education media to demand certainty where certainty does not exist. A clear authoritative pronouncement by a medical man will always be uncritically welcomed. I believe we must insist on the right to give a scientific reply to the basic question, " Why is a child born deformed? " and to say, " We can't answer your question; we just don't know the answer. Ask again in ten years' time and we shall probably be able to give it to you ". At the present time, therefore, I would say that when we are thinking of the welfare of the human embryo in the uterus we are best guided by a middle of the road principle of the kind somewhat surprisingly applied by Nietzsche, in a much wider context when he said:

> Of nothing is it any longer possible to say, ' This is good everywhere and always, and this is bad everywhere and always '. Good and bad must be determined afresh on every occasion, and always in relation to a definite purpose, by which alone anything can be good or bad, for only he who knows whither he saileth knoweth which is his fair wind and which is his foul wind.

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A SOCIO-GENETIC SURVEY OF THE MAJOR CENTRAL NERVOUS SYSTEM MALFORMATIONS IN SOUTH WALES

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The major central nervous system malformations, which consist mostly of the dysraphic syndromes of anencephaly, spina bifida cystica and cranium bifidum, together with certain forms of hydrocephalus, namely the aqueduct malformations and the so-called Dandy-Walker syndrome, can probably be classed together. There is some genetic and much experimental evidence that these are different end-products of the same general process for different noxious agents, such as x-rays, oxygen deprivation, chemicals, dyes and starvation may in susceptible experimental animals produce any

or all of these malformations. There is also a good deal of evidence that they are all threshold phenomena.

In man, these major central nervous system malformations are an urgent medical, epidemiological and social problem. In the British Isles, at least, they are the commonest malformations seen at birth. For example, in Scotland in the years 1941–45, 72 per cent of the malformations causing stillbirth and 39 per cent of those causing neonatal death belonged to this group, while in Birmingham in the years 1940–47 they formed 5.7 per thousand births (Record and McKeown, 1949). There are, however, great geographical variations in the incidence of these malformations. Penrose (1957) has shown that anencephaly is rare in Asian and African communities with the exception of certain Indian populations, and in Europe they are more common in the west than in the east. Within western Europe, France has a lower incidence than south-eastern England and south-eastern England has a much lower incidence than Liverpool, Scotland and Birmingham, while Ireland appeared to have the highest incidence of all. The incidence of the other dysraphic syndromes largely follows the same pattern but with perhaps not quite such obvious differences.

What is the cause of these malformations? From experimental evidence, as Woollam (1964) has shown, whatever the agent producing these malformations it must act before the 29th day after conception, that is, before the time when the neural tube has finally closed. Therefore, direct interference by the mother with her pregnancy is unlikely to be a cause for she is generally not fully aware of the fact that she is pregnant at that stage. Nor do drugs seem to be responsible in man with the possible exception of folic acid deficiency due to aminopterin (Thiersch, 1952). Environmental factors, such as climate, water supply and diet, have all been implicated, but Searle (1959) working in Singapore made some interesting observations after investigating Cantonese and Sikh communities there. Although sharing the same climate and water supply, among the Cantonese Chinese major central nervous system malformations do not occur, whereas the Sikhs have an incidence of anencephaly of approximately 6.5 per thousand births. In Hong Kong, the Cantonese Chinese again do not suffer from these malformations, but unfortunately there is no information on incidence of malformations from the Punjab where the Sikhs live. It is also of interest that while nearly all the hard manual labour in Hong Kong, and for that matter in Singapore, is done by the Chinese women, whether pregnant or not, they do not produce these malformations. This is of importance when women working during pregnancy are blamed as a possible cause of some malformations. Penrose (1957) refers to a Johannesburg investigation where it was found that these malformations are

