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MORTALITY FROM CONGENITAL MALFORMATIONS OF THE CENTRAL NERVOUS SYSTEM IN NORWAY, 1951-65

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Congenital malformations of the central nervous system have long attracted the interest of statisticians and epidemiologists. Various features of the data, frequently conflicting, have been emphasised. Hewitt (1965) found that the mortality of spina bifida decreased markedly from east to west on the North American continent and suggested the hypothesis that

> " . . . both the downward time-trend of recent years and the downward geographical trend as one proceeds westward across America are due to greater outbreeding".

On the other hand, Naggan and MacMahon (1967) adduce good evidence for considering environment rather than genes the more important determinant of frequency. In a Boston hospital series they found that the risk of anencephalus and spina bifida increased with decreasing occupational status in each ethnic group except the Jewish. In all but the highest occupational class the risk for Jews was much lower than in the other ethnic groups. Naggan and MacMahon consider that the most attractive explanation is that exposure to some aetiological factor increases with decreasing socioeconomic status, and that this factor is less prevalent among Jews in the middle and lower economic classes. They also point to the rarity of concordance in monozygous twins. The report from a 24-centre international survey by Stevenson, Johnson, Stewart, and Golding (1966) says in connexion with the twin data on anencephalus:

> "These observations suggest a minimal genotypic contribution to etiology and a rather localised uterine environmental causation. Such a hypothesis has to be reconciled with variations in frequency in different communities and variations by socio-economic levels in the same country, the latter so well shown in the vital statistical data from Scotland and elsewhere".

For spina bifida and hydrocephalus the suggestion is of a

> "relatively more important genotypic contribution to these conditions than to anencephalus".

Leck (1966), analysing data from Birmingham for 1940–65, found that anencephalus and spina bifida both decreased during 1940–49, rose to a peak around 1956, and then fell again. Björo and Iversen (1959) found in a hospital series from Oslo in 1944–58 that there was a deficiency in cases of anencephalus among conceptions estimated to have taken place in the first quarter of the year. No explanation has been found for such fluctuations in frequency with time. If biological rather than statistical artefacts, they point strongly towards a controllable environmental aetiology.

The purpose of the present study is to review the information provided by Norwegian mortality data on the subject. Clearly, the mortality of live born children can at best give only crude indications of true malformation prevalence. According to Leck (1966), nine-tenths of the foetuses with anencephalus die before birth. The distinction between foetal deaths and live births may not be consistently drawn in different places or at different times, and this may result in spurious differences in the mortality rates. In addition, real variations may occur in the proportion of malformed children who are born alive. Spina bifida is more rarely associated with foetal death, but here differential survival past the first year of life may lead to bias. Nevertheless, in the absence of other types of data on a countrywide basis, the pointers provided by mortality statistics may be worth having.

Material

In 1951 the mortality statistics of Norway introduced the Sixth Revision of the International Statistical Classification, thereby providing the following groups for congenital malformations of the nervous system:

Classification Number	*Group*
750	Monstrosity (Anencephalus is practically the only condition included)
751	Spina bifida and meningocele
752	Congenital hydrocephalus
753	Other congenital malformations of nervous system and sense organs (Microcephalus is by far the most common inclusion)

Starting in 1956, these conditions were coded also when they appeared as a contributory cause or complication on the death certificate. The Central Bureau of Statistics annually prepares lists of all deaths in Norway, giving the cause or causes coded for each death, in addition to such information as date of birth and municipality of residence at death. The Institute has examined the lists from the years 1951–65, extracting data on all deaths in which one of the above classification numbers was listed as a cause. Table I gives the number of deaths in each group as underlying and as contributory cause (or complication).

An age limit was set at 3 years, and the 117 deaths at ages above 3 years will not be discussed further. There were 940 relevant diagnoses under 3 years, but in seven cases two diagnoses were mentioned on the same certificate, so that the number of infants is 933.

