Neural tube defects in Western Australia 1966–81 and a review of Australian data 1942–81

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SUMMARY Cases of neural tube defects born in Western Australia during the years 1966–81 were identified from hospital records and death certificates. The overall rate for the 16 year period was 1.81 cases of neural tube defects per 1000 births. The rate rose and then fell over the 16 years. The initial lower rate may have been due to underascertainment, but the recent dramatic fall is statistically significant and has been observed in other Australian states and other parts of the world. This fall was not accounted for by termination of affected pregnancies before 20 weeks' gestation nor by demographic changes in birth order, father's occupation, or parental country of birth. The birth prevalence of neural tube defects determined in previous Australian studies is reviewed in relation to the recent decline in these disorders.

The possibility of preventing neural tube defects (NTD) by periconceptional vitamin supplementation¹ has renewed interest in these malformations and has highlighted the need for accurate documentation of population based trends in prevalence.

Many recent reports have indicated a worldwide fall in the birth prevalence of NTD^{2–4} for which no satisfactory explanation has been found.

We report a study of NTD in Western Australia over the period 1966 to 1981 and review the data available on the geographical and temporal variation of these defects in Australia.

Methods

Case identification—Cases of anencephaly, spina bifida, and encephalocele were identified from death certificates and the records of the only specialist paediatric hospital in the state. The records of the major obstetric hospital (including necropsy information on births in other hospitals) were used as an additional source of ascertainment.

Classification of cases—Cases with anencephaly and spina bifida have been classified as anencephaly. Spina bifida includes cases of spina bifida with and

without concomitant hydrocephalus as well as cases of encephalocele.

Demographic information—Demographic information for each case was obtained from the birth notification paper filed with the Registrar General. Data available were nuptial status, mother's age and birth place, and for nuptial births only, previous issue of marriage, and father's age, occupation, and birth place. Information on the same variables, for total births in Western Australia, was obtained from routine tabulations prepared by the Australian Bureau of Statistics.

Completeness of ascertainment—A separate perinatal death certificate, covering live births and stillbirths over 28 weeks' gestation and deaths in the first four weeks after birth, was introduced in Western Australia in 1963. In 1968 the definition was altered to include all births of 20 weeks' gestation or more.

It is likely, therefore, that some underascertainment occurred in the early years of this study. From 1970 onwards, however, ascertainment is thought to be reasonably complete and consistent from year to year. There is only one specialist paediatric hospital in Western Australia, and it is considered likely that all cases of NTD surviving

more than one month (the period covered by the perinatal death certificate) would be referred to this centre.

Although there is no routine screening programme for NTD in Western Australia, falling trends in the prevalence of NTD at birth should be interpreted in the light of termination of affected pregnancies before 20 weeks' gestation. In Western Australia cases of NTD may be detected before 20 weeks' gestation as a result of ultrasound examination for another reason, or in mothers at high risk because of a previous NTD birth who undergo prenatal diagnosis with ultrasound and amniocentesis. Over the last two years of the study information on terminations of pregnancies affected with an infant with NTD was requested from all potential sources.

Analysis—Information for some variables (previous issue, father's occupation, and father's birth place) was available only for nuptial births, and the analysis was therefore restricted to nuptial births in these instances. Cases with information unknown for a given variable were excluded from analyses involving that variable.

To illustrate trends in birth prevalence, rates based on three year moving averages for anencephaly, spina bifida, and total NTD combined were plotted, together with 95% confidence intervals for the first, last, lowest, and highest rates for NTD. The Chi-square test for linear trend was used to test for trend in rates in anencephaly, spina bifida, and NTD.

A Chi-square test for contingency tables (with correction for continuity where applicable) was used to examine variations in birth prevalence by sex of the infant, parental age and birth place, nuptial status, birth order, and father's occupation.

Miettinen's formula was used for the calculation of confidence intervals (CI) for relative risks.⁵

The data were divided into two five year periods and a six year period (1966–70, 1971–75, 1976–81) and standardisation in relation to selected parental characteristics was performed by the indirect method, using total births for the 16 years as the standard.

