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MAJOR CENTRAL NERVOUS SYSTEM MALFORMATIONS IN SOUTH WALES

I. INCIDENCE, LOCAL VARIATIONS AND GEOGRAPHICAL FACTORS

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The major central nervous system malformations, which include anencephaly, spina bifida cystica, and congenital hydrocephalus, and their variants, have become one of our more urgent medical, social, epidemiological, and aetiological problems now that most of the infective and deficiency diseases in childhood have been eliminated. There is experimental evidence to suggest that anencephaly and spina bifida cystica at least are different end-products of the same process and are closely related aetiologically.

It is possible to produce either anomaly in a susceptible strain of an experimental animal with a variety of noxious agents such as *x* rays, drugs, or deficiency conditions applied during the teratogenic period. In man there is considerable geographical variation in the incidence of this group of malformations, with Western Europe and especially Britain and the communities which have emigrated from these areas having the highest incidence, while Negro and Mongolian populations seem to be less affected (Penrose, 1957; Searle, 1959; Stevenson, Johnston, Stewart, and Golding, 1966). From this it seems that in man, as in experimental animals, certain communities have a greater inherited susceptibility to produce offspring with these malformations and it is probable that environmental factors act as trigger mechanisms. A social class gradient, and seasonal and secular variations reported from some centres suggest this, but so far in man only one drug, namely Aminopterin, has proved to be a causative agent (Thiersch, 1952).

The mining valleys of South Wales were thought to have a high incidence of central nervous system malformation and it was suspected that local variations in the incidence were considerable. It was thought that the area, with its population living in densely populated but relatively isolated groups, would be ideal for an epidemiological study to highlight some of the environmental factors and a family study to elucidate the genetic mechanisms. Some preliminary results have already been published (Laurence and David, 1964, 1966; Laurence, 1966; Carter, Laurence, and David, 1967; Laurence and Tew, 1967). We are now presenting the results, concerning the incidence and local variations together with some of the possible geographical factors with which they may be associated. Pregnancy factors, seasonal variations, and social class effects (Laurence, Carter, and David, 1968), genetic aspects (Carter, David, and Laurence, 1968), and the natural history of spina bifida cystica (Laurence, Carter, Tew, and David, 1968) are the subject of other publications.

AREA AND POPULATION INVESTIGATED

This investigation was centred on the agricultural Vale of Glamorgan and the mining valleys of Glamorgan and Monmouthshire (Fig. 1). It included the whole of Glamorgan with the exception of the West Glamorgan division and the towns of Swansea Neath, Barry, and Cardiff (together with Penarth and the parishes of Whitchurch, Lisvane, Llanederyn, and Llanfedw in the Cardiff Rural District). In Monmouthshire all the mining valleys were included but not Cwmbran, Newport, all of Magor and St. Mellons except Rogerstone, and the agricultural eastern part of the county. The area was divided along the local government administrative boundaries into nine divisions in Glamorgan and three in Monmouthshire. These were largely industrial except for the whole of Glamorgan South-East, half of Pontypridd, and much of mid-Glamorgan which comprise the Vale of Glamorgan.

The Registrar General's estimated total population of the area has remained relatively constant from 1956–1962 at about 850,000. This population is far more mixed in origin than may be supposed. That of

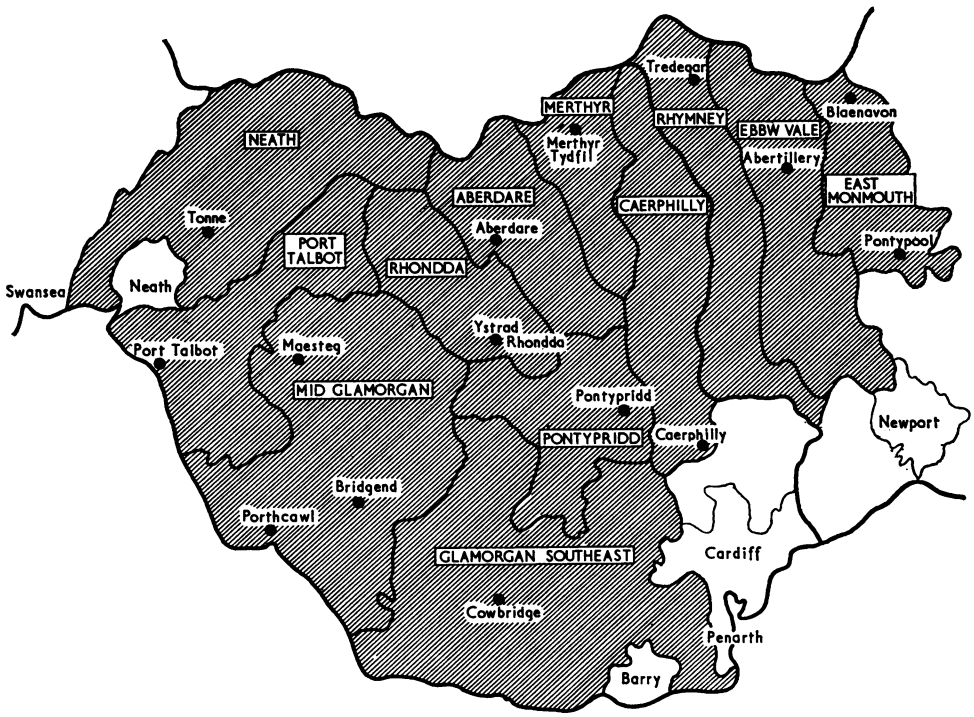

FIG. 1.—Sketch map of part of South Wales. The project area is shaded; the thick lines indicate county boundaries; the lighter, the boundaries of the twelve districts into which the area has been divided, the names of which are given in capitals. The principal towns are indicated.