TABLE I

NUMBER OF DEATHS CAUSED BY CONGENITAL MALFORMATIONS OF THE NERVOUS SYSTEM

International Classification	Age at Death: < 3 yrs: Underlying Cause 1951–65	Contributory Cause 1956–65	Total	3 yrs+: Total
750 Monstrosity	159	0	159	0
751 Spina bifida and meningocele	381	11	392	9
752 Congenital hydrocephalus	261	17	278	61
753 Other congenital malformations of nervous system and sense organs	93	18	111	47
Total	894	46	940	117

Results

Table II gives deaths at age under 3 years by sex, including the contributory causes from the years 1956–65. There is a female excess for Monstrosity and Spina bifida, as well as for all groups combined. However, the female excess in Monstrosity is much less pronounced than, for instance, in the anencephalus material of Naggan and MacMahon (1967) who had only about 30 per cent. males. It would not seem that the discrepancy can be explained by the inclusion under Monstrosity of malformations with a sex ratio different from that of anencephalus. Rather, part of the explanation may be that the period of gestation in the present series of live births is longer than in a series including foetal deaths, and that the sex ratio increases with increasing length of gestation (MacMahon, Pugh, and Ingalls, 1953).

TABLE II

MORTALITY BY SEX

Sex			Male	Female	Percentage Male
Live Births, 1951–65			487,744	459,696	51·5
Deaths at Age < 3 yrs	750	Number	73	86	45·9
		Rate per 10,000 live births	1·5	1·9	
	751	Number	172	220	43·8
		Rate per 10,000 live births	3·5	4·8	
	752	Number	155	123	55·8
		Rate per 10,000 live births	3·2	2·7	
	753	Number	60	51	54·1
		Rate per 10,000 live births	1·2	1·1	
	All Groups	Number	458*	475*	49·1
		Rate per 10,000 live births	9·4	10·3	

* Two males and five females had two of the diagnoses on the certificate.

Table III shows the distribution by month of birth. There is no sign of seasonal differences in any of the four groups. It should be noted, however, that the period of gestation may vary widely, so that the month of birth may bear no fixed relation to the time of conception.

The mortality rates in the twenty counties of Norway is shown in Table IV. Fig. 1 (opposite) gives the location of the counties. Distributions of maternal age and parity are not available by county, but are unlikely to be important for the interpretation of the county mortality differences.

Both Monstrosity and Spina bifida show rate variations which cannot be explained as random (Figs 2 and 3, opposite).

The Spearman rank correlation coefficients among the four malformation groups are as follows:

	751	752	753
750	−·39	−·29	+·31
751		+·29	−·36
752			−·07

Table III

MORTALITY BY MONTH OF BIRTH

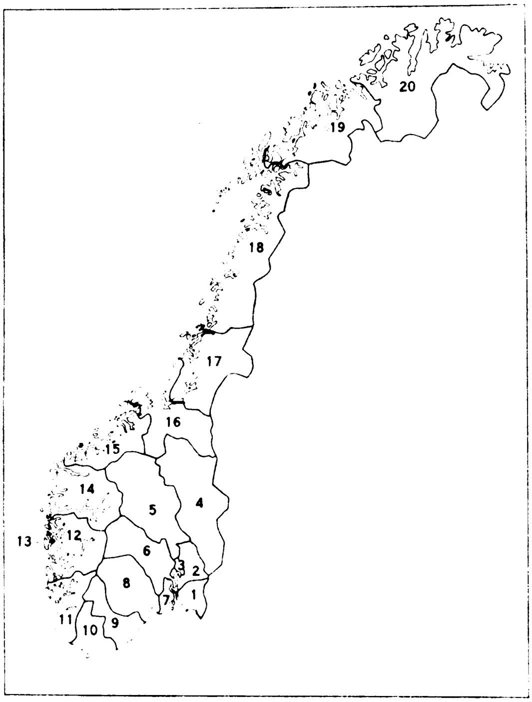
Month of Birth	Live Births 1951-65	Number of Deaths at Age < 3 yrs: Cause Group 750	751	752	753	All	Rate per 10,000 Live Births (all groups)
January	76,146	10	32	22	9	72	9·5
February	73,421	11	35	29	8	82	11·2
March	87,091	12	33	27	13	84	9·6
April	89,292	13	37	28	4	82	9·2
May	87,035	17	37	18	9	80	9·2
June	80,648	20	29	19	15	83	10·3
July	79,371	9	37	17	10	73	9·2
August	76,227	11	24	25	8	69	9·1
September	80,666	18	37	28	7	89	11·0
October	74,748	18	36	25	12	90	12·0
November	69,206	8	33	16	6	63	9·1
December	73,589	12	22	24	10	66	9·0
Total	947,440	159	392	278	111	933	9·8
χ^2 (11 degrees of freedom)		11·6	8·2	10·4	10·9	9·4	