rare amongst the African population, though those of European Gentile origin suffer from them to the same extent as we do in western Europe. On the other hand, the Jews in Johannesburg have approximately one seventh of the Gentile incidence. The same is apparently true in New York (MacMahon *et al.*, 1953). Diet is probably also not an important factor, for during the early nineteen-forties starvation in Europe did not apparently bring with it an increased incidence, nor do most of the communities in Africa and Asia, often living at or below subsistence level, suffer from them. All these points would suggest that racial factors must have an important bearing and might suggest that these malformations have a genetic basis. This could be further supported by a report from Dublin that mothers of anencephalic foetuses have an increased incidence of blood group O (Coffey and Jessop, 1955). However, further study has now shown this not to be so. A genetic basis might also be supported by the findings, as yet unpublished, of Carter and Roberts (1962) that whereas the average risk to any woman of producing a child with a major central nervous system malformation in this country may be one in 250, in a large series of spina bifida cystica cases the risk of such a woman having another such malformation rises approximately tenfold, and if she has already had two amongst her children, then the risk to further pregnancies goes up to one in eight. These figures do not really point to a Mendelian inheritance as Lorber (1963) suggests. The fact that it is very rare for both of uniovular twins to have a major central nervous system malformation also makes it most unlikely for this to be a predominantly genetic problem.

On the environmental side, there is a strong social class gradient. In Scotland, it is four times more common for a mother of social class V to produce a child with anencephalus than it is for a mother from social class I; for spina bifida, it is twice as common, for hydrocephalus, apparently one and a half times as common (Edwards, 1958). This gradient was even more more marked in the recent perinatal mortality survey (Butler, 1962). Seasonal variations have also been reported fairly consistently, and it would appear that spring conceptions are much more at risk. The ratio between the highest and the lowest monthly incidence is 1.7 for anencephaly, but it is not as high as for congenital dislocation of the hip, where it is two, or for hare-lip, where it is three (Edwards, 1961). Virus infections have been implicated but this is very difficult to prove. Pleydell (1960), however, has reported rather peculiar relationships in time and space in cases of anencephaly and spina bifida in Northamptonshire, and he has suggested but not proved that Asian influenza be at fault. Reports from Russia suggest that toxoplasmosis might be the cause, at least in some cases (Beledeij, 1961).

Secular trends have also been reported from Birmingham, where in the years 1940–47 the incidence for the major central nervous system malformations dropped from 7.3 per thousand to 4.4 (Record and McKeown, 1949), while in New York in the years 1945–59 the incidence has halved (Gittelsohn and Milham, 1962). All these factors, as well as peculiarities in sex ratios, parity and maternal age effects, suggest that both environmental and genetic factors play a part in their genesis. As in experimental animals, probably some factors trigger off the development of these malformations in a susceptible community. What precisely these factors are in man we do not yet know and it is the purpose of the present investigation to try to discover them.

The South Wales study

Apart from the fact that one of us (K.M.L.) had been wanting to make a field study of these malformations ever since starting in this field nine years ago, this particular investigation arose from the Perinatal Mortality Survey carried out in the spring of 1958, when it was found that in England and Wales all malformations accounted for 15 per cent of the perinatal deaths (Butler, 1960), as reported in a preliminary survey, while in South Wales it was 18 per cent (Parry, 1960). In England and Wales, 65 per cent of the 15 per cent were central nervous system malformations, but in South Wales it was 86 per cent of the 18 per cent. According to this survey, not only did the incidence of malformations in general seem a little higher in South Wales, but a larger proportion of these malformations were those of the central nervous system. Further, it was noted that of the 14 cases of central nervous system malformations in South Wales, three occurred in one valley and four in another, which had a combined population of about 200,000, while the whole survey in this region covered a population of some 1,000,000. Thus there appeared to be a peculiar localization as well. This, it was felt, would bear further investigation especially as South Wales seemed also to have a high incidence. In addition, the region seemed a particularly suitable one for an epidemiological study. People flocked into the mining valleys from the West Country, Ireland and other parts of Wales and England from the middle of the last century when the coal mines were opened, mingling with the then sparse indigenous population. They moved into ' end valleys ' where until recent years it was difficult to get from one valley to another. Any movement of population that has occurred tended to be away from South Wales altogether. We have then relative genetic isolates with a high malformation rate.

Dr C. O. Carter and one of us (K.M.L.) approached the Mental Health Research Fund to carry out a sociogenetic survey with certain hypotheses which we wanted to test. We wished to know first of all

whether there was a specific genetic predisposition towards this group of malformations and we were particularly interested to find out whether regional variations persist even after migration. In this context we knew that Ireland had a very high incidence and we thought that the pockets of high incidence in South Wales might be accounted for by pockets of ex-Irish immigrants. It was hoped to verify that there is a seasonal variation, a social class gradient and that there is variation between industrial and rural communities.