Glamorgan numbered only about 300,000 in 1861, the time before the coal industry really expanded, and it increased to more than 1,100,000 during the next 50 years. Much of this increase was due to immigration, with more than 400,000 entering the county over the period. 140,000 came from other parts of Wales, with nearly as many from the South and West of England (130,000), and from other parts of the British Isles, including Ireland (20,000) (Thomas, 1930).

The number of births was taken from the Registrar General's annual statistical returns, except for the Cardiff Rural District and Rogerstone where estimates had to be made as the Tables do not give annual returns for such small units. In all but three divisions the number of births was above 7,000. The annual number had increased 7.9 per cent. over the 7-year period 1956–62, from 14,084 to 15,192, with a total of 102,786 (2,842 stillbirths and 99,944 live-births) (Table I).

TABLE I

TOTAL BIRTHS FOR YEAR IN TWELVE AREAS, 1956–62

Area	Population 1961 Census	1956	1957	1958	1959	1960	1061	1962	Total
1. Neath	40,870	600	640	625	618	610	645	646	4,384
2. Port Talbot	60,690	1,127	1,143	1,250	1,142	1,260	1,153	1,181	8,256
3. Mid-Glamorgan	110,974	1,706	1,746	1,847	1,908	1,870	2,090	2,034	13,201
4. Glamorgan South-East	29,881	587	632	658	666	804	755	740	4,842*
5. Pontypridd	62,593	1,015	1,080	1,094	1,078	1,099	1,117	1,097	7,580
6. Rhondda	100,287	1,610	1,690	1,638	1,621	1,610	1,655	1,699	11,523
7. Aberdare	68,730	1,077	1,168	1,091	1,125	1,119	1,093	1,106	7,779
8. Caerphilly	70,653	1,460	1,369	1,375	1,308	1,375	1,393	1,437	9,717
9. Merthyr	59,039	888	1,017	1,005	1,031	1,027	1,001	1,033	7,002
10. Rhymney	81,699	1,547	1,510	1,538	1,452	1,522	1,585	1,535	10,689
11. Ebbw Vale	103,842	1,758	1,776	1,729	1,798	1,813	1,824	1,882	12,580
12. E. Monmouthshire	48,381	709	733	770	707	719	791	804	5,233†
Total	837,639	14,084	14,504	14,620	14,454	14,828	15,104	15,192	102,786

* Estimate only for Cardiff Rural District.
† Estimate only for Civil Parish of Rogerstone.

Ascertainment

The investigation included all births that had occurred in the project area from January, 1956, to December, 1962. The investigation was begun in the Summer of 1960. In the Autumn of that year the co-operation of Hospitals and Local Authorities was sought so that we were from then onwards notified of cases within days of birth. Thus from the end of 1960 ascertainment was made prospectively; practically all the cases born from 1956–60 inclusive had to be ascertained retrospectively.

All cases of anencephaly and its variants, such as iniencephaly, exencephaly, and microcephaly acrania, were included under the heading of anencephaly. When spinal rachischitis was present in addition it was none the less included under anencephaly.

The spina bifida cystica group (henceforth referred to as spina bifida) encompassed myelomeningocoele, syringomyelocoele, hydromyelocoele, and localized rachischitis, as well as the meningocoele and all their variants, whether hydrocephalus was present or not. In this group were also included cases of encephalocoele and cranial meningocoele. Spina bifida occulta, on the other hand, and sacrococcygeal sinus, diastamatomyelia, and other "minor lesions" were excluded whether they were associated with neurological lesions or not.

The only cases of hydrocephalus accepted for inclusion were those in which the condition was present at birth. Cases in which there was doubt whether it might have been acquired as a result of delivery or some post-natal condition were excluded. Where a case of hydrocephalus was found to have an associated spina bifida it was classed as spina bifida. A number of macerated foetuses were reported as being hydrocephalic without autopsy confirmation. They were excluded as, although these foetuses may give the appearance of being hydrocephalic because of the softness or distortion of the head, autopsy examination hardly ever confirms this diagnosis. Cases of hydranencephalus were also excluded as in most this lesion is probably acquired later in intrauterine life, and microcephaly was not included in the investigation.

The place of residence was taken as the address during the major part of the pregnancy. Those cases were excluded in which the mother moved into the survey area for the delivery or shortly before it. The home address given in maternity records was always treated with scepticism as this was sometimes that of the grandparents of the index case. Foetuses born before the 28th week of gestation were classed as abortions and were not included as index cases. No case was accepted as a malformed index case unless documentary evidence was obtained from a death certificate, from hospital records, or from domiciliary birth records with a convincing description.

Altogether 953 cases were notified to us, but of these 118 had to be excluded for various reasons (Tables II and III). The largest group was that of the 44 macerated "hydrocephalics" and the group of 28 hydrocephalics in which there was some suspicion that the hydrocephalus might have been acquired. (Ten others notified as hydrocephalics were subsequently found to have had an associated spina bifida and were classified as such). In this way most of those notified as "congenital hydrocephalus" were eliminated and only the confirmed cases retained; 23 other cases were eliminated on checking the records as they were found to have been wrongly diagnosed.

