rate	0.73	0.74	0.85	0.88	0.87	1.03	0.77	1.11	1.14	0.92
TOTAL Cases	136	141	154	151	186	213	188	210	196	1575
Births	79 016	78 722	79 704	82 502	87 116	89 602	99 648	96 429	88 360	781 099
Rate	1.72	1.77	1.93	1.83	2.13	2.37	1.88	2.15	2.19	2.01

Surviving cases were identified and studied at the four major paediatric neurosurgical units in Sydney.

Early referral for assessment was usual in the first years of the study, and in later years cases which survived 4 to 5 weeks of life without surgical treatment were then referred.

Epidemiological data were obtained from birth and death registrations and by personal interview with parents.

The source of first identification of cases is shown in Table 1.

Six hundred and two cases in 1575 (38.22%) of ASB were stillborn and these accounted for 6.6% of the stillbirths which occurred in the 9-year period studied.

Of 863 cases of spina bifida, 505 (58.5%) died, 438 (50.8%) before the age of 3 months regardless of selection for treatment.

Population data were obtained for the period studied from the Demography Department of the Australian Bureau of Census and Statistics, New South Wales Division.

Encephalocele and meningomyelocele were grouped together as spina bifida (SB). The risk rate per 1000 births for this group, for anencephalus (A) separately, and a total rate (ASB) was calculated. χ^2 test was applied and probability and significance assessed by this method for SB, A, and ASB.

Results

FREQUENCY

An overall birth frequency of 1.10/1000 for spina bifida and 0.91/1000 for anencephalus, and a com-

bined frequency of 2.01/1000 total births was determined.

The cases and rates by year are shown in Table 2.

YEARLY VARIATIONS

Significant inter year variations occurred ($\chi^2 = 36.64$, $P = <0.01$, df 8) due to meningomyelocele ($\chi^2 = 21.85$, $P <0.01$, df 8) and anencephalus ($\chi^2 = 26.85$, $P <0.01$, df 8). For cases of encephalocele the rate was uniform ($\chi^2 = 2.57$, $P <0.1$, df 8).

There is no long-term trend of decline or increase in rate over the 9 years studied here. The rate for 1974 was 2.27/1000, for 1975 2.06/1000, and for 1976 2.19/1000.

SECULAR TRENDS

Long-term trends for ASB as measured by stillbirth and neonatal death registrations from 1950 to 1976 show a high incidence in 1953 to 1957, a decline to a trough in 1965, and an increase in the early 1970s (Fig.).

SEX RATIO

There is a female preponderance of cases for each type of abnormality, the excess of female cases being greatest for anencephalus and least for meningomyelocele (Table 3).

Table 3 Distribution by sex of cases of ASB

	Male	Female	
Anencephalus	246	466	1/1.89
Encephalocele	63	79	1/1.25
Meningomyelocele	332	389	1/1.17
Total	641	934	1/1.45

Fig. Secular trends in anencephalus and spina bifida in New South Wales, 1950-1974.

SEASONALITY

There is a significant variation in month of birth for cases of meningocele and encephalocele combined ($\chi^2 = 26.71$, $P < 0.01$, $df 10$).

The greatest incidence occurs in September (1.42/1000), August (1.36/1000), and October (1.27/1000), corresponding to conception in December, November, and January, as the mean gestation is 38 weeks.

There is a slightly increased rate for cases of anencephalus in July (1.12/1000) and October (1.01/1000) which is not statistically significant. This corresponds to conception in November and February, allowing 1 month shorter gestation period, and December and March, allowing 2 months' shorter gestation (mean gestation for anencephalus is 33 weeks).

There is a deficit of cases of meningocele and encephalocele in April (0.81/1000), May (0.86/1000), and July (0.85/1000), conceptions occurring in July, August, and October, and of anencephalus in April (0.74/1000), June (0.83/1000), and September (0.86/1000), conceptions occurring in July, September, and December.

