

Defects of the central nervous system in Finland: I. Variations in time and space, sex distribution, and parental age

GUSTAV GRANROTH, MATTI HAKAMA, AND LAURI SAXÉN

From the Department of Pathology, University of Helsinki, and Department of Public Health, University of Tampere

SUMMARY Data from the Finnish Register of Congenital Malformations for the years 1965-73 were used in a search for associations between environmental influences and defects of the central nervous system (CNS). The material consisted of 710 cases of CNS defects and their matched-pair controls. Moreover, an 'internal' control group of 259 cases of polydactyly and their matched-pair controls were used. The first report gives information on variations in time and space, sex distribution, and parental age. A higher incidence of anencephaly was noted in the eastern part of the country, but no significant secular or seasonal variations were found. The sex ratio (M/F) was lower than expected in the groups of anencephaly and CNS defects as a whole. High parental age turned out to be a risk factor in the group of all CNS defects, mainly owing to the subgroup of hydrocephaly. The dangers of observational studies due to confounding factors are discussed.

Defects of the central nervous system (CNS) constitute an important medical as well as a social problem which like most congenital defects are likely to be caused by an interaction of both genetic and environmental factors. The purpose of this study is to test some hypotheses concerning the association of environmental factors with CNS defects. This first report gives a description of the material, with information on incidence, seasonal and yearly variations, sex distribution, and parental age. Subsequent reports will deal more specifically with various maternal and exogenous factors associated with CNS defects.

Material and methods

This epidemiological study is based on material from the Finnish Register of Congenital Malformations. Reporting of all congenital malformations detected during the first year of life was made compulsory in Finland in 1963, the year in which the register was founded. The group of CNS defects is one of the 'detector' defects, for which extensive information is collected through the maternity welfare centres. The control for each case is the mother whose delivery preceded that of the study mother in the same maternity welfare

district. The information on both the study and the control cases is collected by interviews with the mothers and from the records of the welfare centres obtained during pregnancy. Thus the information is prospective as well as retrospective. Full details of the organisation of the register have been published elsewhere (Saxén *et al.*, 1974). In those instances where it was possible, the official statistics for the entire country of Finland 1965-73 were used as a control.

This system of 'detector' defects has been in use since 1965, and all notifications of congenital defects to the register during 1965-73 have been used. The defects of the CNS were selected from this material and grouped according to pathological-anatomical changes. In order to get an exact diagnosis of the defects complementary questionnaires were sent to the reporting doctors, to the hospitals where the patients were treated, and/or to the children's welfare centres. There were 710 cases in five main groups: anencephaly, spina bifida, hydrocephaly, microcephaly, and hydranencephaly. In addition there were six cases of different rare defects (for example, septum pellucidum agenesis), but since these cases could not be used to form meaningful statistical groups, they were excluded from the study. The main groups were

further divided into two subgroups, those with the CNS defect as the only recorded defect, and those with additional malformations. No case in which the CNS defect is part of a known syndrome was observed in the latter group. We attempted to keep the groups with solitary defects as uniform as possible, and only cases with malformations secondary to the CNS defect (for example, clubfoot, in combination with severe spina bifida) were included in these groups. If no difference in the association to various factors for the subgroups and the undivided group was observed, only the result for the undivided group is reported.

Cases in which anencephaly was combined with spina bifida were classified as anencephaly, and those in which hydrocephaly was an obvious consequence of spina bifida (for example, in combination with the Arnold-Chiari defect) were classified as spina bifida. In spite of this classification, the group of hydrocephaly may contain some cases of unrecognised spina bifida or even of hydranencephaly. Moreover, the group of hydrocephaly as such is itself certainly heterogeneous owing to various geneses (primary versus secondary). Another weakness in the classification is due to the fact that necropsy was not performed for all deaths. This particularly affects the proportion between the groups of solitary and multiple defects (Table 1).

