Spina Bifida Research in Wales

K. M. LAURENCE, MB, FRCPath, MRCP
Reader in Applied Genetics, Department of Child Health,
Welsh National School of Medicine, Cardiff

In this article, based on investigations carried out in Wales during the last two decades, some of the regional, aetiological, genetic, clinical and social problems posed by spina bifida cystica will be discussed.

INCIDENCE AND EPIDEMIOLOGY
Not until investigations on a total population in South Wales were carried out was it realised that the community there had a higher incidence of spina bifida cystica and anencephaly than most other parts of the British Isles. A study of all births between 1956 and 1962 in Glamorgan and Monmouthshire, excluding some of the larger towns (Laurence et al., 1968a, b), and all births in the same two counties, between 1964 and 1966 (Richards and Lowe, 1971) showed that the average incidence was 7.7 and 7.0 per 1,000 births respectively. This compares with a national average of about 5 per thousand births. South Wales was thus shown to have a very much higher incidence of these two malformations than Britain as a whole. This stimulated an intensive search for predisposing factors as well as the general search for environmental trigger mechanisms thought to play a causal part.

It was found that the industrial valleys had a considerably higher incidence than the coastal towns or the agricultural Vale of Glamorgan (Fig. 1). Within the industrial valleys, the incidence seemed to be highest in the East Monmouthshire valley, with 11 per thousand births, falling steadily towards the west, where the incidence was only 6.2, with a number of townships having an incidence of the order of 12 per thousand births, and one small township with as many as 20 cases per thousand births (Laurence et al., 1968a).

A social class gradient was present, with social classes I and II and non-manual class III having a lower incidence than manual social class III, social class IV, and social class V families (Laurence et al., 1968b; Lowe, 1973). However, the gradient was considerably lower than that found in surveys carried out in Birmingham and Scotland. This may reflect the relatively uniform social class structure of the South Wales population, or it could be indicative of the improvement in the general standard of living, both of which would be expected to lessen any social class effects. As in investigations elsewhere, in South Wales first, third and subsequent births in any family carried a rather higher risk, as did pregnancy in the older mother, risks that are independent of one another. All these features would suggest that a dietary factor may be playing some part in the
genesis of these abnormalities, but so far no specific factor has been positively identified. However, evidence suggesting that a deranged diet containing a considerable excess of carbohydrate, sometimes badly prepared, might act as a trigger (James et al., 1975a) is beginning to accumulate.

The finding of a higher risk to autumn and winter conceptions, when the community at large suffers more frequently from virus infections, and that some quarterly peaks in the incidence seem to coincide with epidemics of influenza, suggested that virus diseases such as influenza A might be a causative factor. However, this failed to stand up to stringent and critical evaluation (Laurence et al., 1968b). In addition, an investigation of space and space/time clustering in over 400 cases born in Cardiff over a 16-year period was entirely negative (Roberts et al., 1975), making it unlikely that some local factor such as an infection might be a significant causative agent.
Although a number of drugs have come under suspicion from time to time, almost none, including the anticonvulsants (Lowe, 1973) have been shown to be teratogenic, nor does folic acid deficiency, which has been the subject of a number of investigations recently, including one in South Wales (James et al., 1975b) seem to be a causative factor. The alkaloids formed in blighted potatoes are now generally not thought to be the cause of neural tube malformations, as had been suggested by Renwick (1972). Additional evidence for this view has come from a retrospective controlled investigation into potato growing and storage by householders in Glamorgan and Monmouthshire (Roberts et al., 1973). Certain preparations containing synthetic oestrogens, used occasionally in pregnancy testing, which have come under suspicion as a cause for some cases of neural tube malformations (Gal et al., 1971) have also been shown to have no significance (Laurence et al., 1971b). Background radiation or radioactive contamination do not appear to be relevant (Laurence et al., 1968a) but heavy metals, including aluminium, copper, cadmium and barium, have come under suspicion and are currently the subject of an intensive joint investigation between the M.R.C's Epidemiological Research Unit and the Tenovus Institute in Cardiff (Norton et al., 1976). There also seems to be a statistically valid negative relationship between the hardness of the water and the malformation rate (Lowe et al., 1971). As soft water seems to be supplied to the industrial valleys, this relationship could be only one of social class. However, as the relationship between the hardness of the water, and the malformation rate also exists in the rest of the British Isles, there may be a real association, though how the quality of the water acts is very much a matter of speculation.