Table IV

MORTALITY BY COUNTY OF RESIDENCE AT DEATH

County	Total Live Births, 1951–65	Number of Deaths at Age < 3 yrs: Cause Group 750	751	752	753	All	Rate per 10,000 Live Births: Cause Group 750	751	752	753	All
01 Östfold	49,770	6	26	17	4	53	1·2	5·2	3·4	·8	10·6
02 Akershus	64,684	8	13	25	10	56	1·2	2·0	3·9	1·5	8·7
03 Oslo	94,041	9	38	20	10	76	1·0	4·0	2·1	1·1	8·1
04 Hedmark	43,222	7	23	10	5	44	1·6	5·3	2·3	1·2	10·2
05 Oppland	42,196	5	15	16	7	42	1·2	3·6	3·8	1·7	10·0
06 Buskerud	40,624	6	26	12	6	50	1·5	6·4	3·0	1·5	12·3
07 Vestfold	43,585	5	13	15	7	40	1·1	3·0	3·4	1·6	9·2
08 Telemark	36,366	4	25	17	4	50	1·1	6·9	4·7	1·1	13·7
09 Aust-Agder	19,311	2	11	6	2	21	1·0	5·7	3·1	1·0	10·9
10 Vest-Agder	30,339	3	31	19	1	53	1·0	10·2	6·3	·3	17·5
11 Rogaland	71,245	8	31	18	6	63	1·1	4·4	2·5	·8	8·8
12 Hordaland	69,200	12	25	13	7	55	1·7	3·6	1·9	1·0	7·9
13 Bergen	26,854	4	7	9	2	22	1·5	2·6	3·4	·7	8·2
14 Sogn og Fjordane	27,618	5	9	12	5	31	1·8	3·3	4·3	1·8	11·2
15 Möre og Romsdal	62,779	11	24	14	7	56	1·8	3·8	2·2	1·1	8·9
16 Sör-Tröndelag	56,767	7	13	11	5	35	1·2	2·3	1·9	·9	6·2
17 Nord-Tröndelag	33,631	9	13	14	3	39	2·7	3·9	4·2	·9	11·6
18 Nordland	70,402	31	32	16	7	86	4·4	4·5	2·3	1·0	12·2
19 Troms	39,783	10	11	9	8	38	2·5	2·8	2·3	2·0	9·6
20 Finnmark	25,023	7	6	5	5	23	2·8	2·4	2·0	2·0	9·2
Total	947,440	159	392	278	111	933	1·7	4·1	2·9	1·2	9·8
χ^2 (19 d.f.)							46·6	63·0	33·8	12·1	48·9
P							< ·001	< ·001	·02	·89	< ·001

(1)



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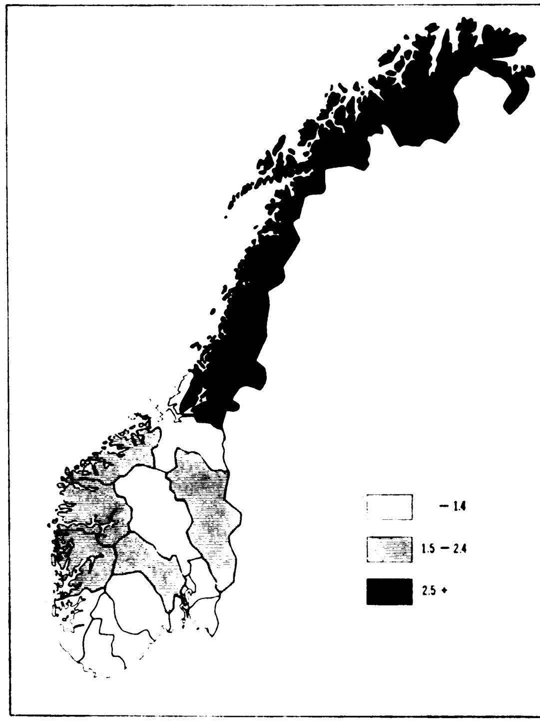