Table 1 Classification of the material

Defect	Only defect	Additional defects	All cases
Anencephaly	162	37	199
Spina bifida	164	75	239
Hydrocephaly	164	52	216
Microcephaly	26	15	41
Hydranencephaly	14	1	15
All CNS defects	530	180	710
Polydactyly	259	0	259

In order to get an 'internal' control group, 259 cases of polydactyly, where polydactyly was the only recorded defect, were collected together with their matched pair controls. Polydactyly was chosen because several pedigrees of dominant inheritance are recorded in the medical literature (Sverdrup, 1922; Johnston and Davis, 1953; Grebe, 1963). The addition of this group to the study enabled the testing of the association of the various environmental factors not only to the CNS defects and their control groups, but also to a group of defects with a strong genetic background.

In this report the common χ^2 test, the binominal test, and the Kolmogorov-Smirnov test were used for determining the statistical significances of the associations.

Results

INCIDENCE OF ANENCEPHALY

Among 621 026 live and still births in Finland during 1965-73 there were 199 cases of anencephaly which gives an incidence of 0.32 per 1000 births. The incidence was highest in the eastern part of the country, the district of Northern Karelia (Pohjois-Karjala) having a rate of 0.61 ‰. The incidences in all the other districts were fairly uniform, the figures being well below 0.5 ‰. Compared with the rest of the country the higher incidence in Northern Karelia was significant at the 5% level. There was a slight difference in the incidence rates between rural (0.38 ‰) and urban (0.28 ‰) areas, although the difference is not statistically significant.

YEARLY VARIATION

The yearly variations in the incidence rates for the different malformations studied during the years 1965-73 were small without any overall statistical significance. Rates for hydrocephaly had a slightly U-shaped curve, with a downward trend from 1965 to 1970 and thereafter again a rising trend; there was a decreasing trend for all CNS defects, but this was not statistically significant.

SEASONAL VARIATION

Because of marked differences in the gestational age of anencephalic children in particular, the seasonal variations were studied with regard to time of birth and time of conception. As can be seen from Figs 1 and 2 there were no significant

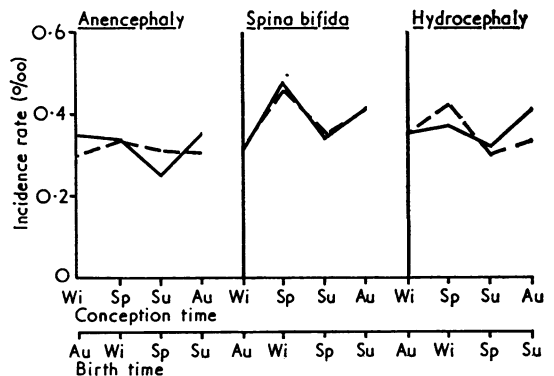


Fig. 1 Seasonal incidence rates of anencephaly, spina bifida, and hydrocephaly.

Conception time —, Birth time - - - -.

Wi = December-February, Sp = March-May, Su = June-August, Au = September-November.

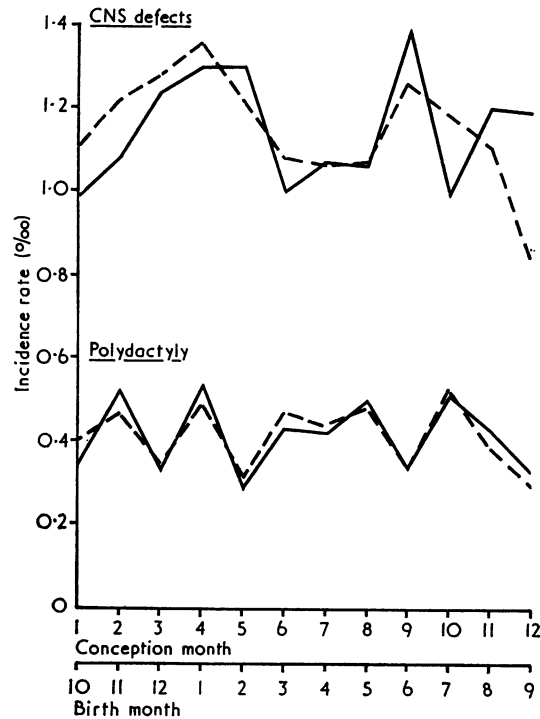


Fig. 2 Seasonal incidence rates of CNS defects and polydactyly. Conception month —, Birth month - - - -.

trends in the over-year distribution for any malformation, neither with regard to time of birth nor to time of conception. Although there seems to be a winter peak with regard to time of birth for all CNS defects and for spina bifida, the differences are not statistically significant even at the 5% level.