Using either 1 month or 2 months' shorter gestation for anencephalus to obtain a combined rate for ASB, there is a statistically significant excess of cases born in September, October, and November, corresponding to conception in December, January, and February ($\chi^2 = 20.40$, $0.01 < P < 0.05$, $df 10$). Observed and expected numbers of cases for gestation by month of conception is shown in Table 4.

CLIMATIC VARIABLES

Multiple regression analysis for 6 climatic variables—monthly average temperature, rainfall, humidity,

Table 4 Cases of ASB observed (and expected) by month of conception

	ASB	A	SB
January	142 (130)	59 (58)	83 (72)
February	132 (120)	56 (54)	76 (66)
March	141 (126)	66 (57)	75 (69)
April	140 (128)	59 (58)	81 (70)
May	120 (120)	56 (54)	64 (66)
June	131 (136)	58 (61)	73 (75)
July	110 (126)	59 (57)	51 (69)
August	120 (130)	64 (58)	56 (72)
September	114 (126)	47 (57)	67 (69)
October	117 (132)	61 (59)	56 (73)
November	143 (130)	53 (58)	90 (72)
December	167 (130)	74 (59)	93 (71)

lowest minimum temperature (a), highest maximum temperature (b), the fluctuation in temperature (b-a)—was performed. Monthly average rates for anencephalus (A) and spina bifida (SB) over 9 years, and combined (ASB), showed a positive correlation between SB rate and ASB rate and average temperature. Numbers of cases for each separate month of each of the 9 years were small; again SB rate correlated with average temperature. Rainfall and humidity did not contribute significantly to the correlation.

REGIONAL VARIATION

Area differences in risk rate by statistical division in New South Wales show an excess of cases in thickly populated urban areas and a deficit in sparsely populated rural areas, with a gradation from the east coast to the central west.

High incidence areas in Sydney are noted in the western and southern suburbs.

Family studies: A. The parents

SOCIAL CLASS

Father's occupation, as coded for demographic statistics, has a number of inconsistencies, which makes it unsuitable as an indicator of social class.

By regrouping this code a 5-class rating was devised in accordance with the Australian National University Classification, which is used for most sociological studies in Australia. The risk rates for ASB per 1000 births are: class I, 1.56; II, 1.82; III, 1.81; IV, 2.55; V, 2.35.

A slight excess of spina bifida over anencephalus in classes IV and V occurred.

A total of 164 cases were registered as ex-nuptial births in 67 238 ex-nuptial births for the 9-year period. The risk rate is 2.44/1000.

BIRTH ORDER

There is a significantly increased risk in birth orders over the fourth (Table 5), a deficit of second born children, and a non-significantly increased first birth order risk ($\chi^2 = 16.69$, $P < 0.01$, $df 5$).

There were more first born female meningomyeloceles, but more first born male encephaloceles and male anencephalics.

MATERNAL AGE

The rate for young mothers is not raised and the only group which shows a significantly raised rate is the 40 to 44 age group where the rate is 3.37/1000 (Table 6).

In correlating maternal age and birth order, data on parity for ex-nuptial births, both live and stillborn, and for stillbirths were not available. However, maternal age groups were known and therefore 68 189 births were distributed in the same proportion for birth order in each maternal age group as nuptial livebirths.

(a) Risks in birth orders by maternal age groups

The risk rate for first born children to young mothers (<19) is not significantly raised at 2.11/1000 (Table

7). However, at first birth rank in the 25 to 29, 30 to 34, and 35 to 39 groups the risk is increased.

There is a significant deficit of cases at second birth rank for all age groups, and a linear risk rate equal to that of the general population at third birth rank.

(b) Risks in maternal age groups by birth order

A U-shaped relationship is apparent for the age groups 25 to 29, 30 to 34, and 35 to 39. In the age group 20 to 24 there is no significant relationship to birth rank.

The social class effect is apparent in the younger age groups. Only 8 of 177 in the <19 group were in class I, and 62 of 510 in the 20 to 24 group. In older age groups a constant at 22% was in class I.

PATERNAL AGE

There is a significantly increased rate for paternal age group 40 to 44 of 2.48/1000.

