ANENCEPHALUS AND SPINA BIFIDA IN BELFAST
(1964 - 1968)

by

J. H. ELWOOD
Department of Social and Preventive Medicine

and

N. C. NEVIN
Human Genetics Unit, Department of Medical Statistics
The Queen's University of Belfast, Northern Ireland

AT the beginning of this century in Belfast, the infant mortality rate was 153 per 1,000 livebirths; by 1970, the rate had fallen to 28 per 1,000 livebirths (Elwood, 1973). On the other hand, the contribution of congenital malformations to the infant death rate has altered only slightly and it is reasonable to assume that as mortality and morbidity continue to fall the relative importance of congenital malformations will increase (Nevin, 1969). The high incidence of neural tube malformations in Belfast has been emphasised by several authors (Stevenson & Warnock, 1959; Stevenson, Johnston, Stewart & Golding, 1966; Elwood, 1970a). A high incidence for anencephalus has been confirmed elsewhere in Ireland, for example, in Cork City and County (Spellman, 1969; 1970), Dublin (Coffey & Jessop, 1955; 1957), and County Galway (Cahalane, Kennedy, McNicholl & O'Dwyer, 1965). Much less information, however, is available about spina bifida in Ireland. Some findings of a study of 350 infants in Belfast having anencephalus and spina bifida have been published (Elwood & Nevin, 1973). The present paper reports additional data and briefly considers some other aspects of neural tube malformations.

METHODS

Since 1957 a register containing biosocial data on all (live and still) births to women resident in Belfast has been maintained by the Belfast Health Department and the University Departments of Social and Preventive Medicine, and of Medical Statistics. These data now are part of the Northern Ireland Record Linkage Project (Cheeseman, 1968). The population studied included all stillbirths of 28 or more weeks gestation and all livebirths irrespective of gestational age delivered to women resident within the statutory boundary of Belfast County Borough during the period from 1st January 1964 to 31st December 1968.

Many mothers living elsewhere in Northern Ireland are admitted to Belfast hospitals for specialist care; births to these non-Belfast residents and to temporary residents were excluded. The at-risk population, so defined, consisted of 41,351 births.

As the study began in 1969, ascertainment was made retrospectively. All infants with anencephalus, iniencephalus, exencephalus, and encephalocele, alone or in combination with one or more additional malformations, including anencephalus with spina bifida, were classified as anencephalus. The group specified
as spina bifida included meningocele, myelomeningocele, and syringomyelocele alone or in combination with hydrocephalus or other defects. Infants with spina bifida occulta, with or without neurological involvement, were excluded.

Infants with neural tube malformations were ascertained from multiple sources including – the birth register, data on all stillbirths and infant deaths collected by the Maternal & Child Care Division of the Municipal Health Department, death certificates provided by the Registrar General for Northern Ireland in which anencephalus or spina bifida was specified, records of the voluntary notification system for congenital malformations in Northern Ireland, data of families with neural tube malformations attending the Genetic Counselling Clinic, and autopsy records of hospitals in the Belfast area. Information from these sources was cross-checked, attention being paid in each case to verifying the diagnosis. Finally affected births, identified by christian names and surname, address and date of birth were linked to the birth register of the population at risk. Cases not successfully matched were discarded. As multiple sources of ascertainment were employed and as the malformations are easily recognizable, ascertainment is probably of the order of 95% or more.

**RESULTS**

The 41,351 total births at risk were followed until each resulted in either death (stillborn or early death) or survival at the age of ascertainment (from 1 to 5 years). Of this birth population, 151 infants had anencephalus, 185 spina bifida, and 24 both anencephalus and spina bifida (Table I). Females were affected significantly more than males (F/M ratio for anencephalus 2.8:1, and for spina