SEX DISTRIBUTION

As mentioned above, many of the children with CNS defects also had multiple malformations. In a few cases the disturbances of the urogenital system were so severe that no sex definition had been made. This occurred in three cases of anencephaly and in one case each of spina bifida and hydrocephaly.

The proportion of males in 621 026 newborns in 1965-73 for the whole country was 1.06. In the 196 children with anencephaly 75 were boys, with a sex ratio of 0.62. When only the 162 cases with a solitary anencephalic lesion were investigated, exactly the same sex ratio was obtained. Although there were more girls than expected in all groups of CNS defects, the group of anencephaly was the only one with a sex distribution significantly different

from the expected one ($P < 0.001$). The overall sex ratio for CNS defects was 0.78, which is significant at the 1% level.

In contrast to the groups of CNS defects, the group of polydactyly contained more boys than expected (1.33), but this sex distribution was not statistically significant (Table 2).

Table 2 Sex distribution of the material

Defect	Number		Ratio
	Boys	Girls	M/F
Anencephaly	75	121	0.62
Spina bifida	111	127	0.87
Hydrocephaly	100	115	0.87
Microcephaly	19	22	0.86
Hydranencephaly	5	10	0.50
CNS total	310	395	0.78
Polydactyly	148	111	1.33

AGE DISTRIBUTION OF PARENTS

The age distribution of the mothers of malformed children was compared with that of all the 613 357 women who had borne children during 1965-73 in Finland. No such control material was available of the fathers and hence the matched-pair controls were used.

For CNS defects as a whole there was an overrepresentation ($P < 0.001$) of mothers and fathers in the higher age groups, which was mainly owing to the parents of hydrocephalic children (Table 3). For anencephaly and spina bifida there was no indication of increased risk with increasing parental age (Table 3 and Fig. 3).

In the two parental groups of children with polydactyly there was tendency towards a U-shaped age distribution curve (Table 3). For mothers this tendency was not statistically significant; for fathers, with only the matched pairs as control, the finding was significant at the 1% level.

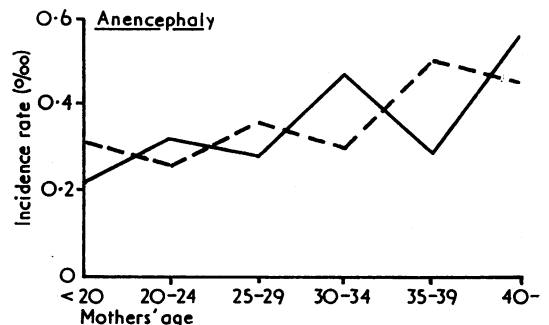


Fig. 3 Incidence rates of anencephaly (—) and of time-area-matched controls (- - - -) by maternal age.

Table 3 The relative risk of birth of a malformed child at different parental ages in terms of unit risk for the total age span

Defect	Mothers' age						Fathers' age					
	< 20	20-24	25-29	30-34	35-39	40-	< 25	25-29	30-34	35-39	40-44	45-
Anencephaly	0.71	1.23	0.78	1.57	0.58	1.24	1.06	1.03	1.15	0.93	0.63	2.33
Spina bifida	1.02	0.79	1.34	0.83	1.24	1.10	1.07	0.74	1.24	0.91	0.77	1.29
Hydrocephaly	0.73	0.88	0.94	1.08	1.25	2.18	0.83	0.89	1.05	0.67	1.20	5.67
All CNS defects	0.90	0.92	0.99	1.18	0.96	1.52	0.95	0.82	1.13	0.86	0.83	2.85
Polydactyly	1.14	1.25	0.77	0.95	0.74	1.50	1.49	0.67	0.92	1.41	1.50	1.40

The maternal and paternal ages in the different groups were also crosschecked, and no diverging distributions could be detected.