TABLE II

REASON FOR EXCLUSION OF 118 CASES

Reason for Exclusion	Supposed Malformation		
	Hydrocephalus	Spina bifida	Anencephaly
Pre-viable	1	—	1
Macerated	44	—	—
Not definitely congenital	28	—	—
Wrong diagnosis	11	9	3
Diagnosis not confirmed	3	—	3
Born before January 1, 1956	—	5	1
Outside area*	1	5	3
Total	88	19	11

*Born or died in area but mother resident outside area during pregnancy.

TABLE III

23 CASES OF WRONG DIAGNOSIS

Supposed Diagnosis	Actual Diagnosis	Number of Cases
Hydrocephalus	Normal	3
	Brain damage	2
	Subdural haematoma	3
	Tumour	1
	Brain cyst	1
	Hydrops foetalis	1
Spina Bifida	Spina bifida occulta	6
	Normal	2
	Scoliosis	1
Anencephaly	No malformations present	3
Total		23

As the majority of deliveries took place in hospital in the area that was investigated (64 per cent. of the control group), the primary ascertainment was from hospital records. Hospital records varied in completeness and accessibility and for staff reasons many hospitals did not keep a diagnostic index. This was

reflected by a return from the hospitals varying between 57 per cent. of all cases ultimately ascertained in an area where the hospital delivery rate was rather lower than average, to 87 per cent. where not only most of the babies were hospital delivered but where there was also considerable interest in the problem under investigation. Over the whole survey area 67 per cent. of the cases were ascertained from hospital records, but 19 per cent. of those delivered in a hospital were not ascertained from any hospital source. The variations in ascertainment from Local Health Authority birth records were as great, varying from 41 per cent. of the cases in one area where nearly all the births were hospital births, to 79 per cent. where the Divisional Medical Officer kept an up-to-date malformation register and showed a high degree of personal interest. Altogether 53 per cent. of the cases ultimately ascertained were referred by Local Health Authorities, but 20 per cent. of the home-delivered malformed infants were not ascertained at all from this source.

The General Practitioners were circularized twice early in 1961, on each occasion with an explanatory letter, a form for completion with the name and address of any woman they could remember to have had an infant with a central nervous system malformation in their practice, and a stamped and addressed envelope. On the first occasion, a reply was received from 7 per cent., on the second from 30 per cent. Only 12 per cent. of the cases were ascertained from this source, 66 of spina bifida (nearly all cases which lived for some time), 23 of anencephaly, and two of hydrocephalus, but eleven cases were added that had not been ascertained from any other source.

The General Register Office provided copies of death certificates of all deaths registered in Glamorgan and Monmouthshire, for all cases born between 1956 and 1962, in which there was a mention of the central nervous system malformations. In addition, for 1961 and 1962, when statutory registration of stillbirths by cause came into force for England and Wales, when there was mention of the relevant malformation we have been receiving copies of part of the stillbirth certificate. Although for 1961 and 1962 ascertainment from this source, of cases which died, should have been complete, there were seven cases not notified to us from the Registrar General (two were missed through an oversight in the Registrar General's office, in three there was no mention of the relevant malformation on the certificate, and two certain cases of anencephaly were not even registered). Thus not even the Registrar General's returns can be relied upon to be absolutely complete.

"Others" consisted of four instances in which one case in the sibship had already been ascertained, and in which a full obstetric history revealed that there had been another affected infant born between 1956 and 1962. One case was discovered by a worker on another research project and one was picked as a control case and transferred to the index group. (This was not included as an index case in the family study). An additional case, a survivor with spina bifida born in 1961 in the Neath district, came to our notice only recently as a result of another investigation, but was found too late to be included in the analysis.

There are some differences in ascertainment rates with the type of malformation, with cases of anencephaly and hydrocephalus notified from fewer sources than those of spina bifida. The average number of referrals for each case was 1·49, 1·35, and 1·81 respectively. Taking the liveborn spina bifida cases alone, these were reported on average 2·01 times each.

Differences in ascertainment between the retrospective and the prospective part of the investigation were seen. If notifications by the General Register Office are excluded, then it is found that for 1956–60 inclusive each case was ascertained from 1·29 sources, while for 1961 and 1962 the figure was 1·41. In the General Practitioner notifications too, where reports averaged only nine cases for each of the four years 1956–59, the figure was nineteen for 1960, 26 for 1961, the year of circularization, and only sixteen for 1962. This would suggest that reports from this source can be expected only for cases coming to the practitioner's notice in the time immediately preceding the request, that cases are quickly forgotten, and that the practitioner cannot be expected to remember to notify cases occurring in the future. Regularly repeated requests would be essential if reasonable notification from this source was required, and this method in turn might become self-defeating.

Of the total cases, 95 per cent. were ascertained from hospital and Local Health Authority sources alone, and it may be arguable whether it was worth the effort and expense involved for less than 2 per cent. of the remainder to circularize the General Practitioners, and for 3 per cent. to scrutinize all the death and stillbirth certificates from the General Register Office (Fig. 2). However, now that stillbirth registration by cause is obligatory, this latter method is perhaps the most rewarding form of ascertainment for such lethal and obvious conditions as the dysraphic malformations, as very nearly all cases which died would be notified. (There was 82 per cent. ascertainment for 1961 and 1962, which represents all the cases which died, except for the seven who

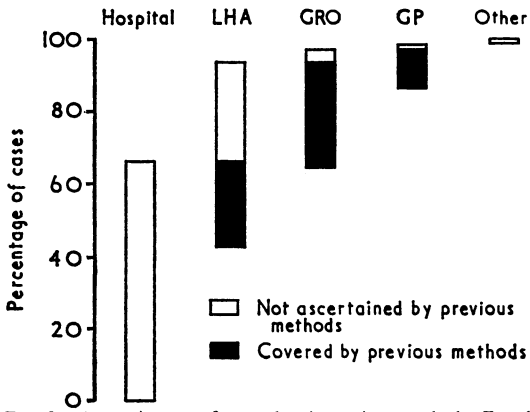

FIG. 2.—Ascertainment of cases by the various methods. For the severe abnormalities ascertainment is over 95 per cent. from Local Health Authority and Hospital sources alone.

were missed). For less lethal conditions this form of ascertainment would be less useful, and the help from General Practitioners would be essential.