Correlating parental ages, raised risk rates were observed where both parents were in the age groups 20 to 24 (2.7/1000, 213 cases) and 40 to 44 (4.6/1000, 25 cases).

PLACE OF BIRTH OF PARENTS

Table 8 shows the risk rate of ASB by relative birth places of parents.

There were 963 cases born to parents both born in Australia. The rate was 2.0/1000. The highest rate was for both parents born in the United Kingdom (3.13/1000). Where the mother was UK-born and the father Australian-born the rate was 2.46/1000, but for an Australian-born mother and a UK-born father the rate was 2.09/1000.

Table 9 shows the rates for each parent by country of origin for the major migrant groups.

Lebanese parents show a high risk rate.

Of the total New South Wales population at the Census in 1971, 18% were born outside Australia and New Zealand. In this study 38.9% of cases were born to couples one of whom was born outside the country.

Table 5 Distribution by birth order standardised for maternal age of cases of ASB

Birth order	0	1	2	3	4	4+
Cases observed	649	405	255	118	60	85
Expected	606	460	244	110	54	52
Risk rate for ASB/1000	2.14	1.75	2.08	2.13	2.21	3.18

Table 6 Distribution by maternal age standardised for birth order

Maternal age group	19	20-24	25-29	30-34	35-39	40-44	45+
Cases observed	177	510	496	222	106	48	2
Expected	176	518	494	238	102	28	—
Risk rate for ASB/1000	2.01	1.96	2.01	1.85	2.05	3.37	2.09

Table 7 Correlation of maternal age and birth order in risk rate for ASB

Maternal age		Birth order					
		0	1	2	3	4	4+
19	Observed	151	21	8	2	0	0
	Expected	142	28	2	—	—	—
	Risk rate	2.11	1.42	—	—	—	—
20-24	Observed	266	176	49	14	2	2
	Expected	270	176	46	12	2	—
	Risk rate	1.96	2.00	2.07	2.24	—	—
25-29	Observed	166	149	110	37	16	16
	Expected	144	174	106	40	12	6
	Risk rate	2.28	1.7	2.06	1.76	2.32	4.83
30-34	Observed	43	39	65	37	20	26
	Expected	32	60	62	32	18	16
	Risk rate	2.57	1.3	2.01	2.27	2.02	3.00
35-39	Observed	18	14	22	22	11	26
	Expected	10	16	20	18	12	18
	Risk rate	3.09	1.67	2.08	2.32	1.73	2.73
40-44	Observed	4	6	2	6	11	13
	Expected	2	2	4	4	4	8
	Risk rate	2.79	3.62	1.00	2.71	5.5	2.86
45+	Observed	1	0	0	0	0	2
	Expected	—	—	—	—	—	—
	Risk rate	—	—	—	—	—	—

Table 8 Risk rates for ASB by birthplaces of parents

			Mother				
			Australia/NZ	UK	Europe	Rest	Not known
Father	Australia/NZ	Observed	963	49	22	7	
		Expected	960	38	22	8	
		Risk rate	2.0	2.46	1.99	1.75	0
	UK	Observed	56	72	3	1	
		Expected	52	42	3	2	
		Risk rate	2.09	3.13	1.80	1.02	0
	Europe	Observed	42	5	112	5	
		Expected	50	6	162	4	
		Risk rate	1.65	1.66	1.37	2.16	0
	Rest	Observed	12	—	2	36	
		Expected	12		4	34	
		Risk rate	1.87		1.16	2.05	0
Not known		(131)	(3)	(6)	(3)	(45)	

ABORIGINAL CASES

The ascertainment of rate among parents of part-aboriginal descent has intrinsic difficulties.

Part-aboriginal citizens are not identified as such on formal documents, and the total number of births is difficult to ascertain, as is the total population.

The surviving cases of spina bifida are known. Other cases were identified by place of birth, stated as Aboriginal Reserve, and surname as confirmed by staff of the various settlements. Any case not confirmed or in doubt, with the occupation of father or the address inconsistent with aboriginal social identity, was excluded.