The value of epidemiological studies that rely on malformations recorded after the 28th week of gestation or at birth has to be seen in relation to accumulating evidence that about three-quarters of all fertilised ova, including the vast majority of malformed embryos, never reach term (Roberts and Lowe, 1975). It may be necessary to discover why a malformed fetus is retained in the uterus rather than why it has become malformed, and to look critically at early abortions (Roberts and Lloyd, 1973).

**NATURAL HISTORY AND TREATMENT**

In the absence of active treatment to protect the exposed neural plaque, it quickly becomes infected and the complicating ascending meningitis is usually rapidly fatal. Hydrocephalus, on the other hand, is a more slowly fatal condition and in a number of patients it arrests spontaneously. Some of those who escape meningitis and survive hydrocephalus may well develop progressive renal failure from which they may die a few years later. Formerly, when no active surgical intervention was practised, spina bifida cystica was a relatively lethal condition and the few survivors tended to be either mildly affected and able to make their own way in life without much help, or grossly handicapped physically and mentally and often
to be found in the long-stay mental institutions. In a follow-up investigation of 315 liveborn cases of spina bifida in South Wales between 1956 and 1962, when little or no active treatment was given, less than 13 per cent were alive at the age of eight years (Laurence and Tew, 1967, 1971).

With the introduction of promising shunting operations for the relief of progressive hydrocephalus (Spitz, 1959) and the early closure of the spinal lesions by Sharrard and his co-workers (1963), a more aggressive approach was adopted in South Wales, resulting in a 50 per cent survival to the age of eight (Laurence, K. M., 1973a). Early closure involving the mobilisation of skin, often with the aid of tension-relieving incisions so that the exposed neural tissue could be covered, has greatly reduced the incidence of meningitis. However, the operation is still frequently complicated by ascending infection with mixed organisms that has proved difficult to combat satisfactorily, resulting in brain damage and rapid progression of the hydrocephalus. The shunting operations, too, have not proved to be as problem-free as had been hoped. Not only do they tend to be unsuccessful in the presence of even mild intracranial infection but, more importantly, the valves frequently get colonised or blocked at the upper end by brain or choroid plexus, or at the lower end by clot formation around the cardiac catheter. They then have to be revised or removed entirely. As a temporary measure, in those infected patients in whom a shunt operation could not be carried out, isosorbide, an oral osmotic agent, was tried in more than 20 patients in a double blind trial. It was found to be effective in the majority and to decrease the CSF production by 50 per cent, but it had adverse effects and caused dehydration in a number of infants (Shurtleff et al., 1973) and this approach is now used only occasionally. To help in the identification of shunt blockage in hydrocephalus, the symptoms of which are often non-specific and the signs inconclusive, Evans et al. (1975) developed a simple X-ray valvography method to demonstrate patency of both the upper and the lower end of the Holter shunt system. It has now been used in more than 50 patients and has become part of the routine method of investigating problem cases.

Urinary incontinence is not only socially undesirable, but may be severely damaging to the kidneys because of the back pressure with which it is often associated. In an investigation carried out by Verrier-Jones and Williams (1966) it was shown that three-quarters of the patients whom they investigated had established renal tract abnormalities that would predispose them to urinary infection. This was confirmed in a subsequent study by Thomas and Hopkins (1971) who also found that 50 per cent of suprapubic urine aspirates were infected, mostly with *Escherichia coli*. Using antibody titre levels, they found it possible to distinguish those children who had a bladder bacteriuria from those who had renal parenchymal involvement, important information in planning the management of the problem. It had been believed that urinary diversion operations such as that described by Mogg (1965) and Howell (1966), involving
the transplantation of the ureters from the bladder into an isolated loop of large bowel, from which the urine is drained through a stoma on the anterior abdominal wall to a bag, would be the answer to both the social and the medical problems of patients with urinary incontinence. Well managed, such a procedure can be very satisfactory. However, increasing difficulties are encountered with complications of the operation itself, problems with management of the appliance, especially at night and in the less intelligent. Increasingly, the operation is now carried out only where there are urgent medical indications, such as neurogenic bladder with vesico-ureteric reflux and progressive renal damage. The other patients seem to manage reasonably well with penile appliances in males, or with pads and rubber pants. Faecal incontinence proves a less difficult problem and can generally be managed by medical means.

To obtain ambulation in partially or even completely paralysed infants, often with deformed limbs, requires numerous manipulations and operations on tendons, muscles, joints, and bones, necessitating repeated hospital admissions, sometimes prolonged, over the years. Some procedures, such as the correction of club foot, are of undoubted value, enabling the foot to take pressure. Other operations, such as the one designed to stabilise the kyphotic spine, and the posterior iléo-psoas transplantation to stabilise a dislocated hip, are not always so valuable; frequently the kyphosis is not corrected and the child cannot walk with greater ease (Weisl and Matthews, 1973). Even with repeated surgical procedures, only a small minority of children are totally ambulant without aids; the majority of children will need crutches in addition to braces, often extending to the waist. Some are chairbound from the start, others become chairbound because they find it increasingly difficult to use their crutches as they get older and, often, more obese.