Case finding of NTD in South Australia, 1966–73—The review of previous Australian studies of the birth prevalence of anencephalus and spina bifida includes unpublished data for South Australia for the period 1966–73. Case finding methods were similar to those for Western Australia in the same period and were based on examination of stillbirth and death records, the records of the only specialist paediatric hospital in South Australia receiving cases of spina bifida, and through postal inquiry to all obstetric hospitals in South Australia. Cases were classified as outlined above. Rates were based on the official statistics for total births.

Results

Over the 16 year period 1966 to 1981, 597 cases of NTD were identified. Births in Western Australia in this period totalled 330 071, giving a birth prevalence of 1.81 NTD per 1000 births (table 1). The rates for anencephaly and spina bifida were 0.83 and 0.98 per 1000 births respectively. For NTD the rate rose initially from 1966 to 1972 when it stabilised before reaching a peak in 1976. After this the downward trend was both consistent and substantial. The pattern of these trends is illustrated in the figure. The 95% confidence intervals about the high and low three year rates suggest that both the rise and subsequent fall were greater than would be expected from chance variation due to small numbers. The initial increase, as noted under methods, could be partly an artefact due to underascertainment resulting from the change in definition of stillbirths in 1968 from 28 to 20 weeks' gestation, and to other deficiencies in case finding in the early years of the study but it is unlikely to be wholly due to this. The strength and consistency of the decline after 1976 which coincided with similar falls in other Australian states is likely to be real. Parallel movements in rates also occurred for anencephaly and spina bifida, with the latter showing greater variation.

The fall in rate from 1976 to 1981 is statistically significant for both defects considered together (χ^2 for trend = 7.89, $p < 0.005$, 1 df) and for anencephaly (χ^2 for trend = 8.9, $p < 0.003$, 1 df). The fall observed for spina bifida alone was not statistically significant (χ^2 for trend = 1.18, $p < 0.278$, 1 df).

Table 1 Neural tube defects, Western Australia 1966–81

Year of Birth	All births	Anencephaly		Spina bifida		All NTD	
		No	Rate	No	Rate*	No	Rate
1966	17 459	14	0.80	10	0.58	24	1.38
1967	18 268	17	0.93	18	0.99	35	1.92
1968	19 899	15	0.75	16	0.80	31	1.56
1969	21 476	13	0.61	15	0.70	28	1.30
1970	22 425	17	0.76	23	1.03	40	1.78
1971	23 569	24	1.02	21	0.89	45	1.91
1972	22 152	26	1.17	23	1.04	49	2.21
1973	20 442	19	0.93	25	1.22	44	2.15
1974	20 346	15	0.74	27	1.33	42	2.06
1975	20 370	18	0.88	26	1.28	44	2.16
1976	20 517	29	1.41	22	1.07	51	2.49
1977	20 418	15	0.74	22	1.08	37	1.81
1978	19 224	15	0.78	20	1.04	35	1.82
1979	20 653	14	0.68	17	0.82	31	1.50
1980	20 788	14	0.67	21	1.01	35	1.68
1981	22 065	9	0.41	17	0.77	26	1.18
		(11)	(0.50)*			(28)	(1.27)*
Total	330 071	274	0.83	323	0.98	597	1.81

* Rates per 1000 births (figures in parentheses include pregnancies terminated before 20 weeks' gestation).

Only two cases of NTD were identified as terminated before 20 weeks' gestation, both in 1981, and inclusion of these cases does not alter the significance of the falling rate (table 1).

Fig 1 Birth prevalence of neural tube defects, Western Australia, 1966–81. Rates per 1000 total births, based on three year moving averages. Bars indicate 95% confidence intervals.

Girls had consistently higher rates of NTD prevalence than boys in all years and for both defects (table 2). The rate for boys with spina bifida was greater than the rate for boys with anencephaly, but not significantly so, and no significant variation of the sex ratio occurred over the study period.

Table 2 Birth prevalence of neural tube defects by sex of infant, Western Australia, 1966–81

	1966–70		1971–75		1975–81	
	No of NTD cases	Rate	No of NTD cases	Rate	No of NTD cases	Rate
Anencephaly:						
Boys	29	0.57	33	0.60	34	0.53
Girls	47	0.98	69	1.32	62	1.03
Spina bifida:						
Boys	38	0.74	54	0.99	50	0.79
Girls	43	0.89	68	1.31	69	1.15
Total:						
Boys	67	1.31	87	1.57	84	1.32
Girls	90	1.87	137	2.63	131	2.18

For all years considered together, no statistically significant association was observed between the prevalence of NTD and maternal age, paternal age, or nuptial status. A significantly increased risk of NTD prevalence was found for fourth and subsequent births, for parents born in the United Kingdom, and for fathers whose occupation was in the unskilled category (tables 3, 4, and 5). A significantly lower risk of NTD was observed among

fathers born in other European countries (table 4). When the data were grouped into the three time periods and standardised for birth order (table 3), the fall in rate was still of the same order of magnitude (20%). The fall was also unaltered by standardisation for parental country of birth and father's occupation.