| TABLE I |
| Population studied - Belfast County Borough (1964-68) |

| Data and Sex | Observed Number | Incidence per 1,000 (live and still) births |
|--------------|-----------------|-------------------------------------------|
| Male:        |                 |                                           |
| Births (live and still) | 21,484          |                                          |
| Anencephalus            | 41             | 2.1                                      |
| Anencephalus with Spina Bifida | 5             |                                           |
| Spina Bifida          | 76             | 3.5                                      |
| Female:       |                 |                                           |
| Births (live and still) | 19,867          |                                          |
| Anencephalus            | 110            | 6.5                                      |
| Anencephalus with Spina Bifida | 19           |                                           |
| Spina Bifida          | 109            | 5.5                                      |
| Total:        |                 |                                           |
| Births (live and still) | 41,351          |                                          |
| Anencephalus            | 151            | 4.2                                      |
| Anencephalus with Spina Bifida | 24           |                                           |
| Spina Bifida          | 185            | 4.5                                      |
The incidence of anencephalus which includes the 24 infants having anencephalus with spina bifida was 4.2 per 1,000 total births, and of spina bifida was 4.5 per 1,000 total births. These figures are extremely high, exceeding those reported for South Wales (Laurence, Carter & David, 1968) and also those for spina bifida in the Irish Republic (Coffey, 1970).

The distribution of the observed cases of neural tube malformations within the electoral wards of Belfast (Table II and Figure) compared with the number expected, based on the population at risk, shows significant variation with respect to anencephalus ($\chi^2=42.2$; d.f. = 4; $0.30 > P > 0.20$). Initial inspection of these distributions suggested an association between religious domination and incidence. However, a rank correlation analysis between the percentage of Roman Catholics in each ward and the incidence of anencephalus does not confirm this hypothesis ($r = -0.04$; $S$ error = 0.27; $t = 0.15$; $P > 0.90$), nor is there a significant association with the incidence of spina bifida ($r = +0.39$; $S$ error = 0.27; $t = 1.45$; $0.20 > P > 0.10$). The data on the proportions of Roman Catholic by electoral ward (Park, 1962) refer to adult residents and not to reproductive mothers. As there is evidence that fertility rates are higher in Roman Catholics than in other religious denominations (General Register Office, 1965), the problem of any association between the incidence of neural tube malformations and religion in Ireland has yet to be satisfactorily answered.

### Table II

#### Distribution of Anencephalus and Spina Bifida by Belfast Residential Area (Electoral Ward)

| Residential area (electoral ward) | Births (live and still) | Anencephalus | Spina Bifida | Percentage of **Roman Catholics** |
|-----------------------------------|------------------------|--------------|--------------|----------------------------------|
|                                   | No.                    | No.          | Rate*        | No.          | Rate*        |
| 'Inner' Belfast:                  |                        |              |              |                |              |
| Smithfield                        | 935                    | 10           | 10.7         | 2             | 2.1          | 91           |
| St. George's                      | 1,004                  | 9            | 9.0          | 2             | 2.0          | 4            |
| Court                             | 1,101                  | 13           | 11.8         | 8             | 7.3          | 30           |
| Dock                              | 1,515                  | 4            | 2.6          | 6             | 4.0          | 5            |
| Sub-total                         | 4,555                  | 36           | 7.9          | 18            | 3.9          | 44           |
| 'Outer' Belfast:                  |                        |              |              |                |              |
| Duncairn                          | 3,586                  | 20           | 5.6          | 13            | 3.6          | 13           |
| Falls                             | 5,376                  | 18           | 3.3          | 27            | 5.0          | 93           |
| Ormeau                            | 3,411                  | 12           | 3.5          | 16            | 4.7          | 10           |
| Windsor                           | 1,655                  | 6            | 3.6          | 2             | 1.2          | 15           |
| Clifton                           | 5,123                  | 23           | 4.5          | 22            | 4.3          | 34           |
| St. Anne's                        | 2,283                  | 10           | 4.4          | 16            | 7.0          | 41           |
| Shankill                          | 3,145                  | 11           | 3.5          | 12            | 3.8          | 6            |
| Victoria                          | 3,026                  | 9            | 3.0          | 11            | 3.6          | 5            |
| Woodvale                          | 3,314                  | 16           | 5.0          | 15            | 4.7          | 8            |
| Cromac                            | 2,016                  | 2            | 1.0          | 14            | 6.9          | 24           |
| Pottinger                         | 3,961                  | 12           | 3.0          | 19            | 4.8          | 15           |
| Sub-total                         | 36,796                 | 139          | 3.8          | 167           | 4.5          | 24           |
| Total                             | 41,351                 | 175          | 4.2          | 185           | 4.5          | 29           |