There were 38 cases identified as having one or both parents of part-aboriginal origin. In 2 cases a part-aboriginal mother was married to a white Australian, and in one to an Englishman. There were 23 cases of meningomyelocele (11M, 12F), 3 cases of encephalocele (1M, 2F), and 12 cases of anencephalus (4M, 8F).

Table 9 Risk rates for ASB for the major migrant groups in New South Wales

		Mother	Father	Both parents
Italy	Rate (Cases)	1.30 (29)	1.44 (40)	1.27 (26)
Greece		1.45 (34)	1.49 (36)	1.50 (33)
Yugoslavia		1.43 (17)	1.17 (17)	1.27 (14)
Germany		1.40 (12)	1.79 (16)	1.23 (1)
Netherlands		1.75 (11)	0.84 (7)	1.06 (3)
Malta		2.31 (20)	1.98 (19)	1.98 (13)
Lebanon		2.37 (18)	2.38 (19)	2.52 (18)
Egypt		2.06 (5)	1.68 (5)	2.44 (3)
Austria		3.32 (5)	2.22 (5)	3.08 (1)

The population of persons of aboriginal descent in NSW in the 1971 Census was 23 101. Age specific fertility rate and total birth estimates give a crude birth rate of between 50 to 60/1000, which gives 11 340 births over the 9-year period studied and a rate of ASB of 3.35/1000. Five instances of recurrent cases occurred in part-aboriginal parent families.

Family studies: B. The sibs

RECURRENT CASES

Fifty-eight families with 2 or more affected children were identified, of which 52 families had 2 affected children (including 2 paternal half sibs with meningomyelocele). Five families had 3 affected and one also had a hydatidiform mole. One family had 4 affected. Four sets of concordant twins were also recorded, but these are excluded from the analysis. One family with 3 cases of Meckel's syndrome of recessive basis is included. Of the 65 recurrences, 46 were in consecutive pregnancies.

The time intervals between births of affected children were: 12 to 18 months, 30 cases; 2 years, 8 cases; 3 years, 4 cases; 4 years, 9 cases; 5 years, 1 case; 6 years, 5 cases; 7 years, 1 case; 8 years, 1 case; 9 years, 2 cases; 10 years, 3 cases and 15 years, 1 case. The average time intervals between children in the Australian population is 1st to 2nd, 3 years; 2nd to 3rd, 4 years. Sibs born before the index case were identified from the Registrar General's records, but the number of sibs born after an index case could not all be traced.

The percentages of older sibs affected are: 26 in 791 (3.28%) brothers; 33 in 790 (4.17%) sisters; and 59 in 1581 (3.73%) of all sibs.

In spina bifida index patients, of 463 brothers 1 was anencephalic and 15 were meningomyeloceles; of 460 sisters 4 were anencephalic and 18 were meningomyeloceles. Thus 3.46% of brothers, 4.78% of sisters, and 4.12% of all sibs of both sexes were affected. Subdividing by sex of index patient produces 18 in 463 (3.89%) for sibs of male and 20 in 460 (4.34%) for sibs of female cases.

In anencephaly index patients, of 328 brothers 5 had anencephalus and 4 had meningomyelocele; of 330 sisters 7 had anencephalus and 5 had meningomyelocele. Thus 2.74% of brothers, 3.64% of sisters, and 3.19% of both sexes were affected. Subdividing by the sex of the index patient produces 1 in 328 (0.3%) for 1 male sib of a male, and 20 in 330 (6.06%) female sibs of a female.

Fewer male sibs of male index cases were affected than female. (One male sib with congenital hydrocephalus was born after a male spina bifida index case.) Forty-four meningomyeloceles were followed by 35 meningomyeloceles and 9 anencephalics. Twenty-

one anencephalics were followed by 12 anencephalics and 9 meningomyeloceles.

A first affected female child (40 cases) was followed by a female affected in 30 cases and a male in 10 cases. A first affected male (25 cases) was followed by a male in 9 cases and a female in 16 cases. Male to female ratio of first affected child is 1:1.6.

Both parents were Australian-born in 44 cases. Both were part-aboriginal in 2. Three part-aboriginal mothers were married to white Australians in 2 instances and an Englishman in one.