Ascertainment is probably fairly complete, because of the nature of the conditions under investigation, and because of the employment of methods involving several sources. Nevertheless there may have been under-reporting for 1956 amounting to as much as 10 per cent., but the ascertainment over the whole period is probably at least 95 per cent. complete.

INCIDENCE

A total of 425 (200 males and 225 females) cases of spina bifida, 364 (91 males, 271 female, 2 not known) of anencephaly, and 46 (17 male, 29 female) of hydrocephalus was ascertained (Table IV). The overall incidence of the three malformations was 8·12 per 1,000 total births. Of these 4·13 were accounted for by spina bifida, 3·54 by anencephaly, and 0·45 by hydrocephalus. For male births this was 3·78, 1·73, and 0·32, and for female births 4·48, 5·40, and 0·58 respectively. The spina bifida incidence is the highest reported for any series for a whole population. That for anencephaly is exceeded only in the Northern Ireland series of Stevenson and Warnock (1959). The incidence of hydrocephalus is unusually low, probably because in this survey all instances secondary to spina bifida were classed as spina bifida, only cases of truly congenital hydrocephalus were included, and cases in which the presence of hydrocephalus was in doubt, as, for example, in certain macerated stillbirths, were excluded.

SECULAR TRENDS

Over the years the total number of cases ascertained each year increased from 92 in 1956 to 135 in 1961 (Table IV and Fig. 3), but at the same time the total number of births had also increased by 8 per cent. Taken as rates, apart from 1956 when there were only 6·53 per 1,000 births, with possible under-reporting, the incidence fluctuated between 7·58 and 8·93. The individual malformations tended to fluctuate rather more, probably because of the smaller number involved. If 1956 is excluded, then no statistically significant secular trend is detectable either for the total central nervous system malformations ($\chi^2=2{\cdot}99$; d.f.$=5$; $P=0{\cdot}7$) or for the two major groups taken separately.

Information from the Malformations Register in South Wales for 1965 and 1966 showed incidences of 7·8 and 9·2 per 1,000 births respectively (Lowe and

TABLE IV

INCIDENCE PER YEAR, 1956–62

Year	Anencephaly		Spina Bifida		Hydrocephalus		Total (incl. hydrocephalus)	
1956	2·77	(39)	3·33	(47)	0·43	(6)	6·53	(92)
1957	4·48	(65)	3·58	(52)	0·55	(8)	8·61	(125)
1958	2·46	(36)	4·78	(70)	0·34	(5)	7·58	(111)
1959	3·66	(53)	3·53	(51)	0·48	(7)	7·68	(111)
1960	3·64	(54)	4·58	(68)	0·40	(6)	8·62	(128)
1961	3·90	(59)	4·76	(72)	0·27	(4)	8·93	(135)
1962	3·81	(58)	4·27	(65)	0·66	(10)	8·74	(133)
Total 1956–62	3·54	(364)	4·13	(425)	0·45	(46)	8·12	(835)

Number of cases given in brackets.

Rates per 1,000 total births:

1956–62 Total	$\chi^2=8{\cdot}20$;	d.f.$=6$;	$0{\cdot}20<P<0{\cdot}30$
1956–62 Linear regression	$\chi^2=4{\cdot}46$;	d.f.$=1$;	$P<0{\cdot}05$
1957–62 total	$\chi^2=2{\cdot}99$;	d.f.$=5$;	$P<0{\cdot}70$

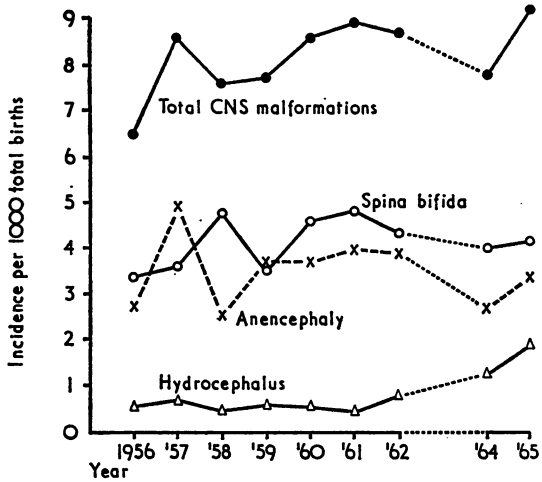

FIG. 3.—Graph showing incidence per 1,000 births from 1956 to 1965. No reliable information is available for 1963 and the figures for 1964 and 1965 were obtained from the South Wales Malformations Survey (Lowe and Richards, 1967). The higher figure for hydrocephalus may be due to the inclusion of some acquired cases.

Richards, 1967)*. If it is accepted that for the first year of that survey there was under-reporting and also that some cases of acquired hydrocephalus were included, especially in the second year, then these results confirm that there is indeed no secular trend.