* Calculated per 1,000 (live and still) births; **See: Park (1962)
FIG. 1 INCIDENCE OF SPINA BIFIDA PER 1,000 (LIVE AND STILL) BIRTHS
BY RESIDENTIAL AREA WITHIN BELFAST 1964-68
Compared with other cities with populations of 250,000 or over in the United Kingdom, Belfast has a high infant mortality rate, 30.6 per 1,000 live and stillbirths (Elwood & Pemberton, 1971). There is considerable variation in both perinatal and post-perinatal mortality rates between the fifteen electoral wards of Belfast. For example, the highest perinatal mortality rate was in Smithfield Ward (53.5), almost twice that for Pottinger Ward (27.3). Significantly, higher rates occurred in the ‘Inner’ compared with the ‘Outer’ Belfast areas, 45.9 and 35.3 respectively. Neural tube malformations accounted for 15 percent of all perinatal mortality in Belfast but the proportion varied considerably by electoral ward. For example, these malformations were responsible for 33 percent of all such deaths in Court Ward, and for only 12 percent in Shankill Ward. ‘Inner’ Belfast fared less favourably than ‘Outer’; 21 percent as opposed to 15 percent of all such deaths was due to neural tube malformations.

| Data                      | Number of persons per room | Total |
|---------------------------|---------------------------|-------|
|                           | 1 | 1-2 | 2+ |       |
| Total Births              | No. | 16,668 | 21,352 | 3,331 | 41,351 |
| Anencephalus              | No. | 77 | 70 | 28 | 175 |
| Rate                      | 4.6 | 3.3 | 8.4 | 4.2 |
| Spina Bifida (fatal)      | No. | 32 | 73 | 9 | 114 |
| Rate                      | 1.9 | 3.4 | 2.7 | 2.8 |
| Spina Bifida (non-fatal)  | No. | 33 | 32 | 6 | 71 |
| Rate                      | 2.0 | 1.5 | 1.8 | 1.7 |
| Spina Bifida (all)        | No. | 65 | 105 | 15 | 185 |
| Rate                      | 3.9 | 4.9 | 4.5 | 4.5 |
| Both defects              | No. | 142 | 175 | 43 | 360 |
| Rate                      | 8.5 | 8.2 | 12.9 | 8.7 |

For both defects: $\chi^2=7.4; \text{ d.f.}=2; 0.01>P>0.001$

As housing and socio-economic conditions vary in electoral wards, the relationship between the incidence of neural tube malformations and an overcrowding index based on the number of persons per room was examined (Table III). The incidence of neural tube malformations rises as the degree of overcrowding increases ($\chi^2=7.4; \text{ d.f.}=2; 0.01>P>0.001$). For spina bifida, the association exists for infants who die early in life but not for non-fatal cases.

The influence of such biosocial factors as maternal age and parity also were examined. Mothers less than 20 years of age had below average rates for both defects (3.6 and 2.5 per 1,000 for anencephalus and spina bifida respectively), mothers aged 40 or more years had average rates (4.4 and 4.5 per 1,000 births); but mothers between 20 and 24 years had the highest rates (4.9 and 5.0 per 1,000 births). A history of one or more previous abortion or stillbirth was associated with an ‘above average’ risk of an anencephalic or spina bifida infant compared with mothers who had no such previous reproductive experience. A significant trend
with the number of previous livebirths is present in anencephalus ($\chi^2=14.7$; d.f.$=7$; $0.05>P>0.02$) but not in spina bifida ($\chi^2=6.7$; d.f.$=7$; $0.50>P>0.30$). The incidence of anencephalus was high in first pregnancies (5.2 per 1,000) after which it declined to 2.5 per 1,000 for the third pregnancy to increase again after four pregnancies.

Finally, the survival of the 185 spina bifida children in Belfast was compared with that of spina bifida children in other parts of the United Kingdom. Of the total cases observed 71 (38 per cent) were alive at the time of ascertainment (Table IV). The survival rate was lower in female than male spina bifida children (34 per cent and 45 per cent respectively). Over the five years studied, survival had not altered significantly. Spina bifida children whose mothers were resident in ‘Inner’ Belfast fare much worse than those in ‘Outer’ Belfast, only 18.9 per cent compared with 39.5 per cent respectively being alive (Table V). A greater proportion of spina bifida infants were alive at their first birthday in Belfast than in Liverpool, Birmingham, or South Wales (Table VI). In the Irish studies survival rates beyond the perinatal period are not available, but the proportion of Belfast spina bifida infants alive at the second week, 72.5 per cent, is not very different from Coffey’s (1970) finding for the whole of the Irish Republic, 73.6 per cent in 1953-4 and 66.7 per cent in 1961-62.