In 14 families of recurrent cases (24%), one (4), or both parents (10), were migrants: Maltese (3), Greek (2), Lebanese (1), Turkish (1), German (1), British (2), Italian (1), 3 Australian-born mothers with father born in UK (2) and Italy (1), and 1 Australian-born father with mother born in Germany.

In assessing the risk after 2 affected cases, 18 families could not be traced to complete the sibships after 2 affected cases. Of the remaining 44 families, 27 had not had any further children; of the other 17 families, 2 had miscarriages, 1 had a termination, 1 a hydatidiform mole, and 7 normal males, 14 normal females, and 7 affected children (3F, 4M) were born.

Seven affected children in 28 sibs indicates a 1 in 4 risk which is probably greater than that which really exists, due to lack of ascertainment of sibs born to the other 18 families.

CAUSE OF DEATH OF SIBS

One hundred and fourteen sibs previously deceased and 1581 normal live-born sibs were identified excluding cases of neural tube defect (45), accidental deaths (4), and deaths due to infection (4).

Of 1695 sibs, 61 died as a result of stillbirth, obstetric complication, prematurity, or congenital abnormality other than neural tube closure defect in the first 28 days of life, which means a perinatal mortality rate of 35.98/1000 compared with the average for New South Wales of 24.76/1000 (1972).

TWIN STUDIES

Thirty-five twin pairs were identified among index cases with ASB; both twins were affected in 4 instances. The expected number of affected twin cases, where the rate of ASB is 2.01/1000, and average New South Wales twinning rate is 10.74/1000, is 34.65.

Among previously born sibs 18 sets of twin sibs were identified.

Fourteen monochorionic and 18 dichorionic twins were identified; in 3 instances chorion status could not be established. Equal susceptibility is likely. Distribution by abnormality was equal.

There were 31 twin pairs with one child affected, 18 anencephalics, 11 meningomyeloceles, and 2 encephaloceles.

There were 4 twin pairs with both affected: 2 males (M) both meningomyelocele; 2 females (M) both encephalocele; 2 females (M) one anencephalus, one meningomyelocele; and 2 females (D) one anencephalus, one meningomyelocele.

There was a higher concordance rate (3 in 14; 21.4%) for monozygotic than for dizygotic twins (1 in 18; 5.5%). The latter is the recurrence risk for sibs.

Death or neural tube closure defect in the co-twin occurred in 9 pairs where the index case was female, compared with 1 affected male twin of a male case. Allowing for the F/M ratio of 2:1, the presence of an affected female twin appeared to confer an increased risk of death and additional abnormality on the other twin, regardless of its sex and of prematurity.

Two sets of triplets were found outside the period analysed: 1961 (M) 3 female, 1 with anencephalus, 2 normal (all died); 1975 (D) 1 female who survived, 1 male with meningomyelocele, and 1 male who was normal (both died).

SEX OF THE PRECEDING SIBS

There were equal numbers of male and female sibs recorded before index cases.

However, subdividing by sex of the index case, there is an observed excess of the opposite sex sibs in total and in the immediately preceding sib before the index case. The results were: total M/F before *female* index case, 492/457; total of sibs before *male* index case, 299/333; M/F of sibs immediately preceding 386 *female* cases of spina bifida, 96/85; anencephalus, 105/100; total, 201/185; M/F of sibs immediately preceding 232 *male* cases of spina bifida, 68/78; anencephalus, 41/45; total 109/123.

Discussion

This study shows that New South Wales has a combined frequency of 2.01/1000 total births for neural tube defects.

The incidence is slightly higher than that of South Australia and Western Australia (Simpson, 1977) for the same years. It is not statistically significant and may be due to underreporting.

Previous Australian studies (Collmann and Stoller, 1962; Stevenson *et al.*, 1966) based on hospital birth series have assessed the rates as slightly lower, possibly for the same reason.