EDUCATIONAL PROBLEMS
Handicapped spina bifida children will not have had normal opportunities to become socialised or to learn from the rough and tumble of childhood because they are relatively immobile and are likely to have spent a long time in hospital; in addition, a significant proportion will grow up with some intellectual deficit. In the ‘pre-operation’ series the mean I.Q. of the 18 children with meningoceles was 94, that of the 37 cases with myelocele was 90, whereas 8 children with encephaloceles had a mean I.Q. of 56. The girls, on the whole, had more deficit than the boys. School attainments were more disappointing, with a considerable number of the children not fulfilling expectation (Laurence and Tew, 1971). The children born between 1964 and 1966 who received ‘total care’ were tested when aged 5, using a battery of tests and were given school attainments tests at 7 years of age. In this group, the mean I.Q. of the 9 cases of meningocele was 102, and that of the 46 surviving children with myel signifies was 77 (Laurence, 1972a, 1974c; Tew, 1973; Tew and Laurence, 1973).
From previous studies partly carried out in London it was known that there is a close negative correlation between the degree of hydrocephalus, whether associated with spina bifida or not, and the I.Q. (Laurence, 1969a, 1972b). In the intensively operated spina bifida group, a similar relationship existed, those children with hydrocephalus that has been shunted having a mean I.Q. of 70, children with spontaneously arrested hydrocephalus having an I.Q. of 84, and the spina bifida children who had escaped significant hydrocephalus having an I.Q. of 90. Further, the children who have had to have repeated revisions of their shunts tended to fare worse and the attainments of the spontaneously arrested cases seemed to deteriorate somewhat over the years, suggesting that in them some progression was occurring. The control children and the sibs of the spina bifida

Fig. 2. Wechsler I.Q. scores of 59 spina bifida survivors of the 1964-1966 'total care' series. There were 20 without hydrocephalus, 8 with arrested hydrocephalus and 31 with shunt-treated hydrocephalus. The mean I.Qs are indicated by open triangles. (Modified from Fig. 1 of Tew and Laurence, 1975a.)
cases had I.Qs of around 106 (Tew and Laurence, 1975a) (Fig. 2). The intellectual deficit, in addition to the emotional disturbances, the difficulties in mobility, the continence problems, the problems with upper limb function, such as fine finger movement (Wallace, 1973), have to be taken into account in the type of education provided.

The problems of accommodating these children in schools were investigated in the 56 survivors of the 1964-1966 cohort (Laurence, 1970; Laurence, E. R., 1973; Laurence and Laurence, 1975). Twenty-seven with a mean I.Q. of 98 were in primary schools and 29, including the majority of children with myeloceles and mostly girls, with a mean I.Q. of 66 were in special schools. Six children, all with I.Qs of less than 76, who started in the local primary schools, were transferred. It was found that willing primary school teachers were hampered by already large classes, lack of experience and little ancillary help. Relationships with welfare and medical services, from which information regarding the child’s needs could be made available, were not well established.

From studies of intelligence testing, on the same subjects five years apart, by the Weschler Intelligence Test, it was concluded that the test had a good predictive value in spina bifida (Tew and Laurence, 1974), but that parents usually had a particularly distorted idea of their children’s performance when they were within the moderately retarded range (I.Q. 60-80) and tended to be hostile towards the testing process and the psychologist when their child’s performance was poor (Tew et al., 1974a, b).