Review of Australian data

Table 6 summarises previous studies of the birth prevalence of NTD in Australia. Before 1966 these related principally to the separate conditions of anencephaly and spina bifida, and were variously based on total population or hospital data. The rate for anencephalus varied from 0.7 to 0.9 per 1000 births and that for spina bifida from 0.6 to 1.2 per thousand. From these intermittent studies, the combined rate of NTD in Australia has been assumed to be of the order of 2.0 per 1000 births.⁶

Since 1966 the birth prevalence of NTD has been more extensively and consistently studied. In the period 1966–73 population based studies using comparable case finding methods were conducted in New South Wales, South Australia, and Western Australia. The period rates for these three states were virtually identical at 2.0 per 1000 births, lending support to the previous estimates. In the extended New South Wales study (1965–80), however, there was evidence of a trend in rates over time similar in pattern to those reported in this study, with an initial rise in the total NTD rate from 1.7 in 1965 to a peak of approximately 2.4 in 1976, followed by a decline, the quadratic trend being significant for both anencephaly and spina bifida. No such trend was observed in South Australia (table 7) and therefore it cannot be assumed that the rising rates observed in New South Wales and Western Australia occurred in other parts of Australia.

Since 1975 additional studies conducted in Victoria and Tasmania have shown lower overall rates of total NTD of 1.7 and 1.6 respectively. In both states there has been evidence of decline in rates as shown in table 8 which also includes data from New South Wales and the present study. There is thus clear evidence of a decline in rates in four Australian states since 1975. The fall in prevalence in Victoria is statistically significant for anencephaly and both defects together, but not for spina bifida alone.

The Tasmanian data showed a significant fall for all NTD (χ^2 for trend = 10.28, $p < 0.001$, 1 df). The small numbers of births (around 7000 annually) probably accounts in part for the wide fluctuations in rates by year, and were too small to examine anencephaly and spina bifida separately. From table 7 there is thus clear evidence of a general decline in rates in four Australian states.

Table 3 Birth order by grouped study years (nuptial births only)

Birth order	1966–70		1971–75		1976–81		1966–81		Rate NTD per 1000	Relative risk (95% CI)
	All births (n=88 877) %	No of NTD cases	All births (n=94 175) %	No of NTD cases	All births (n=107 200) %	No of NTD cases	All births (n=290 252) %	No of NTD cases		
1	36.1	38	38.2	51	36.1	73	36.8	162	1.52	1
2	28.8	44	33.5	70	37.8	61	33.6	175	1.79	1.18(0.95–1.45)
3	18.0	25	17.0	40	18.1	27	17.7	92	1.79	1.18(0.96–1.35)
≥4	17.1	38	11.3	42	8.0	21	11.9	101	2.93	1.93(1.51–2.46)
Total	100.0	145	100.0	203	100.0	182	100.0	530		
Crude rate										
NTD/1000 births		1.63		2.16		1.70		1.83		
Standardised rate										
NTD/1000 births		1.57		2.16		1.74				

Table 4 Birth prevalence of NTD by parental birth place 1966–81

Birth place of parent	No of NTD	Rate per 1000	Relative risk	95% Confidence interval
Mother:				
Australia	425	1.75	1.00	—
United Kingdom	105	2.45	1.40**	1.13–1.73
Other Europe	39	1.32	0.75	0.54–1.04
Other	24	1.61	0.92	0.60–1.40
Father (nuptial cases only):				
Australia	381	1.90	1.00	—
United Kingdom	101	2.39	1.26*	1.01–1.57
Other Europe	41	1.09	0.58**	0.42–0.80
Other	18	1.27	0.66	0.41–1.05

*p<0.05; **p<0.01.

Discussion

Relatively stable rates over time of the prevalence of NTD have been observed in Australia until the last decade, with rates of around 1 per 1000 for both anencephaly and spina bifida.