In our survey we specifically excluded the larger conurbations such as Neath, Whitchurch, Barry, Penarth, Cardiff and Newport as it was felt that these communities were probably too mixed and too mobile to yield the sort of information we were seeking. The area then consisted largely of the industrial valleys of Monmouthshire and most of those of Glamorgan (population about 770,000) and included a large agricultural area, the Vale of Glamorgan, though unfortunately with a relatively small population (about 30,000).

We planned to ascertain all the cases between 1956 and 1962 and from information that we had at the outset of the investigation we expected to find about 500, but to our surprise we ascertained 884. In our ascertainment we obtained help from the local health authorities, hospital record departments, general practitioners and latterly the Registrar General. Local health authority records were not always complete and hospital records were not easy to use since few hospitals had the space, time or staff to have a diagnostic index. The general practitioners were circularized; from the first circulation we obtained a 7 per cent response but a reminder two months later produced a much better result and we had a 30 per cent response. Even amongst this comparatively small number of replies we found numerous cases that had not been ascertained either through the hospital or local health authority records.

For the years 1961 and 1962, the years since compulsory certification of the cause of stillbirth has been in force, we have had the assistance of the Registrar General and have added a considerable number of cases for those two years which we had not already obtained (table I). Even the Registrar General's notifications were not complete and we were able to supply him with an extra nine cases for these two years which we had ascertained from our own sources. In four, the malformation concerned, which ought to have been obvious enough, was not even mentioned on the death certificate, and two were missed by the Registrar General's staff. More serious however, the death of three—two stillbirths and one neonatal death—were apparently never registered. This illustrates the great importance of ascertaining cases from as many sources as possible

in an epidemiological study.

For the first four years the ascertainment is rather lower than for the last three. It is likely that in the latter the numbers are fairly complete, but that quite a lot of cases are missing from the earlier years; thus any incidence figures that are computed would be underestimates. As the work is still proceeding only provisional results can be given.*

Results of the survey

Among the 884 cases there were 353 anencephalics and 405 cases of spina bifida together with 126 hydrocephalics (table II). Particular care is being taken to exclude all cases of acquired hydrocephalus, but it is often difficult to distinguish a case of acquired hydrocephalus coming on soon after birth from a truly congenital one and the figure for hydrocephalus may thus have to be reduced a little, perhaps to around about 100. On the other hand, that for spina bifida will probably be slightly greater as no doubt a few of the cases of hydrocephalus will be found to have an associated spina bifida.

TABLE I
ASCERTAINMENT OF CASES
884 CASES

1956	98
1957	124
1958	120
1959	124
1960	139
1961	140*
1962	139*

*Full registration of stillbirths

TABLE II
TYPE OF MALFORMATION
884 CASES

Anencephalics	353
Hydrocephalics ..	126
Spina bifida cystica ..	405

It may be worth while looking at the incidence of malformations for one year. There were about 14,000 births with 139 central nervous system malformations in 1960, giving an incidence of just below 10 per 1,000 births (table III). The national average is somewere around five per 1,000; for Birmingham it is a little above this at 5.7, while Scotland is said to have a high malformation rate, 6.3 (referring to stillbirths and neonatal deaths only) (Edwards, 1961), and Belfast, which is regarded as having a very high incidence, has one of 8.4 (Stephenson and Warnock, 1959). All these rates refer to total populations, whereas figures of 10.2 for Liverpool (Malpas, 1937) and of 12 per cent for Dublin (Coffey and Jessop, 1955) relate to hospital admissions and therefore selected groups only. A figure of 2.7 from Zurich (Ehrat, 1948) may not be complete but

*The figures for tables I—VI have been brought up to date for April 1964.

that of 1.4 for Japan (Neel, 1958) is almost certainly reliable (table IV). For the British areas, except perhaps Liverpool with its rather selected hospital group, the proportion of cases accounted for by anencephaly is relatively constant, which is not surprising as anencephaly cannot be misdiagnosed or mis-categorized. On the other hand, the figures for hydrocephalus and for spina bifida vary greatly and it is likely that a considerable proportion of the hydrocephalus group really belong to the spina bifidas.

TABLE III

INCIDENCE OF C.N.S. MALFORMATIONS IN 1960

Population		*800,000
Total live births	13,654	14,010
Total stillbirths	356	
Number of C.N.S. malformations ..		139
Incidence per 1,000 births		9.9

*Estimate.