SOCIAL PROBLEMS

After the birth of a child with a neural tube malformation, the parents may be faced with a succession of problems. These were investigated by following the series of 126 unselected families in which a child was born between 1964 and 1966 with one of the forms of spina bifida and received ‘total care’. Twenty couples who had an anencephalic fetus were also included. Using semi-structured schedules, the mother was interviewed within days of the birth of the child, re-interviewed one month later, and thereafter at six-monthly intervals. For the survivors at one year, matched control families were chosen and investigated in a similar manner. Today, 56 of the spina bifida children aged between 9 and 11 years survive. In a paper by Hare et al. (1966) based on an appraisal of the difficulties in the first two years, it was found that the first problem was the shock of having an abnormal baby and of being told about the event. Although relatively few parents complained about the manner in which this was done, in some the handling seemed inept. However, in spite of this, only two sets of parents rejected their abnormal child. Thereafter, the parents had to face worries associated with the immediate transfer to another hospital for the closure of the open lesion, and then, usually, repeated hospital admissions and out-patient attendances, seeing a number of different specialists and consultants and often
being given only scant, partial or conflicting explanations and information. The repeated hospital visits proved a considerable emotional, physical and financial burden. Although the parents feared the reaction of relatives and neighbours, both proved supportive. Although most parents worried about a recurrence of a malformation in a future pregnancy, few sought genetic advice and most of those who did appeared to have been given misleading information. It was concluded that there was need for care, skill and sympathy in telling both parents about the malformation, that it would be advantageous to have a Parents Association and that there was need for one clinician with specialised experience to co-ordinate the provision of social and medical help for the families. It was also suggested that special centres to deal with the medical and surgical problems of all affected infants in an area should be set up and that there was need for adequate genetic counselling and advice on contraception. It is of interest that all these suggestions were acted upon within a very short time in South Wales, where there has now been good provision for most aspects of spina bifida care for a number of years.

The emotional effect of the handicapped child on the parents at first seemed surprisingly slight (Hare et al., 1972), but as the child grew older they seemed to become worried by incontinence, mental retardation (I.Q. less than 80) and locomotor disability, though it seemed to make relatively little difference whether this was mild or severe (Tew and Laurence, 1975b). Inevitably, the handicapped child eventually presents a serious challenge to the stability of the marital relationship, and in a significant proportion of cases the quality of the relationship had deteriorated over the nine years (Tew et al., 1974a); the divorce rate in the index families was twice that of the controls and of the national average. The mother who became pregnant before marriage and who subsequently gave birth to a malformed child seemed to be particularly predisposed to divorce or separation. If, however, the malformed infant was stillborn or died relatively quickly, there seemed to be little effect on the marital relationship. Nearly always the separated father re-married. The only mothers who re-married were those who had children who were relatively unscathed (Tew et al., 1976). The brothers and sisters of the handicapped children did not remain unaffected either; though they had a normal I.Q. distribution, they had four times the normal frequency of maladjustment (Tew and Laurence, 1973).

GENETICS AND PREVENTION
Dysraphic neural tube malformations, like most other common malformations, seem to be caused by a polygenically inherited predisposition interacting with some environmental trigger, probably of a relatively minor kind (Carter, 1965). In the absence of positively identified preventable triggers for these neural tube malformations, which seem to be more common in families where both parents bear a Welsh name (Richards et al., 1972) prevention rests on genetic counselling and pre-natal identification of abnormal fetuses followed by selective abortion.
Before genetic counselling can be realistic, accurate information about recurrence risks has to be available. This was obtained in a large family study on 835 cases in whom family information was available (Carter et al., 1968; Laurence, 1969b). From this it emerged that the risk to affected sibs (first degree relatives) is in the order of 1 in 20, or 7 to 8 times the population incidence. The risk to 2nd and 3rd degree relatives is appreciably lower, the latter having a risk near the population incidence. The risk to children of parents who have spina bifida appears to be similar to the risk to sibs at about 1 in 25 (Laurence and Beresford, 1975). From another study still in progress (Laurence et al., 1968c; Laurence et al., 1971a), it would appear that ‘complicated’ but not simple spina bifida occulta is part of the neural tube malformation complex carrying the same sort of risk.

Genetic counselling consultations for spina bifida and related malformations have increased from one or two per annum in 1966 to nearly 100 in 1974. However, it was apparent that those coming forward for counselling tended to be from Social Class I, II and III and that many from Social Class IV and V seek advice only when they have a surviving spina bifida child, have had more than one affected child, or have a very strong family history (Laurence, K. M., 1973b).