The Australian population has a low incidence of ASB compared to such countries as Ireland (Penrose, 1957), South Wales (Laurence *et al.*, 1968), and

Lebanon (Abou-Daoud, 1966), but a higher rate than Israel (Naggan, 1971), the Far East (Neel, 1958), Japan, Africa, and France (Frézal *et al.*, 1964).

There is a similarity in secular trends in New South Wales to patterns noted in other parts of the world.

MacMahon and Yen (1971) noted a decline in 3 intervals in Boston and Providence in America from 1950 to 1965, which is also present in New South Wales.

A peak in 1954 to 1955 followed by a sharp decline to 1967 was noted in England and Wales (Rogers and Morris, 1971).

The geographical isolation of Australia renders inapplicable many of the factors considered to influence secular trends on other continents, such as prohibition and troughs of economic decline. Even the influenza pandemic was delayed in onset and attenuated in Australia.

Internal variations in the population, such as maternal age and parity, and migration patterns in a younger developing country like Australia, contrasted with the United Kingdom, are divergent. Socio-economic trends, living conditions, and dietary patterns are not comparable.

The female preponderance of cases for each type of abnormality is less marked, as was observed in other countries of low frequency, such as Israel (Naggan, 1971) and among negroes (Gittelsohn and Melham, 1965).

The female excess increases with increased risk factors, such as seasonality and yearly variation.

Seasonal variation in risk rates for ASB in New South Wales is due to meningomyelocele, and the peak of conceptions in summer (December, January, and February) differs from the peak observed in British studies (Carter and Evans, 1973) in spring conceptions (February, March, April). In fact, a trough of conceptions of meningomyelocele occurs in spring (July, August, and October) in this study.

A peak of spring conceptions and a trough for those in autumn persist in British studies for spina bifida, even where the incidence of anencephalus does not vary (Smithells and Chin, 1965). In Hungary (Czeizel and Revecs, 1970) an excess of spring conceptions of spina bifida, but not anencephalus, was noted in the 1960s. A winter excess of anencephalus births in some, but not all, regions of Canada was noted (Elwood, 1975).

Studies of climatic factors have been unrewarding, and the correlation between high risk rate and higher average temperature in New South Wales merely confirms the seasonal variation, rather than incriminating hyperthermia as an aetiological agent. The positive association with hours of sunshine and daylight in Scotland observed by Record (1961) is supported.

Humidity and rainfall did not contribute significantly to the correlation in rate. A comparison of the climatic similarities of spring in the United Kingdom and summer in New South Wales for higher conception rates of ASB, and of autumn in the United Kingdom and spring in New South Wales for lower conception rates, and also a study of seasonality of spontaneous abortions, may clarify the matter. Regional variations over New South Wales with a gradient from eastern coastal areas of higher incidence to central western areas of low incidence correspond with urban/rural ratios. The variations in risk rates in Sydney suburbs closely parallel socioeconomic status distributions as described by Davis and Spearritt (1971).

However, high rates are due to the interrelation of a number of risk factors which indicate genetic/environmental interaction, such as older maternal age and increased parity, migrant population, poor socioeconomic levels and living conditions, and a possible correlation with industrial suburbs and coal mining areas.

No effect of hardness or softness of water supply was detected and the geological characteristics of areas of high incidence compared with low were non-contributory.

Increased risk rates for first births and birth order greater than the fourth, standardised for maternal age, are comparable with overseas series. However, an excess of first born male encephalocèles and anencephalics has not been noted previously. Again, differential abortion rates, or the fact that males are more severely affected, may be relevant. The increased risk for first births at younger maternal age is not significant. Correlating maternal age and parity, the first birth effect appears in the age groups 25 upwards, and the older age effect at later birth order, and the U-shaped relationship of birth order and maternal age shown in Scotland (Record, 1961), England, and Wales (Carter, 1969), is evident. The social class effect is evident in first births to young mothers who do not show an increased risk rate, but does not play a significant part in the older age groups.

There was an increased risk rate for ASB among ex-nuptial births, which showed a first birth order, young maternal age, and social class effect.

An older paternal age effect was observed, either as a reflection of older maternal age, or as a separate biological effect.