A fall in rate in recent years has been documented in four Australian states, as well as in many other parts of the world. The reasons for this fall have not been identified. Terminations of pregnancies

affected with NTD have been included in some studies^{4 16 18} as well as the present study, and account for only a small proportion of the fall.

No consistent alteration of the male to female ratio for either defect was seen over time; this was in contrast with some studies, though not all, in which a decline in rate was associated with a rise in the proportion of boys affected.^{2 19}

The risk of NTD was greater in fourth and subsequent births in Western Australia although not also in first births, as has been observed in some other studies.¹⁹ Standardisation for birth order in these data shows that the reduction in the proportion of high parity and thus high risk Western Australian

Table 5 Birth prevalence of NTD by father's occupation 1966–78. Nuptial births only

Occupational group	No of NTD cases	Rate per 1000 births	Relative risk	95% Confidence interval
Professional	62	1.52	1.00	—
Semiprofessional	73	1.91	1.26	(0.89–1.78)
Skilled	139	1.79	1.17	(0.87–1.57)
Unskilled	167	2.28	1.50*	(1.12–2.01)
Armed forces, other	9	1.69	1.11	(0.37–3.32)

*p<0.01.

Table 6 Birth prevalence of NTD in Australia before 1975

Source reference	State or city	Period	Total births	Total NTD Rate per 1000	Anencephaly Rate per 1000	Spina bifida Rate per 1000
⁷	Sydney*	1942–64	90 684	—	0.7	—
⁸	Melbourne*	1942–62	228 976	1.3	0.7	0.6
⁹	Victoria	1954–65	753 097	—	0.7	—
¹⁰	Melbourne*	1949–58	69 740	—	0.8	—
¹¹	South Australia	1956–65	206 328	—	—	0.8
			(Live births only)			
¹²	Melbourne*	1943–63	?	—	—	1.2
¹³	Melbourne*†	1961–64	11 765	0.8	0.5	1.4
¹⁴	Melbourne*	1971–75	10 454	2.7	1.2	1.6
¹⁵	New South Wales	1965–73	781 099	2.0	0.9	1.1
Unpublished data	South Australia	1966–73	171 753	1.94	0.99	0.95

*Hospital series.

†Single births only.

Table 7 *Birth prevalence of neural tube defects, South Australia, 1966-73*

Year of birth	All births	Anencephaly		Spina bifida		All NTD	
		No	Rate	No	Rate	No	Rate
1966	20 319	24	1.2	23	1.1	47	2.3
1967	20 386	8	0.4	22	1.1	30	1.5
1968	21 207	27	1.3	17	0.8	44	2.1
1969	21 977	25	1.1	21	0.9	46	2.1
1970	22 617	13	0.5	19	0.8	32	1.4
1971	22 966	27	1.2	22	0.9	49	2.1
1972	21 844	25	1.1	19	0.9	44	2.0
1973	20 407	22	1.1	21	1.0	43	2.1
Total	171 753	171	1.0	164	0.9	335	1.9

mothers in recent years is not a reason for the fall in birth prevalence of NTD.

When one or other parent was born in the United Kingdom the risk of NTD was greater than for Australian born parents, and parents born in other European countries had a lower rate of NTD. Parents from the United Kingdom, a high risk area for NTD^{15 19 20} appear to retain their high risk, at least to some degree, when they migrate to Australia. The relative contribution of genetics and environment to this risk is not clear.^{15 19} These differences will be examined in more detail in another paper.

Minor changes in the distribution of parental birth place have occurred over the study period, but standardisation for these variables again leaves the fall in rate of NTD unaltered.

An association of the prevalence of NTD at birth with paternal occupation was observed in these as in other data.¹⁹ Standardisation for occupation over the study period had no effect on the falling rate, but as an indication of social, nutritional, and educational status, father's occupation is a very crude measure. Significant changes in some of these variables may have occurred which this study is unable to address but which may be relevant to the fall in the prevalence of NTD at birth.⁴

While the recent fall in NTD birth prevalence is encouraging, the possibility must be recognised that this may not be permanent but part of long term cyclical variation. In support of this it is noted that in both New South Wales and Western Australia, rates actually rose concurrently before the recent decline.