Although it is common experience that parents with a high recurrence risk will generally not chance further children, especially if they already have a family, recent developments in pre-natal diagnosis of anencephaly and open spina bifida are enabling such families to risk further pregnancies with reasonable assurance that an affected fetus will be identified early enough for the pregnancy to be terminated. Scanning with ultrasound at 12 to 16 weeks, a non-invasive safe investigation, will almost certainly identify anencephaly (Laurence, 1976) but to identify open spina bifida requires amniocentesis at 16 weeks, followed by alphafeto protein estimation (Laurence, 1974a). This procedure, which has a small potential danger of miscarriage, will enable 9 out of 10 of all serious cases of spina bifida to be identified and enables a recurrence risk of 1 in 20 to be reduced to one of less than 1 in 150. Carrying out an amnion cell culture and cytogenetics at the same time should also eliminate chromosome abnormalities. However, encephaloceles, closed myelocoeles, and meningoceles will not be identified (Laurence et al., 1973; Laurence, 1974b). So far in South Wales, in 327 amniocenteses carried out on pregnancies at risk for neural tube malformations or anxiety, 6 spina bifida or anencephalic fetuses have been identified, of which 5 have been terminated. An encephalocele has been missed as was expected, but also one case of open spina bifida where the AFP level was only marginally above the normal level (Laurence et al., 1975). A further anencephalic, one of twins, was allowed to go to term because of the normal male co-twin. In addition, 3 fetuses with chromosome malformations were terminated, and one in the very early days of amniocentesis for neural tube malformations was missed (Table 1). Unfortunately, these methods will only identify about 1 in 10 cases occurring in the
Table 1. Outcome of amniocentesis for pregnancies at high risk for neural tube malformations or associated with anxiety and serum AFP screening between 1973 and 1975 (number of pregnancies).

| Amniocentesis indication | Fetal loss related | Fetal loss unrelated | Anencephaly | Encephalocele | Spina bifida | Chromosome malformation | Other malformation | Normal child | Total |
|--------------------------|--------------------|---------------------|-------------|---------------|-------------|------------------------|-------------------|-------------|-------|
| CNS malformations        | 3                  | 6                   | 3(2)        | 1             | 4(3)        | 3(2)                   | 1                 | 282         | 303   |
| Anxiety only             | -                  | -                   | 1(1)        | -             | -           | 1(1)                   | -                 | 18          | 20    |
| Maternal serum AFP screening | -                | -                   | 1(1)        | -             | -           | -                      | -                 | 3           | 4     |
| Total                    | 3                  | 6                   | 5(4)        | 1             | 4(3)        | 4(3)                   | 1                 | 303         | 327   |

Number of terminations shown in brackets.
community as most instances of neural tube malformation turn out to be the first occurrence in a family unit. To enable these first cases to be identified as well, improvements of a screening test dependent on levels of AFP in maternal serum must be awaited (Laurence, 1974a). So far, estimation of serum levels of AFP has not proved as sensitive or as selective as the test on amniotic fluid (Harris et al., 1974).

PROGNOSIS

An examination of the lives of 51 adult survivors with spina bifida, aged between 17 and 56 living in South Wales, revealed that they were leading remarkable lives. In spite of the fact that over two-thirds are either able to get around only with the help of braces and crutches, or were even chairbound, at the same time as being partially or totally incontinent, three-quarters were either in open competitive employment, working as housewives, or in full-time studies. Most of them were coping with their mobility and incontinence problems and were leading full social lives. Almost half were married and nearly all of these had children of their own. However, nearly all of these adults had escaped hydrocephalus and seemed of normal intelligence (Beresford and Laurence, 1975; Laurence and Beresford, 1975; Laurence and Beresford, 1976). The optimistic view of the future cannot, unfortunately, be maintained for the children now growing up following the 'total

![survival curve](image)

Fig. 3. Survival curve drawn from a life table for both the unoperated (1956-1962) and the operated (S1964-1966) series of spina bifida infants. Encephaloceles have been excluded. A semilog scale has been used for the Y axis. (Modified from Fig. 2 of Laurence, 1974c.)
Table 2. Physical disability of examined survivors at mean age of 9 years

| Disability grade | Function                          | 1956-1962 | 1964-1966 |
|------------------|-----------------------------------|-----------|-----------|
| I                | Unaided ambulation, totally continent | 44.4%     | 30.5%     |
| II               | Ambulant with aid, partially incontinent or operated | 26.0%     | 14.6%     |
| III              | Chairbound and incontinent        | 29.6%     | 55.5%     |

Fig. 4. Wechsler I.Q. scores of tested survivors of both unoperated and operated series. Meningoceles and myeloceles are shown separately; encephalocles have been excluded. The mean I.Qs of the unoperated is 89.4, the operated 80.9. (Modified from Fig. 3 of Laurence, 1974c.)
care' treatment policy. Although three or four times as many survive, the survivors of surgery, many of whom would have died in the past, have a distinctly poorer intellectual status, largely as the result of their hydrocephalus, in spite of shunt operations, and are much more physically handicapped (Laurence, 1974c; Figs. 3 and 4; Table 2). It is the realisation of this fact that is causing some clinicians to question the wisdom of universal 'total care' for this group of malformations, foremost among them being Dr Lorber of Sheffield, who has advocated more stringent selection criteria for surgery (Lorber, 1975). It is also one of the reasons for the great effort that is being made to find for this group of malformations a satisfactory screening method that can be safely used in all pregnancies.

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