**Table IV**

**Proportions of Spina Bifida Survivors at time of Ascertainment by Sex and Year**

| Sex       | Year of Birth | Total 1964-68 |
|-----------|--------------|---------------|
|           | 1964 | 1965 | 1966 | 1967 | 1968 |       |
| Male:     |       |      |      |      |      |        |
| All       | 16   | 18   | 16   | 13   | 13   | 76     |
| Alive     | 4    | 10   | 6    | 7    | 7    | 34     |
| %         | 25   | 55   | 37   | 54   | 54   | 45     |
| Female:   |       |      |      |      |      |        |
| All       | 26   | 25   | 16   | 20   | 22   | 109    |
| Alive     | 9    | 9    | 4    | 5    | 10   | 37     |
| %         | 35   | 36   | 25   | 25   | 45   | 34     |
| Both Sexes: |     |      |      |      |      |        |
| All       | 42   | 43   | 32   | 33   | 35   | 185    |
| Alive     | 13   | 19   | 10   | 12   | 17   | 71     |
| %         | 31   | 44   | 31   | 36   | 48   | 38     |

Test of secular trend in number of survivors

- Male: $\chi^2=2.97$; d.f.$=4$; $P>0.50$
- Female: $\chi^2=4.15$; d.f.$=4$; $P>0.30$
- Both Sexes: $\chi^2=4.43$; d.f.$=4$; $P>0.30$
TABLE V

Survival Times of 185 Spina Bifida Children in Belfast

| Data               | 'Inner' Belfast | 'Outer' Belfast | All Belfast |
|--------------------|-----------------|-----------------|-------------|
|                    | No.  | %    | No.  | %    | No.  | %    |
| Total observed     | 18   | 100  | 167  | 100  | 185  | 100  |
| Stillborn          | 4    | 22.2 | 26   | 15.6 | 30   | 16.2 |
| Death in 1st week  | 4    | 22.2 | 17   | 10.2 | 21   | 11.3 |
| Death in 2-52 weeks| 3    | 16.6 | 51   | 30.5 | 54   | 29.2 |
| Death in 1 year or over | 2    | 11.1 | 7    | 4.2  | 9    | 4.9  |
| Alive              | 5    | 18.9 | 66   | 39.5 | 71   | 38.4 |

TABLE VI

Spina Bifida Survival Rates in Four Communities in the United Kingdom

| Area and Period of Observation | Total No. (%) | Stillborn No. (%) | Died 0-365 Days No. (%) | Alive at First Birthday No. (%) |
|--------------------------------|---------------|-------------------|-------------------------|---------------------------------|
| Belfast 1964-68 (Elwood & Nevin, 1973) | 185 (100) | 30 (16.2) | 75 (40.5) | 80 (43.3) |
| Liverpool 1960-62 (Rickham & Mawdsley, 1966) | 203 (100) | 46 (22.7) | 84 (41.4) | 73 (35.9) |
| Birmingham 1960-62 (Knox, 1967) | 132 (100) | 29 (22.0) | 71 (53.8) | 32 (24.2) |
| South Wales 1956-62 (Laurence & Tew, 1971) | 425 (100) | 110 (25.9) | 239 (56.2) | 76 (17.9) |

DISCUSSION

This study, like earlier investigations of neural tube malformations in Northern Ireland (Stevenson & Warnock, 1959; Stevenson et al, 1966; Elwood & Warnock, 1969; Elwood, 1970a) confirms the extremely high incidence of both anencephalus and spina bifida, exceeding those reported from other parts of the world (Stevenson et al, 1966). The explanation for the high incidence of these defects in Ireland is far from clear. The rates of anencephalus and/or spina bifida among children of migrants from Ireland are considerably lower than those reported in Ireland itself but higher than the country of domicile (Naggan & MacMahon, 1967; Leck, 1969). If neural tube malformations were determined only by genetic factors, then the frequency of affected offspring of parents of Irish ancestry would be similar to that of the county of origin.
As with other common malformations, the aetiology appears to be multifactorial with an important genetic factor and a substantial environmental component. The genetic factor is probably polygenic but the mechanism by which it acts is not known. The environmental component is also unknown. Consideration of birth order, maternal age, and the secular and seasonal variation in the incidence has not clarified the environmental factor. Whatever the environmental factor may be, it is important to remember that probably only fetuses that are genetically ‘susceptible’ are at risk.