Whereas such rises may be spurious due to incomplete case finding, periodic variations have been well documented in other populations¹⁹ and continued research into the reasons for variation with time, as well as the aetiology of NTD, is necessary.

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References

- Smithells RW, Sheppard S, Scorch CJ, *et al.* Possible prevention of neural tube defects by periconceptional vitamin supplementation. *Lancet* 1980; i: 339-40.
- Romijn JA, Treffers PE. Anencephaly in the Netherlands: a remarkable decline. *Lancet* 1983; i: 64-5.
- Windham GC, Edmonds CD. Current trends in the incidence of neural tube defects. *Pediatrics* 1982; 70: 333-7.
- Owens JR, McAllister E, Harris F, West L. Nineteen year incidence of neural tube defects in area under constant surveillance. *Lancet* 1981; ii: 1032-5.
- Miettinen O. Estimability and estimation in case-referent studies. *Am J Epidemiol* 1976; 103: 226-35.
- Renwick JH. Anencephaly and spina bifida are usually preventable by avoidance of a specific but unidentified substance in certain potato tubers. *Br J Prev Soc Med* 1972; 26: 67-88.
- Jones WR. Anencephalus: a 23-year survey in a Sydney hospital. *Med J Aust* 1967; 1: 104-6.

Table 8 *Birth prevalence of NTD in Australia 1975-81. Rate per 1000 births*

Source reference	State	1975	1976	1977	1978	1979	1980	1981
10*	New South Wales	2.00	2.40	2.05	1.70	1.90	1.65	
17	Tasmania	3.02	2.37	0.89	1.60	1.92	1.04	0.82
18	Victoria	1.85 (1.87)	1.74 (1.82)	1.71 (1.77)	1.42 (1.54)	1.46 (1.53)	1.28 (1.48)	
Present study	Western Australia	2.16	2.49	1.81	1.82	1.50	1.68	1.18 (1.27)

*These rates were read from a graph. There may therefore be slight inaccuracies. Rates in parentheses include terminations of pregnancy.

- ⁸Stoller A, Collmann RD. Patterns of occurrence of births in Victoria, Australia, producing Down's syndrome (mongolism) and congenital anomalies of the central nervous system: a 21-year prospective and retrospective study. *Med J Aust* 1965; **1**: 1-4.
- ⁹Collmann RD, Stoller A. The occurrence of anencephalus in the state of Victoria, Australia. *Mental Deficiency Research* 1968; **12**: 22-35.
- ¹⁰Betheras FR. Obstetrical aspects of foetal hydrocephalus and anencephalus. *Aust NZ J Obstet Gynaecol* 1962; **2**: 31-3.
- ¹¹Beal S. The occurrence of spina bifida cystica in South Australia. *Med J Aust* 1967; **2**: 597-8.
- ¹²Smith ED. *Spina bifida and the total care of spinal meningomyelocoele*. Illinois: Thomas, 1965.
- ¹³Stevenson AC, Johnston HA, Stewart MIP, Golding DR. Congenital malformations. A report of a study of series of consecutive births in 24 centres. *Bull WHO* 1966; **34**, suppl 9: 30.
- ¹⁴Drew JH, Parkinson P, Walstab JE, Beischer NA. Incidence and types of malformations in newborn infants. *Med J Aust* 1977; **1**: 945-9.
- ¹⁵Field B. Neural tube defects in New South Wales, Australia. *J Med Genetics* 1978; **15**: 329-38.
- ¹⁶Mathers CD, Field B. Some international trends in the incidence of neural tube defects. *Community Health Studies* 1983; **VII**: 60-6.
- ¹⁷Department of Obstetrics and Gynaecology University of Tasmania, and Tasmania State Committee of the Royal College of Obstetrics and Gynaecology. *Obstetric and neonatal report*. Tasmania 1976-81.
- ¹⁸Danks DM, Halliday JL. Incidence of neural tube defects in Victoria, Australia. *Lancet* 1983; **i**: 65.
- ¹⁹Elwood JM, Elwood JH. *Epidemiology of anencephalus and spina bifida*. Oxford: Oxford University Press, 1980.
- ²⁰Hobbs MST, Carney A, Field B, Simpson D, Kerr C. Incidence of anencephalus and spina bifida and variation in risks according to parental birth place in three Australian states. *Br J Prev Soc Med* 1974; **28**: 66 (abstract).