Discussion

Anencephaly, especially in its pure form, should be an easily detectable malformation. Because of the nature of the malformation these children are not capable of surviving for long. In Finland death certificates are compulsory for all deceased and for all stillbirths from the 28th week of gestation. The certificates are centrally registered and available for inspection. Thus it is possible to have complete information on the incidence of anencephaly in the country.

The other malformations in this study were mainly not lethal, and although reporting of congenital malformations in newborns is compulsory in Finland, the reporting is incomplete and moreover many malformations are missed during the perinatal period (Hakosalo, 1973). Therefore, no incidence figures for geographical distributions of the other malformations are reported. It was estimated that the reporting rates from the different places and hospitals are probably constant over time, and that the reports in other respects are representative. Moreover, the matched-pair system makes the findings comparable. Thus all the various factors in this report were investigated with respect to the different groups of malformations. In some instances the groups of microcephaly and hydranencephaly were too small for meaningful statistical analyses and therefore were excluded from this report.

Although anencephaly is a well-defined entity and a good detector defect, its incidence rates may be difficult to compare owing to variations in the mode of registration in different populations. However, it seems that the incidence rates for Finland and Sweden, where the malformation registers are alike, are low especially compared with those of the British Isles. Incidence rates from some other areas are listed in Table 4.

In Finland and Sweden the incidence of anencephaly is low, 0.32 ‰ and 0.37 ‰ respectively. This is remarkable as these neighbouring

Table 4 Incidence rates of anencephaly from various geographical areas

Area	Rate (‰)	Author	Year
Dublin, Ireland	5.7	Coffey and Jessop	1958
Belfast, Ireland	4.2	Elwood and Nevin	1973
South Wales	3.54	Laurence <i>et al.</i>	1968
Glasgow, Scotland	2.83	Wilson	1970
Birmingham, England	2.41	Leck <i>et al.</i>	1968
USA, 12 hospitals from different parts	1.4	Chung and Myrianthopoulos	1968
Taipei, Taiwan	1.17	Emanuel <i>et al.</i>	1972
Budapest, Hungary	1.1	Czeizel and Révész	1970
New York, the Sloane Hospital for Women	0.87	Milic	1969
Israel	0.61	Halevi	1967
Czechoslovakia	0.50	Kučera	1965
Sweden	0.37	Källén and Winberg	1968
Finland	0.32	Granroth <i>et al.</i>	1977

populations are racially different. The majority of the Finns have their origin in north-eastern Asia (the Fenno-Ugrian group), while the Swedes are of Germanic origin and certainly are more closely related to the English who have a high incidence of anencephaly. On the other hand, Finland and Sweden have much in common—such as, climate, culture, and mode of living. Hence the similarities in the incidence of anencephaly favour environmental rather than genetic factors. The increased incidence in the eastern part of the country remains unexplained. The living conditions there are, and have been, different from those of the more prosperous western part. Many hereditary diseases have also been shown to exist in the eastern part of Finland (Norio *et al.*, 1973).

MacMahon and Yen reported rates of neural tube defects from two USA hospitals back to 1832 and 1885 (MacMahon and Yen, 1971). They found increased rates of CNS defects between 1920 and 1949 with a peak between 1929 and 1932, when the rates were more than three times those preceding or following the epidemic period. An abnormal constituent of liquors—because of the federal prohibition of liquor in that period—as well as socioeconomic factors (the depression) were suggested as possible causes. Socioeconomic factors such as starvation have also been proposed (Gesenius, 1952). Many of the time clusters reported have no explanations (Leck and Rogers, 1967; Elwood, 1973; Janerich, 1973). Some of them, such as the one found here for hydrocephaly with a

downward trend in 1965-70, may be owing to random variation.