There are a number of epidemiological associations which indicate possible environmental factors: there is a marked geographical gradient in the incidence of neural tube malformations in the United Kingdom which steadily increases from the south and east to the north and west. The incidence (per 1,000 total births) in the south-east is about 1.5 for anencephaly and 2.0 for spina bifida, in Wales 4.13 and 3.54, and in Northern Ireland 4.2 and 4.5 respectively. This variation may depend on a variety of factors.

In England and Wales family size is smaller and the incidence of neural tube malformations lower. Differences in regional parity and maternal age between birth populations at risk, however, accounted for less than 5 per cent of the excess of the Northern Irish anencephalic rate over that of England and Wales (Elwood, 1970b). From an investigation of the geographical variation of neural tube malformations in South Wales, Richards, Roberts & Lloyd (1972) also concluded that differences in biosocial factors such as parity and social class did not explain the marked area differences.

An attempt has been made to explain the geographical variation of anencephalus and spina bifida with hardness of water supply which in general, is high in the south-east and low in the north-west (Fedrick, 1970). However, more detailed studies of individual regions do not confirm the association (Fielding & Smithells, 1971).

More recently dietary factors have been implicated in the aetiology of neural tube malformations. Renwick (1972) has put forward evidence supporting a hypothesis that potatoes might be the common factor. He has postulated that the blight fungus, Phytophthora infestans, induces a teratogen in certain potato tubers and has suggested that 95 per cent of cases of spina bifida would be prevented if potatoes were no longer eaten in Britain. This hypothesis has been considered elsewhere (Elwood & Nevin, 1973; Elwood, 1972) but an obvious test that has been applied to the hypothesis is that of animal experiments. Poswill, Hamilton & Sopher (1972) fed female marmosets blighted potatoes and found skull defects in some of the offspring. Details of the skull defect are not yet published but the abnormality apparently differs from the human malformations. Further assessment of Renwick’s (1972) hypothesis must await additional animal work and perhaps a potato avoidance trial in mothers who have had a previous infant with anencephalus and/or spina bifida.

The present study indicates that in Belfast, once every five days, a baby is born with either anencephalus or spina bifida. Mothers resident in ‘Inner’ Belfast and those living in overcrowded conditions are at greater risk. As infants with anencephalus are stillborn or live only a few hours, management is mainly the concern of obstetricians. However, spina bifida presents a more formidable problem, as
patients are usually liveborn and mostly have serious loss of function of the lower limbs, bladder, and rectum. Active surgical intervention has raised the survival rate without unfortunately reducing the proportion of survivors who are seriously handicapped. The present investigation shows a higher survival rate in Belfast children with spina bifida than in any other area in the United Kingdom. An explanation for this is not clear but an important question to be answered is whether the better survival rate is due to less severely affected cases occurring in Ireland compared with England and Wales. In Northern Ireland, as a result of the high incidence and the better survival rate, spina bifida has become a major community problem, greater than for other areas of the United Kingdom. As the environmental component in the aetiology of neural tube malformations remains unidentified, at present, genetic counselling and early detection in utero with selective termination of affected fetuses are the only available methods for the control of these malformations. The early diagnosis of anencephalus has been achieved by ultrasound B scan (Campbell, Johnstone, Holt & May, 1972) and by the finding of high levels of alpha fetoprotein (AFP) in amniotic fluid (Brock & Sutcliffe, 1972; Lorber, Stewart & Ward, 1973). As yet spina bifida cannot be diagnosed in utero with certainty but high AFP concentrations in the amniotic fluid in early pregnancy may also prove helpful in the diagnosis of a fetus with a myelocoele (Brock & Sutcliffe, 1972; Nevin, Nesbitt & Thompson, 1973).