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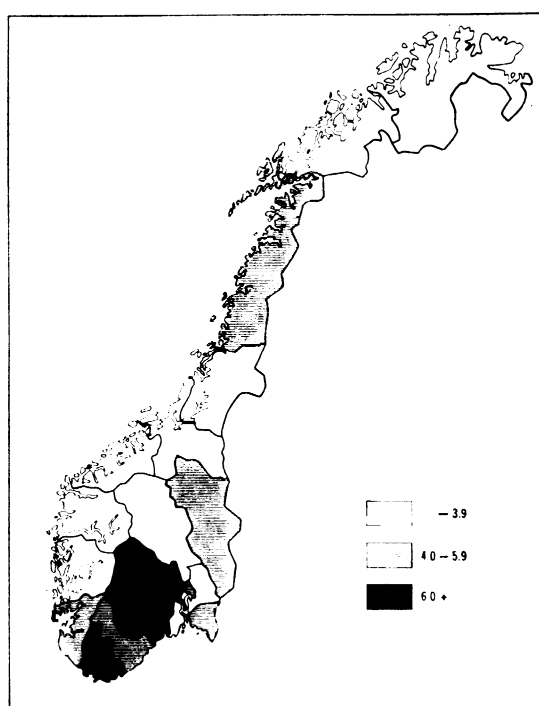

FIG. 1.—Location of the twenty counties of Norway.

FIG. 2.—Monstrosity (International Classification No. 750). Deaths per 10,000 live births, 1951–65.

FIG. 3.—Spina bifida (International Classification No. 751). Deaths per 10,000 live births, 1951–65.

None of these is significant at the 5 per cent. level. However, the negative coefficient between 750 and 751 is noteworthy in view of the positive correlation between anencephalus and spina bifida found in other studies.

Monstrosity shows a striking excess in the northern counties, detectable in each of the three 5-year periods. The distribution suggests an association with unfavourable socioeconomic conditions. It is well known, for instance, that the northern counties in Norway have a relatively high infant mortality rate, particularly in the post-neonatal period. In order to correlate the rates in Table IV with county characteristics, the mortality rate at age 4 weeks to 1 year during the period 1954–65 was computed for each county. Further, four percentages, mutually intercorrelated, were computed from the 1960 census data. The first two of the percentages may be considered indices of unfavourable socioeconomic conditions, whereas the last two may be related to the existence of genetic isolates. The following rank correlation coefficients were obtained:

Counties ranked according to:	*Mortality 1951–65* 750	751	752
Infant mortality 4 wks–1 yr, 1954–65	+·35	+·06	−·17
Percentage of population in 1960 who were:			
(1) Living more than one person to a room	+·67**	−·47*	−·44
(2) Living in dwellings without water or w.c.	+·37	+·15	+·16
(3) Born in county of residence	+·51*	+·10	−·08
(4) Born in municipality of residence	+·63*	−·17	−·16

*P<·05 **P<·01

Thus, Monstrosity, but not Spina bifida or Hydrocephalus, shows a definite association with the chosen indices. It is probably unwarranted to draw conclusions from the variations among the coefficients for group 750. Of course, the observed associations may be secondary to the geographical variations of some aetiological factor which cannot be characterised as socioeconomic. In this connexion it may be noted that cancer of the thyroid gland shows a distribution similar to that of Monstrosity (Pedersen, 1956). The rank correlation coefficient is +·71 between the county rates for 750 in Table IV and the sex-age-adjusted county incidence of thyroid cancer for 1953–61 computed from the data published by the Norwegian Cancer Registry (1961, 1964).

The percentage of males in the Monstrosity group in the four northern counties was 54·4, compared to 41·2 in the other counties. The difference is not significant.

If socioeconomic factors—or inbreeding—were important in the aetiology, one would expect rates to be higher in rural than in urban areas. However, Table V shows only minor differences.