Social class, as measured by the father's occupation and regrouped on prestige scale, shows a deficit in class I and an excess in classes IV and V, which is observed in most large scale studies.

There is not a sharp gradation in living standards from class I to V in Australia. Classes IV and V may live in crowded accommodation, have poor nutrition,

and bad eating habits, but rather than an environmental factor reflected by social class, various ethnic groups with greater genetic susceptibility form classes IV and V.

Migrant studies show that parents from areas of high incidence, such as the UK and Lebanon, maintain a higher risk, maternal greater than paternal, for both parents than the Australian population, but lower than the country of origin.

The majority of affected infants were conceived in Australia. Migration patterns are such that the father has been resident longer than the mother. As ethnic variation may be due to genetic or environmental factors with the maintenance of cultural differences such as diet, further studies in the next generation of migrant families may provide information, as in Israel (Naggan, 1971), where the difference in the ethnic groups disappeared between the first and second generations after migration.

An increased risk rate is observed in the Australian part-aboriginal population which has risk factors such as older maternal age, high birth rank, poor socioeconomic circumstances, illegitimacy, and possible teratogens in folate and zinc deficiency and alcohol intake. However, the maternal effect and an increased recurrence risk suggest a genetic predisposition.

Studies of families with recurrent cases confirmed that either anencephalus or meningomyelocele may recur or alternate in affected sibs.

A spectrum of abnormalities from minor vertebral abnormalities and closed lipomeningocele to the full expression of defective closure of the neural tube of anencephalus and craniorachschisis was noted within families.

Of these families 24% were migrants. An empirical recurrence risk for ASB of 1 in 22.5 was recorded. The risk in sibs born before an affected case was 3.73% (1 in 26.8), an 18.5-fold increase over the general population risk. After 2 affected children 7 in 28 recurrences were identified.

A raised perinatal mortality rate of non-specific cause among sibs, excluding neural tube defect, was observed.

There was no deficiency of affected twin pairs. Four twin pairs with both children affected and 31 with 1 child affected were identified. Mono- and dichorionic twins were equally affected. However, there was a higher concordance rate for monozygotic pairs (21.4%) than dizygotic (5.5%), which favours genetic effect. The presence of an affected female twin appeared to confer an increased risk of death and additional abnormality on the other twin.

Sequential interaction between successive full term sibs as postulated by Knox (1970), where the IP (M/F) sex ratio preceding females is higher than the IP sex ratio preceding males, is observed in our data.

However, there is an increased number of sibs of the opposite sex immediately before the index case, and in the total number of sibs, though there were equal total female and male sibs. This excess of sibs of the opposite sex is also observed in families of recurrent cases. However, in families of twin cases there was no excess of males before females.

The twin studies and variations in sex ratio with seasonality and birth order, and the excess of the opposite sex in the sib immediately preceding an index case, are indications of a sequential interaction. The formation of a teratoma as the result of partial destruction of the submissive twin has been suggested (Rogers, 1976).

There is evidence that there is a factor common to ASB, twinning (Rogers, 1976), miscarriage (Clarke *et al.*, 1975), disordered ovulation (clomiphene therapy), infertility, female births, and hydatidiform moles.

The aetiology of neural tube defects is, as yet, undetermined. A complex genetic environmental interaction is postulated.

The relatively low incidence of ASB in Australia, as determined in this study, with recurrence risks in families comparable with overseas studies, a maternal age effect, and high risk migrant groups, suggests that the genetic component is relatively important, while the background environmental agent is less significant.

Detailed analyses of environmental factors in relation to this data, such as potato blight (Renwick, 1972), hardness and softness of water supply, geological characteristics, heavy metal concentrations, or viral infections showed no correlation with increased risk rates for ASB.

Antenatal diagnosis and maternal serum screening have made the detection of cases possible. Selective termination of affected fetuses is classed as prevention. True prevention lies in the identification of the aetiological agents. Comparative epidemiological studies, assessment of world wide secular trends, migration patterns, and studies of families of recurrent cases from the genetic and environmental aspects will provide the final clue.

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