LOCAL VARIATIONS IN INCIDENCE

It was suspected that there were considerable variations in incidence. In order to test for those local variations malformation rates were computed for each of the twelve local health divisions. Even if 1956 is included with its probable under-reporting, the number of cases ascertained in each division did not vary from year to year beyond the statistically permitted limits in view of the small numbers involved (Table V). However, when the years are grouped, then for 1956–59 a marked excess of cases was reported for Rhymney, and less for Caerphilly and Mid-Glamorgan, while for 1960–62 there was a very great excess for East Monmouthshire alone.

Variation in the malformation rates between the various divisions proved to be considerable, the lowest rate (5·78) being recorded in Glamorgan South-East, the agricultural and dormitory area, and the highest in East Monmouthshire (11·08). There was, in fact, a West/East gradient which seems statistically significant, with the lower incidence in the Neath and Port Talbot and the highest in Caerphilly and the Monmouthshire divisions (Table VI, overleaf).

(The East/West gradient was tested by comparing the distance of the weighted centre of population of each division from the North/South grid of Pontypool; $\chi^2=21\cdot23$; d.f.$=11$; $P<0\cdot05$, linear regression $\chi^2=9\cdot69$; d.f.$=1$; $P<0\cdot005$, deviations about linear mean regression $\chi^2=11\cdot71$; d.f.$=10$; $P<0\cdot5$). A similar gradient was seen for anencephaly and spina bifida separately which also seemed significant. For anencephaly Glamorgan South-East had again the lowest incidence (1·45) and there was again a West/East gradient from Neath (2·51) to Caerphilly and the Monmouthshire divisions (varying from 3·74 to 4·73). Variations for spina bifida were

Year	1964	1965
*Total CNS malformations	7·82	9·22
Anencephaly	2·63	3·31
Spina bifida	4·04	4·09
Hydrocephalus	1·16	1·82

(rates per 1,000 births)

TABLE V

NUMBER OF CASES PER YEAR IN TWELVE AREAS, 1956 TO 1962

Area	1956	1957	1958	1959	1960	1961	1962	Total
1. Neath	4	3	2	4	6	2	6	27
2. Port Talbot	4	8	11	6	9	6	11	55
3. Mid-Glamorgan	18	20	18	13	13	15	14	111
4. Glamorgan South-East	3	2	2	5	3	9	4	28
5. Pontypridd	7	9	1	8	10	11	14	60
6. Rhondda	9	9	10	14	12	16	16	86
7. Aberdare	4	11	6	7	8	8	12	56
8. Caerphilly	14	16	17	10	15	12	9	93
9. Merthyr	2	12	9	5	5	10	8	51
10. Rhymney	13	19	15	17	16	14	9	103
11. Ebbw Vale	8	13	15	16	18	20	17	107
12. East Monmouthshire	6	3	5	6	13	12	13	58
Total	92	125	111	111	128	135	133	835

within rather narrower limits, apart from East Monmouthshire which had the very high incidence of 6·69. The variation was between 3·19 and 4·43, again with a West/East gradient (Figs 4, 5, and 6).

TABLE VI

INCIDENCE PER 1,000 TOTAL BIRTHS IN TWELVE AREAS

Area	Anencephaly		Spina Bifida		Hydrocephalus		Total	
1. Neath	2·51	(11)	3·19	(14)	0·46	(2)	6·16	(27)
2. Port Talbot	2·91	(24)	3·27	(27)	0·48	(4)	6·66	(55)
3. Mid-Glamorgan	3·41	(45)	4·70	(62)	0·30	(4)	8·41	(111)
4. Glamorgan South-East	1·45	(7)	4·34	(21)	—	(—)	5·78	(28)
5. Pontypridd	2·77	(21)	3·96	(30)	1·19	(9)	7·92	(60)
6. Rhondda	3·64	(42)	3·38	(39)	0·43	(5)	7·46	(86)
7. Aberdare	2·96	(23)	3·60	(28)	0·64	(5)	7·20	(56)
8. Caerphilly	4·73	(46)	4·43	(43)	0·41	(4)	9·57	(93)
9. Merthyr	3·14	(22)	4·00	(28)	0·14	(1)	7·29	(51)
10. Rhymney	5·15	(55)	4·12	(44)	0·37	(4)	9·64	(103)
11. Ebbw Vale	3·74	(47)	4·29	(54)	0·48	(6)	8·51	(107)
12. East Monmouthshire	4·01	(21)	6·69	(35)	0·38	(2)	11·08	(58)

Number of cases given in brackets.

The weighted centre of population of each division was measured from the North/South grade of Pontypool for the East/West gradient.

Total	$\chi^2 = 21{\cdot}33$;	d.f. = 11;	$P < 0{\cdot}05$
Linear regression	$\chi^2 = 9{\cdot}69$;	d.f. = 1;	$P < 0{\cdot}005$
Deviations about linear regression	$\chi^2 = 11{\cdot}71$;	d.f. = 10;	$0{\cdot}30 < P < 0{\cdot}50$
Spina bifida linear regression	$\chi^2 = 4{\cdot}05$;	d.f. = 1;	$P < 0{\cdot}05$
Anencephaly linear regression	$\chi^2 = 6{\cdot}13$;	d.f. = 1;	$P < 0{\cdot}05$