TABLE IV

INCIDENCE OF THE MAJOR C.N.S. MALFORMATIONS

	South Wales	*Birmingham*	*Liverpool*	*Dublin*	*Belfast*	*Scotland*	*Zurich*	*Japan*
Anencephalus (per cent)	40	40	31	39	55	37	22	44
Hydrocephalus (per cent)	14	32	41	28	18	30	30	22
Spina bifida cystica (per cent)	46	28	28	33	27	33	48	34
Incidence per 1000 births	9.9	5.7	10.2*	12.7*	8.4	6.3†	2.7‡	1.4

*Hospital figures only. †Probably incomplete. ‡Stillbirths and neonatal deaths only.

Local variations in South Wales

The area of investigation was divided into the various divisional health authorities and the incidence of the malformations per

thousand births over the seven year period worked out for each (table V). Very striking variations became apparent with the highest incidence in the east Monmouth division, with one of 12.8 per 1,000. Towards the west of the area the incidence gradually decreases with 10.2 per 1,000 in Caerphilly and Gelligaer, 8.3 in Merthyr, 8.0 in the Rhondda and 7.1 in Port Talbot and Glyncorrwg, though there are some irregularities such as that of nine per 1,000 for Neath rural. The low incidence of 3.0 per 1,000 for Glamorgan south-east, the largely agricultural Vale of Glamorgan, where the ascertainment is however probably not complete, is of special interest as it approximates the incidence of the agricultural populations in south-eastern England. These large local authority health divisions, however, hide the even more marked variations that occur. Taking the incidence for the whole seven years in four townships, Aberbargoed had the very high incidence of almost 21 per 1,000 births; Porthcawl, a seaside place, surprisingly had a relatively high incidence and so had Bridgend. Blaenavon, on the other hand, had a surprisingly low incidence (table VI and figure 2). However, these are based on rather small numbers of cases, while those for the health authority divisions are very much more reliable being based, except in the case of Glamorgan south-east and Neath rural, on populations of between 60,000 and 120,000. Variations in incidence like these have been reported before by Edwards (1958), analysing Scottish figures when he found incidences ranging from 3.4 in the Highlands to 8.3 and 7.6 in Glasgow and East Lothian. Thus, local variations are not unique, but perhaps these extreme variations are unusual.

TABLE V

C.N.S. MALFORMATIONS 1956-1962 INCLUSIVE

Health authority area	*Incidence per 1000 births*
East Monmouth	12.8
Ebbw Vale	10.5
Rhymney	10.0
Caerphilly and Gelligaer	10.2
Merthyr	8.3
Aberdare and Mountain Ash	7.5
Rhondda	8.0
Pontypridd	8.3
Mid-Glamorgan	8.9
Neath rural	9.0
Port Talbot and Glyncorrwg	7.1
Glamorgan south east ex. Barry, Penarth and Whitchurch	3.0

TABLE VI

INCIDENCE OF C.N.S. MALFORMATIONS IN 4 TOWNS

Town	*Population 1961*	*Births 1956–62*	*Number of malformations*	*Rate per 1000 births*
Porthcawl ..	11,086	1,071	13	12.0
Aberbargoed ..	5,158	579*	12	20.9
Blaenavon ..	8,451	853	10	8.5
Bridgend ..	15,174	1,884	24	12.9

*Estimate.

It is intended to try and discover some of the reasons for the high general incidence and more particularly for these local variations Disease and drugs during pregnancy have already been discussed; other possible factors might include work during pregnancy, faulty diet, bad hygiene, consanguinity and intermarriage, and differences in ethnic groups, climate, water supply and background radiation. The affected families and their controls are being interviewed and enquiries are being made about parents, grandparents, and great-grandparents to elucidate their ethnic origin. A detailed family tree and pregnancy history are obtained to help in the genetic aspects. Information about illness during pregnancy, home circumstances, occupation and attitudes is also gathered. In view of the large number of cases, in only four of the areas are the families ascertained for all the seven years to be interviewed. In the remaining eight areas, only the 1960, 1961 and 1962 cases are to be seen. For the earlier cases, the help of the local health authority health visitors is being enlisted to obtain certain basic information only. This means that the work is being concentrated on the later years when ascertainment was better and when memory is still fairly fresh, and when fewer families have moved. So far 398 index cases and 100 control families have been interviewed by one of us (P.A.D.), leaving a further 177 controls and 154 index cases to be visited and 278 cases to be dealt with through the health visitors. Fourteen index cases and four controls have so far refused investigation. It has taken two years and it is expected to take a further 18 months to finish the investigation completely, including interviewing, analysis and writing up. Not all the factors that have been mentioned can possibly be investigated by ourselves alone in an investigation of this sort and it is intended to enlist outside help with background radiation, climate and water supply. It is hoped to have some definite