TABLE V

MORTALITY BY TYPE OF MUNICIPALITY

Area				Urban	Rural
Total Live Births, 1951–65				269,966	677,474
Mean Maternal Age (yrs)				28·5	28·9
Percentage at age 40+				3·9	5·6
Percentage at birth order 5+ (legitimate births only)				2·8	8·5
Deaths at Age < 3 yrs	750	Number		38	121
		Rate per 10,000 live births		1·4	1·8
	751	Number		115	277
		Rate per 10,000 live births		4·3	4·1
	752	Number		84	194
		Rate per 10,000 live births		3·1	2·9
	753	Number		29	82
		Rate per 10,000 live births		1·1	1·2
	All Groups	Number		265	668
		Rate per 10,000 live births		9·8	9·9

Monstrosity has a rural excess, but it might easily have arisen by chance (P = ·2). Also, parity is higher in rural births.

The time-trend of these malformations has been studied by separating the three 5-year periods, as in Table VI (opposite). Since contributory causes are available for the last two periods only, the rates per 10,000 live births are based on underlying cause only.

Deaths at age under 1 year and deaths at age 1–3 years have been shown separately. The point to note here is that deaths at age 1–3 from Spina bifida increased very markedly in the last 5-year period. Leck (1966) noted a similar tendency in the Birmingham series. This increase in survival will tend to bias the time trend if based only on infant deaths.

Monstrosity, which in Table IV was the only group related to unfavourable socioeconomic conditions, shows no downward trend. The mortality attributed to Spina bifida, even when all deaths under age 3 are included, falls off markedly. At the same time, however, there is an increase in mortality assigned to group 753—other congenital malformations of nervous system and sense organs. One must suspect that a change in terminology has occurred. The net result is a slight fall in the rate for

TABLE VI
MORTALITY TIME-TREND

Years			1951–55			1956–60			1961–65		
Total Live Births			312,390			315,104			319,946		
Age at Death (yrs)			< 1	1–3	Total < 3	< 1	1–3	Total < 3	< 1	1–3	Total < 3
Number of Deaths (underlying and contributory causes)	750	Underlying	44	0	44	58	0	58	57	0	57
	751	Underlying	144	4	148	118	5	123	94	16	110
		Contributory				6	1	7	2	2	4
	752	Underlying	67	18	85	70	19	89	66	21	87
		Contributory				4	4	8	5	4	9
	753	Underlying	19	4	23	24	3	27	34	9	43
		Contributory				6	3	9	6	3	9
	All Groups	Underlying	274	26	300	270	27	297	251	46	297
		Underlying+Contributory				282	35	317	262	54	316
Rate per 10,000 Live Births (underlying cause only)	750		1·4		1·4	1·8		1·8	1·8		1·8
	751		4·6		4·7	3·7		3·9	2·9		3·4
	752		2·1		2·7	2·2		2·8	2·1		2·7
	753		0·6		0·7	0·8		0·9	1·1		1·3
	All Groups		8·8		9·6	8·6		9·4	7·8		9·3

all groups combined. This fall can be fully explained by the trend towards a more favourable pattern of maternal age and parity:

Years		1951 –55	1955 –60	1961 –65
Live Births	Mean maternal age	29·7	29·1	27·6
	Per cent. age 40+	6·0	5·4	4·1
Legitimate Live Births	Per cent. birth order 1	37·9	35·2	34·2
	Per cent. birth order 5+	7·4	6·6	6·7

SUMMARY

Deaths ascribed to congenital malformations of the central nervous system in Norway in 1951–65 have been analysed with respect to sex, month of birth, county, urban-rural residence, and time trend.

Monstrosity (Anencephalus) and Spina bifida showed a female excess, in contrast to the male excess for Hydrocephalus.

No association was found with month of birth.

Monstrosity was clearly in excess in the northern counties. The county rates for this group were positively correlated to indices of unfavourable socioeconomic conditions and to the percentage of the population born in the municipality of residence at the 1960 census. The county differences for Spina bifida, although statistically highly significant, did not fall into a distinct pattern and did not correlate with the indices mentioned.

There were no significant urban-rural rate differences, but the Monstrosity rate was higher in the rural areas.

In the course of the 15-year period, the rate for Spina bifida went down, but there was a simultaneous increase in the rate for group 753—Other congenital malformations of nervous system and sense organs.

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