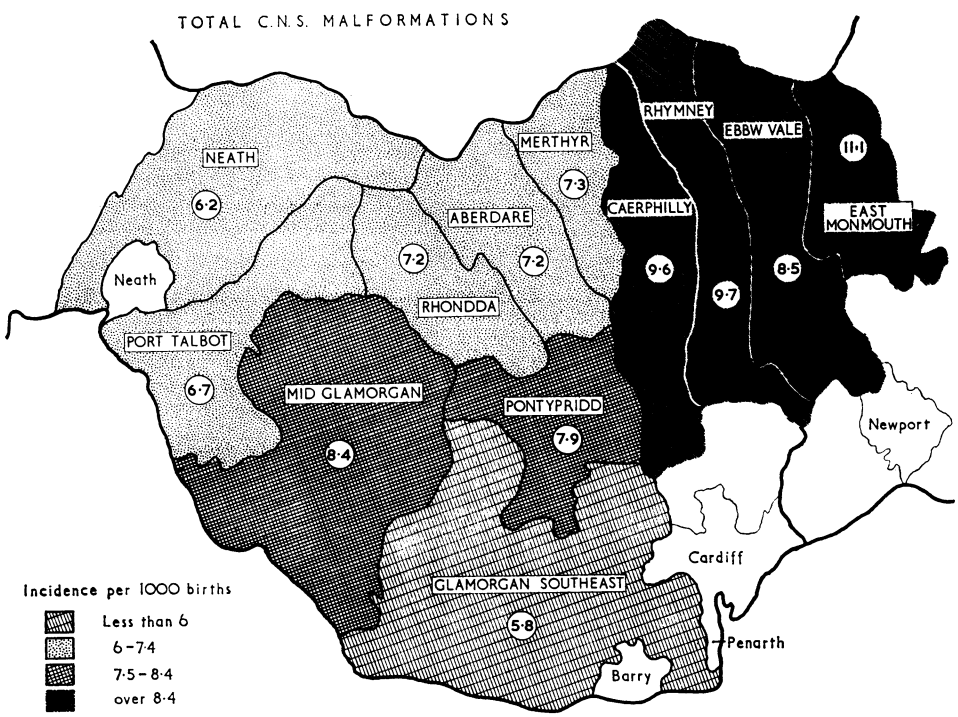

FIG. 4.—Sketch map of the project area separated into twelve divisions. The shading indicates the incidence of total central nervous system malformations; the actual incidence per 1,000 births is written in.

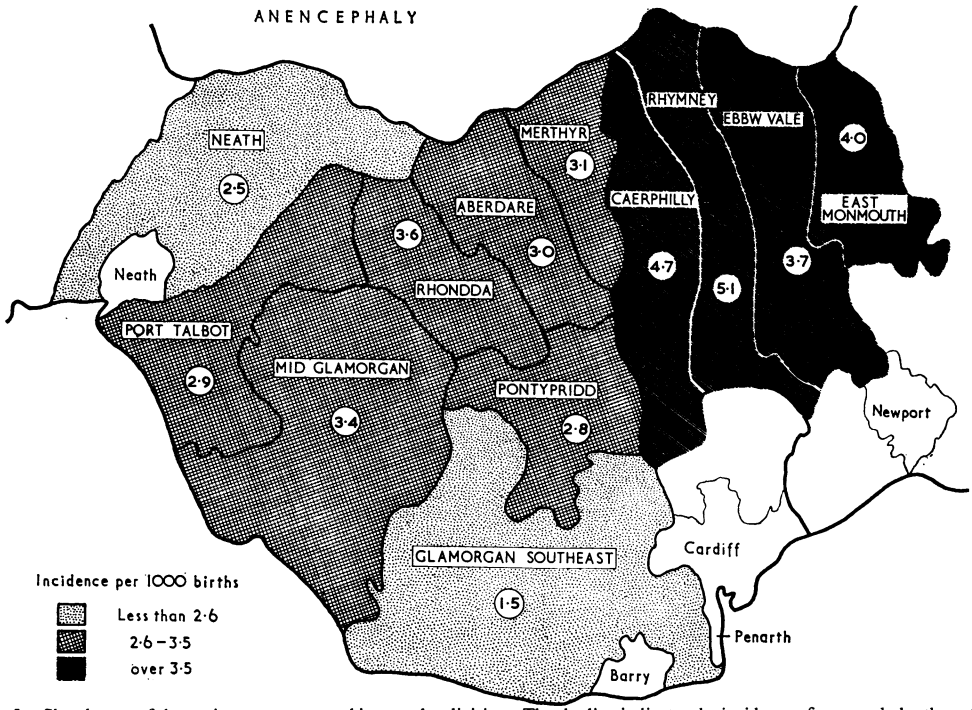

FIG. 5.—Sketch map of the project area separated into twelve divisions. The shading indicates the incidence of anencephaly; the actual incidence per 1,000 births is written in.