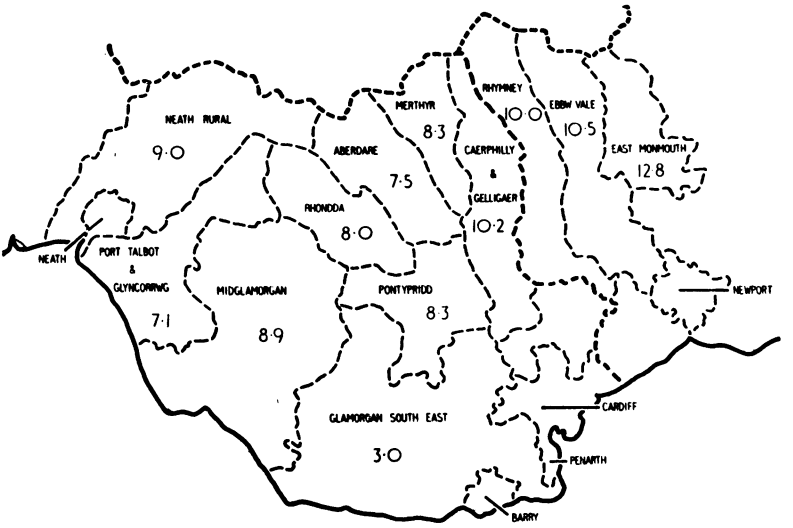

Figure 1. Sketch map of area of investigation. The heavy broken line is the county boundary; the lighter broken line the health division boundaries. The incidence of central nervous system malformations per 1,000 births is written below the name of the area.

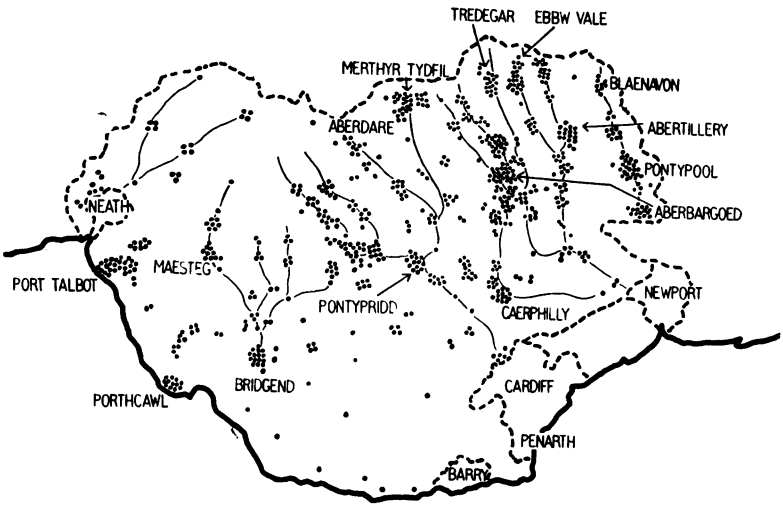

Figure 2. Sketch map of area of investigation. The broken line indicates the boundary of the area of investigation; the light lines indicate the line of the valleys and each of the dots represents one case. The names of the main places of interest are indicated.

data on genetic and incidence aspects, and we may possibly unravel some of the other factors.

We are just about to launch out on an investigation into the stresses imposed upon the family by the birth of a child with a central nervous system malformation with a grant from the Joseph Rowntree Memorial Trust, for I have noticed that the effect upon the family of the birth of a child with a central nervous system malformation is rather more severe than that of children with any other malformation. Some families break down under these stresses but others resolve their problems. By studying these families in detail over a period of two years or more, we hope to be able to suggest ways in which these families should be approached and helped. Thus our current investigation may uncover some avoidable precipitating factors that give rise to the malformations and may enable us to find out facts which would be of value in genetic counselling, while the second investigation may suggest ways and means of helping the affected families.

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