ACKNOWLEDGEMENTS

We wish to thank Dr. J. McA. Taggart, Medical Officer of Health for Belfast; Dr. H. A. Warnock; Dr. K. M. Corbett and staff; Division of Maternal and Child Care for allowing us to examine their records; the Registrar General for Northern Ireland; Professor E. A. Cheeseman and Professor J. Pemberton for assistance; Mrs. J. Smith-Davidson and Mrs. I. Hay for data preparation.

Requests for reprints to Dr. N. C. Nevin, Human Genetics Unit, Department of Medical Statistics, Institute of Clinical Science, Grosvenor Road, Belfast BT12 6BJ.

REFERENCES

BROCK, D. J. H. and SUTCLIFFE, R. G. (1972). Lancet, i, 197.
CALAHANE, S. F., KENNEDY, J. D., McNICHOLL, B. and O'DWYER, E. (1965). J. Irish med. Ass., 57, 135.
CAMPBELL, S., JOHNSTONE, F. D., HOLT, E. M. and MAY, P. (1972). Lancet, ii, 1226.
CHEESEMAN, E. A. (1968). In Acheson, E. D. (Ed.) 'Record Linkage in Medicine', E. & S. Livingstone, Edinburgh, p. 70.
COFFEY, V. P. (1970). J. Irish med. Ass., 63, 343.
COFFEY, V. P. and JESSOP, W. J. E. (1955). Irish J. med. Sci., Sixth Series, 349, 30.
COFFEY, V. P. and JESSOP, W. J. E. (1957). Brit. J. prev. and soc. Med., 11, 174.
ELWOOD, J. H. (1970a). Brit. J. prev. and soc. Med., 24, 78.
ELWOOD, J. H. (1970b). Devel. Med. and Child. Neurol., 12, 582.
ELWOOD, J. H. (1972). New Scientist, 56, 602.
ELWOOD, J. H. (1973). Irish J. Med. Science, in press.
ELWOOD, J. H. and NEVIN, N. C. (1973). Brit. J. prev. and soc. Med., 27, 73.
ELWOOD, J. H. and PEMBERTON, J. (1971). Arch. Dis. Childh., 46, 332.
ELWOOD, J. H. and WARNOCK, H. A. (1969). Irish J. med. Science, 2, 17.
FEDERICK, J. (1970). Nature (Lond.), 227, 176.
FIELDING, D. W. and SMITHHELLS, R. W. (1971). Brit. J. prev. and soc. Med., 25, 217.
GENERAL REGISTER OFFICE (1965). ‘Census of Population 1961, Fertility Report’, H.M.S.O. Belfast.
Knox, E. G. (1967). Develop. Med. Child. Neurol., 9, Suppl. 13, p. 14.

Laurence, K. M., Carter, C. O. and David, P. A. (1968). Brit. J. prev. and soc. Med., 22, 146.

Laurence, K. M. and Tew, B. J. (1971). Arch. Dis. Childh., 46, 127.

Leck, I. (1969). Brit. J. prev. and soc. Med., 23, 166.

Lorber, J., Stewart, C. R., Ward, A. M. (1973). Lancet, i, 1187.

Naggan, L. and MacMahon, B. (1967). New Eng. J. Med., 277, 1119.

Nevin, N. C. (1969). Roy. Soc. Health J., 89, 281.

Nevin, N. C., Nesbitt, S. and Thompson, W. (1973). Lancet, i, 1383.

Park, A. T. (1962). J. Statistical and Social Inquiry Society Ireland, 20, 1.

Poswillo, D. E., Hamilton, W. J. and Soper, D. (1972). Nature, 239, 462.

Renwick, J. H. (1972). Brit. J. prev. and soc. Med., 26, 67.

Richards, I. D. G., Roberts, C. J. and Lloyd, S. (1972). Brit. J. prev. and soc. Med., 26, 89.

Rickham, P. P. and Mawdsley, T. (1966). Develop. Med. Child. Neurol., Supplement, 11, 20.

Spellman, M. P. (1969). J. Irish Med. Ass., 62, 316.

Spellman, M. P. (1970). J. Irish Med. Ass., 63, 339.

Stevenson, A. C. and Warnock, H. A. (1959). Ann. Hum. Gen. (Lond.), 23, 382.

Stevenson, A. C., Johnston, H. A. Stewart, M. I. P. and Golding, D. R. (1966). Congenital Malformations. Bull. World Health Organisation, 34, Supplement.