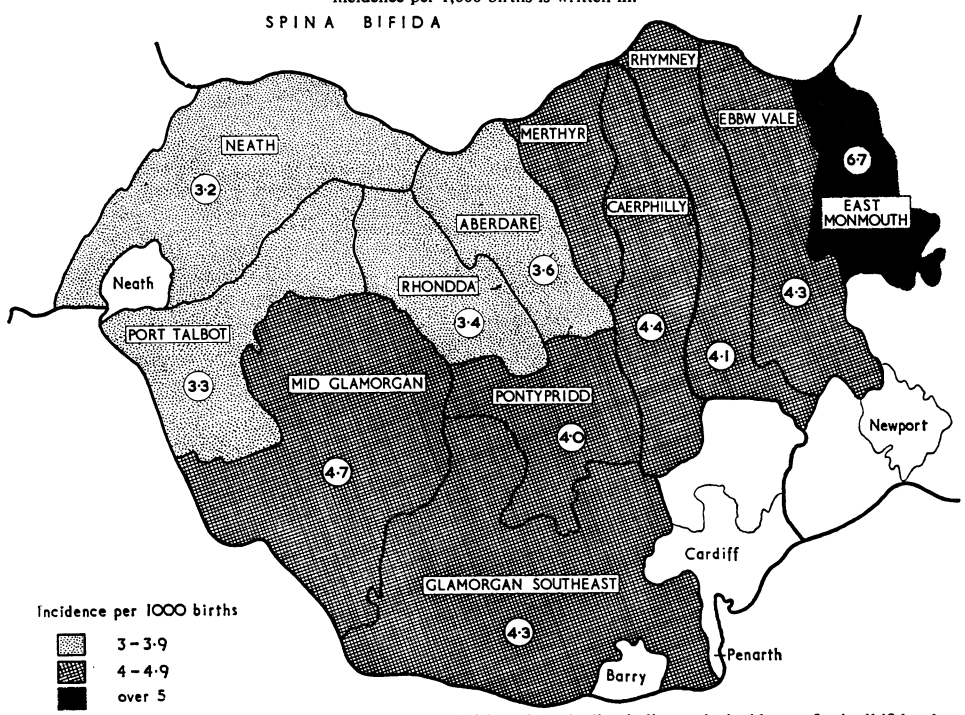

FIG. 6.—Sketch map of the project area separated into twelve divisions. The shading indicates the incidence of spina bifida; the actual incidence per 1,000 births is written in.

The project region was divided into an area of low incidence consisting of Neath, Port Talbot, mid-Glamorgan, Glamorgan South-East, Pontypridd, Rhondda, Aberdare, and Merthyr, and one of high incidence including Caerphilly, Rhymney, Ebbw Vale, and East Monmouthshire. Not only was there a considerable difference in the incidence in the total central nervous system malformations, but also for all three malformations separately. The difference was consistent from year to year for all three malformations (Table VII and Fig. 7). The only exception was in 1962, when the spina bifida rate was somewhat higher in the low incidence area (4·71) than in the high incidence area (3·53), with the result that the total central nervous system malformation rate was also slightly reversed (8·90 and 8·48 respectively). This is within the random variation.

Possible geographical and climatic factors have been examined to see if any could help to explain the local variations.

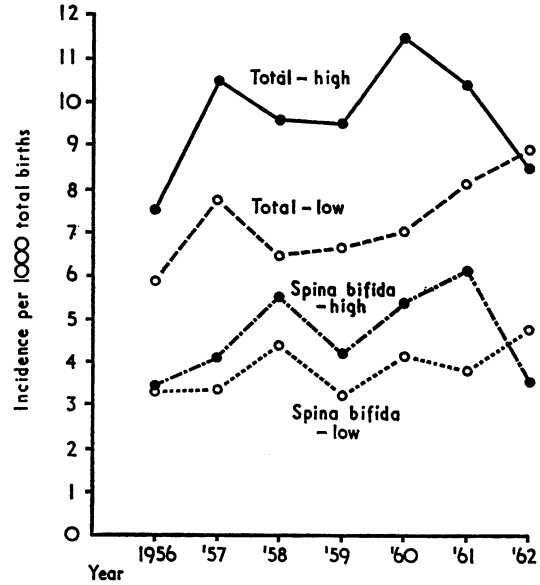

FIG. 7.—Graph showing the incidence of total central nervous system malformations and of spina bifida for 1956 to 1962 separately for the high and the low incidence areas. The difference is consistent over the years except in 1962 for spina bifida.

(1) GEOLOGICAL BACKGROUND

The area consists of carboniferous rocks comprising coal measures of the South Wales coal field surrounded by a narrow outcrop of millstone grit and carboniferous limestone, while the area to the south of the coal field contains triassic marl and sandstone together with an extensive outcrop of lower lias in the Vale of Glamorgan. There was no obvious relationship between the local incidence of abnormalities and the occurrence of any type of rock formation.

The distribution of fourteen trace elements, including copper, iron, lead, cobalt, manganese, and chromium, was examined by the stream sediment

TABLE VII

MALFORMATION RATE PER YEAR FOR HIGH AND LOW INCIDENCE AREAS, 1956 TO 1962

Year	Total Births		Anencephaly		Spina Bifida		Total Malformation Rate	
1956	High	5,474	3·65	(20)	3·37	(19)	7·49	(41)
	Low	8,610	2·20	(19)	3·25	(28)	5·91	(51)
	Total	14,084	2·77	(39)	3·33	(47)	6·53	(92)
1957	High	5,388	5·20	(28)	4·08	(22)	10·57	(54)
	Low	9,116	4·05	(37)	3·29	(30)	7·78	(71)
	Total	14,504	4·48	(65)	3·58	(52)	8·61	(125)
1958	High	5,412	3·51	(19)	5·54	(30)	9·61	(52)
	Low	9,208	1·88	(17)	4·34	(40)	6·40	(59)
	Total	14,620	2·46	(36)	4·78	(70)	7·58	(111)
1959	High	5,265	4·37	(23)	4·18	(22)	9·50	(50)
	Low	9,189	3·26	(30)	3·15	(29)	6·62	(61)
	Total	14,454	3·66	(53)	3·53	(51)	7·67	(111)
1960	High	5,429	5·71	(31)	5·34	(29)	11·42	(62)
	Low	9,399	2·44	(23)	4·14	(39)	7·01	(66)
	Total	14,828	3·64	(54)	4·58	(68)	8·62	(128)
1961	High	5,593	4·11	(23)	6·08	(34)	10·37	(58)
	Low	9,511	3·78	(36)	3·78	(38)	8·08	(77)
	Total	15,104	3·90	(59)	4·76	(72)	8·93	(135)
1962	High	5,658	4·42	(25)	3·53	(20)	8·48	(48)
	Low	9,534	3·45	(33)	4·71	(45)	8·90	(85)
	Total	15,192	3·81	(58)	4·27	(65)	8·74	(133)
1956 to 1962	High	38,229	4·16	(169)	4·63	(176)	9·44	(361)
	Low	64,557	3·00	(195)	3·85	(249)	7·18	(464)
	Total	102,786	3·54	(364)	4·13	(425)	8·12	(835)