There are many reports of a winter excess of the births of children with CNS defects, especially anencephaly (Edwards 1958; Leck and Record, 1966; Elwood, 1970; Wilson, 1971). In a report from Scotland (Elwood and MacKenzie, 1971) there was a significant winter excess for anencephaly in Glasgow but a summer excess in Aberdeen. Several studies from Europe and USA show no seasonal trend in the distribution of CNS defects (Milham, 1962; Westlund, 1969; Wehrung and Hay, 1970; Elwood and Nevin, 1973). According to Renwick (1972, 1973) blight-infested potatoes may play a role in the genesis of neural tube defects. He found a peak in the incidence of anencephaly-spina bifida (ASB) in children conceived in May or June, when the risk for late blight attack of potatoes is greatest. He also maintained that the risk for an ASB defect would be roughly proportional to the amount of potatoes consumed.

In Finland the variations of the four seasons are very marked, the summers being light and warm, the winters dark with temperature peaks down to -30° to -40° C. The potato consumption per caput in 1969-70 was 263 g/day (Central Statistical Office, 1974), which is among the highest rates reported in the world. Rates for anencephaly did not show an increased risk for any season. In the groups of spina bifida and total CNS defects the risk seemed highest in winter, but the variation was not statistically significant. As, moreover, the incidence of anencephaly is low in Finland there does not appear to be any correlation with either blighted potatoes or the amount of potato consumption.

Sex distributions of the children with CNS defects in this study are in good conformity with those in many other studies (Record and McKeown, 1949; Timonen *et al.*, 1968; Czeizel and Révész, 1970; Wilson, 1970; Hay, 1971). The sex ratio (M/F) especially for anencephaly is low, and also in the other groups of CNS defects the sex ratio seems to be constantly below 1.0. Probably male CNS-malformed fetuses, and especially anencephalic ones, are aborted to a higher extent than female ones during early pregnancy, and some unknown factor in the female fetuses may prevent an early abortion. The sex ratio for polydactyly (1.33) was also in good conformity with the ratio for polydactyly in other reports (Hay, 1971). Because polydactyly in a high percentage is inherited it is conceivable that this defect may be partially sex-linked.

The reports on the influence of parental age on the origin of CNS defects vary. In a large study from 12 hospitals in the USA, Chung and Myrian-

thopoulos (1968) found no correlations within races. Also in South Wales in 1964-66 (Richards *et al.*, 1972) and New York State in 1945-67 (Janerich, 1972) no correlations were found. Many authors report a higher incidence of CNS defects with increasing maternal age, especially of hydrocephaly (Record and McKeown, 1949; Ingalls *et al.*, 1954; Hay and Barbano, 1972), and anencephaly (Coffey and Jessop, 1957, 1958). U-shaped maternal age curves with high incidences below 20 and over 35 years of age have been reported for anencephaly (Record, 1961; Wilson, 1971) and for both anencephaly and hydrocephaly (Edwards, 1958). Leck (1972) reported that anencephaly and spina bifida are particularly common among first births to young mothers. Mainly only the maternal age has been studied, but Czeizel and Révész (1970) found significantly higher age curves for fathers also in all groups of CNS defects except anencephaly.

The rising incidence of hydrocephaly with parental age is supported by the age-specific risk indicators given in Table 3. For anencephaly, the relative risks did not increase with age (Table 3) even though the incidence rates showed an increasing trend with maternal age (Fig. 3). This complex relationship shows the dangers of observational studies: high maternal age might be associated with high risk areas or other risk factors for anencephaly. In fact, this could be shown in our material in Northern Karelia, where the incidence of anencephaly was significantly higher than in the rest of the country the mean maternal age was 26.72 years as compared to 26.17 in the rest of the country ($P < 0.001$). In Northern Karelia there were 4.2% mothers over 40 years of age whereas the corresponding figure in the rest of the country was 2.7% ($P < 0.001$). Such confounding may be the cause of the varying conclusions found in the literature on the relationship between CNS defects and parental age.

This study was supported by grants from the Finnish Medical Foundation, the Finska Läkaresällskapet, the Research Department, Rinnekoti Institution for the Mentally Retarded, and the Vasa Läkarförening, Finland.

Reprints from Professor L. Saxén, Department of Pathology, University of Helsinki, SF-00290 Helsinki 29, Finland.

References

Central Statistical Office (1974). *Statistical Yearbook of Finland 1973*. CSO: Helsinki.

- Chung, C. S., and Myrianthopoulos, N. C. (1968). Racial and prenatal factors in major congenital malformations. *American Journal of Human Genetics*, **20**, 44-60.
- Coffey, V. P., and Jessop, W. J. E. (1957). A study of 137 cases of anencephaly. *British Journal of Preventive and Social Medicine*, **11**, 174-180.
- Coffey, V. P., and Jessop, W. J. E. (1958). A three years study of anencephaly in Dublin. *Irish Journal of Medical Science*, **393**, 391-413.
- Czeizel, A., and Révész, C. (1970). Major malformations of the central nervous system in Hungary. *British Journal of Preventive and Social Medicine*, **24**, 205-222.
- Edwards, J. H. (1958). Congenital malformations of the central nervous system in Scotland. *British Journal of Preventive and Social Medicine*, **12**, 115-130.
- Elwood, J. H. (1970). Anencephalus in Belfast. Incidence and secular and seasonal variations, 1950-66. *British Journal of Preventive and Social Medicine*, **24**, 78-88.
- Elwood, J. H. (1973). Epidemics of anencephalus and spina bifida in Ireland since 1900. *International Journal of Epidemiology*, **2**, 171-175.
- Elwood, J. H., and MacKenzie, G. (1971). Comparisons of secular and seasonal variations in the incidence of anencephalus in Belfast and four Scottish cities 1956-66. *British Journal of Preventive and Social Medicine*, **25**, 17-25.
- Elwood, J. H., and Nevin, N. C. (1973). Factors associated with anencephalus and spina bifida in Belfast. *British Journal of Preventive and Social Medicine*, **27**, 73-80.
- Emanuel, I., Huang, S-W., Gutman, L. T., Yu, F-C., and Lin, C-C. (1972). The incidence of congenital malformations in a Chinese population: The Taipei collaborative study. *Teratology*, **5**, 159-169.
- Gesenius, H. (1952). The increase of births of monsters in Berlin and its suburbs in the post-war years. *The International Journal of Sexology*, **6**, 24-26.
- Grebe, H. (1963). Malformaciones de los miembros. In *Genetica Humana*, volume 2, pp. 185-350. Edited by P. E. Becker. Toray: Barcelona.
- Hakosalo, J. K. (1973). Cumulative detection rates of congenital malformations in a ten-year follow-up study. *Acta pathologica et microbiologica Scandinavica (A)*, Supplement **242**, 1-59.
- Halevi, H. S. (1967). Congenital malformations in Israel. *British Journal of Preventive and Social Medicine*, **21**, 66-77.
- Hay, S. (1971). Sex differences in the incidence of certain congenital malformations: A review of the literature and some new data. *Teratology*, **4**, 277-286.
- Hay, S., and Barbano, H. (1972). Independent effects of maternal age and birth order on the incidence of selected congenital malformations. *Teratology*, **6**, 271-279.
- Ingalls, T. H., Pugh, T. F., and MacMahon, B. (1954). Incidence of anencephalus, spina bifida, and hydrocephalus related to birth rank and maternal age. *British Journal of Preventive and Social Medicine*, **8**, 17-23.
- Janerich, D. T. (1972). Anencephaly and maternal age. *American Journal of Epidemiology*, **95**, 319-326.
- Janerich, D. T. (1973). Epidemic waves in the prevalence of anencephaly and spina bifida in New York State. *Teratology*, **8**, 253-256.
- Johnston, O., and Davis, R. W. (1953). On the inheritance of hand and foot anomalies in six families. *American Journal of Human Genetics*, **5**, 356-372.
- Källén, B., and Winberg, J. (1968). A Swedish register of congenital malformations. Experience with continuous registration during 2 years with special reference to multiple malformations. *Pediatrics*, **41**, 765-776.
- Kučera, J. (1965). Die Erfassung der angeborenen Missbildungen in der CSSR. *Annales paediatrici*, **204**, 141-151.
- Laurence, K. M., Carter, C. O., and David, P. A. (1968). Major central nervous system malformations in South Wales. I. Incidence, local variations and geographical factors. *British Journal of Preventive and Social Medicine*, **22**, 146-160.
- Leck, I. (1972). The etiology of human malformations: Insights from epidemiology. *Teratology*, **5**, 303-314.
- Leck, I., and Record, R. G. (1966). Seasonal incidence of anencephalus. *British Journal of Preventive and Social Medicine*, **20**, 67-75.
- Leck, I., Record, R. G., McKeown, T., and Edwards, J. H. (1968). The incidence of malformations in Birmingham, England, 1950-1959. *Teratology*, **1**, 263-280.
- Leck, I., and Rogers, S. C. (1967). Changes in the incidence of anencephalus. *British Journal of Preventive and Social Medicine*, **21**, 177-180.
- MacMahon, B., and Yen, S. (1971). Unrecognized epidemic of anencephaly and spina bifida. *Lancet*, **1**, 31-33.
- Milham, S., Jr (1962). Increased incidence of anencephalus and spina bifida in siblings of affected cases. *Science*, **138**, 593-594.
- Milic, A. M. B. (1969). The occurrence of anencephaly at the Sloane Hospital for Women 1942-1967. *Bulletin of the Sloane Hospital for Women in the Columbia-Presbyterian Medical Center, New York City*, **15**, 11-13.
- Norio, R., Nevanlinna, H. R., and Perheentupa, J. (1973). Hereditary diseases in Finland: Rare flora in rare soil. *Annals of Clinical Research*, **5**, 109-141.
- Record, R. G. (1961). Anencephalus in Scotland. *British Journal of Preventive and Social Medicine*, **15**, 93-105.
- Record, R. G., and McKeown, T. (1949). Congenital malformations of the central nervous system. I. A survey of 930 cases. *British Journal of Preventive and Social Medicine*, **4**, 183-219.
- Renwick, J. H. (1972). Hypothesis: Anencephaly and spina bifida are usually preventable by avoidance of a specific but unidentified substance present in certain potato tubers. *British Journal of Preventive and Social Medicine*, **26**, 67-88.
- Renwick, J. H. (1973). Prevention of anencephaly and spina bifida in man. *Teratology*, **8**, 321-323.
- Richards, I. D. G., Roberts, C. J., and Lloyd, S. (1972). Area differences in prevalence of neural tube malformations in South Wales. A study of possible demographic determinants. *British Journal of Preventive and Social Medicine*, **26**, 89-93.

- Saxén, L., Klemetti, A., and Härö, A. S. (1974). A matched-pair register for studies of selected congenital defects. *American Journal of Epidemiology*, **100**, 297-306.
- Sverdrup, A. (1922). Postaxial polydactylism in six generations of a Norwegian family. *Journal of Genetics*, **12**, 217-240.
- Timonen, S., Malm, E., Lokki, O., and Vara, P. (1968). Factors influencing perinatal mortality and malformations in the new-born. *Annales paediatricae Fenniae*, **14**, 35-42.
- Wehrung, D. A., and Hay, S. (1970). A study of seasonal incidence of congenital malformations in the United States. *British Journal of Preventive and Social Medicine*, **24**, 24-32.
- Westlund, K. (1969). Mortality from congenital malformations of the central nervous system in Norway, 1951-65. Life Insurance Companies' Institute for Medical Statistics at the Oslo City Hospitals Report No. 12. *British Journal of Preventive and Social Medicine*, **23**, 28-33.
- Wilson, T. S. (1970). Congenital malformations of the central nervous system among Glasgow births 1964-68. *Health Bulletin of Edinburgh*, **28**, 32-38.
- Wilson, T. S. (1971). A study of congenital malformations of the central nervous system among Glasgow births 1964-1968. *Health Bulletin of Edinburgh*, **29**, 79-87.