sampling technique carried out by the Geochemical Research Group, Imperial College, London, in all areas except the Neath Division. Apart from isolated high values for copper, zinc, lead, and chromium in streams draining triassic rocks, and iron, copper, and lead apparently associated with the restricted areas of the coal measures, no very striking values were recorded. There was no obvious relationship between the occurrence of any one of the elements tested for and the variation in the central nervous system malformation incidence.

(2) Water Supply

The water supply for the South Wales communities is almost entirely surface water collected in reservoirs lying on old red sandstone in Breconshire and some lying on carboniferous rock in Glamorgan. A little water is supplied from artesian wells in the coastal strip and occasionally water is drawn from shallow wells in country districts. There appeared to be no relationship between the type of water supplied and the variation in the incidence of malformations.

(3) Rainfall and Sunshine

South Wales, along with Ireland, Scotland, and North-West England is one of the high rainfall regions of the British Isles (Ordnance Survey, 1967). There might, thus, appear to be a positive relationship between the high incidence areas mentioned and high rainfall, as has been reported from Holland (Rootselaar and Beks, 1967). Within the project area, however, the considerable rainfall differences ranging from 85″ in the west to 40″ in the eastern and coastal regions run counter to the malformation incidence and thus rainfall *per se* is probably not one of the important aetiological factors. Nothing can be said about sunshine as information is very incomplete. There is even less data about its quality with records of such factors as the distribution and persistence of mist and fog and air pollution which would influence the solar radiation and amount of ultra-violet light reaching the ground.

(4) Radiation

There are no geological strata in South Wales which have a high radioactivity which might explain local differences (Ponsford, 1955). On the other hand, radioactive fall-out from nuclear explosions was higher in Wales than elsewhere in the United Kingdom, as evidenced by the values for Strontium 90 estimated from the bones of newborns (Bryant, Henderson, Jury, Morton, Parkes, and Webber, 1963, and earlier reports). This is probably largely due to the high rainfall. There is no indication that the Strontium 90 values run in parallel with the high incidence of central nervous system malformations, for there is no real difference between the values found in bones collected from the east and the west of the region. Any slight variation can almost certainly be accounted for by sampling differences. Nor was the 1959 increase in Strontium 90 values paralleled by any similar increase in the incidence of malformations. Thus it is unlikely that radioactivity is a factor at the moment.

(5) Population Density and Urban/Rural Ratio

The bulk of the population is disposed in townships which are mostly industrial and in straggling industrial communities and villages. However, a number of areas which are almost exclusively agricultural and rural were included. The towns of Porthcawl (seaside), Bridgend (light industry and market), and Pontypridd (industrial) with an average population density of 4·8 persons per acre have incidences of 11·7, 10·0, and 12·8 respectively, with Pontypool in the East Monmouthshire division and another township in the Rhymney division having incidences of 11·3 and 20·0 per 1,000 births respectively. On the other hand, in the relatively flat agricultural Vale of Glamorgan, the Glamorgan South-East and the Llantrisant and Llantwit Fadre District (including three small country towns having a combined population of less than 7,000) have a population density of less than 0·6 persons per acre and a malformation incidence of 5·6 and 4·3 per 1,000 births respectively. In Penybont of the Mid-Glamorgan division, where the predominantly rural area is intermingled with small industrial townships, the incidence is somewhat higher (6·73 per 1,000 births) (Table VIII, overleaf).

There would thus appear to be a rural/urban gradient in incidence. However, the number of cases is rather small especially in the agricultural areas. An industrial/non-industrial gradient in the urban areas is not possible to compute because of the nature of the communities.

The position in Port Talbot, a town with a large steelworks employing the bulk of the male population, is rather more confused, as nearly all the wards include either seaside housing developments or large rural areas, so that the population density of only about 2·2 persons per acre is not meaningful. The incidence in the wards with the seaside development which do not get the prevailing winds from the steelworks is 5 per 1,000 births, while that of the remaining wards of the town is 8 per 1,000 births.

The incidence rates in the straggling industrial small towns and villages vary considerably from 5·3 in the Rhondda Fach and 6·7 in the Maesteg valley to 8·1 in the Ogmore valley and 9·2 in the Rhondda

TABLE VIII

LOCAL INCIDENCE AND POPULATION DENSITY (persons/acre)

Locality	Type of Locality	Area	No. of Cases	Total Births	Population Density	Incidence per 1,000 Total Births
Bridgend	Light industry and market town	3	19	1,917	12·5	9·7
Pontypridd	Industrial town	5	45	4,079	4·4	12·8
Porthcawl	Seaside town	3	13	1,111	3·2	11·7
Pontypool	Heavy industrial town	12	49	4,354	2·5	11·2
Port Talbot	Heavy industrial town with rural area	2	43	6,820	2·2	6·3
Aberbargoed	Small industrial town	10	12	579	6·4	20·1
Porth and district	Industrial town	6	42	5,338	6·0	8·0
Cowbridge Rural	Agricultural	4	15	2,474	0·5	5·8
Cardiff Rural	Agricultural and dormitory	4	12	2,277	0·6	5·3
Llantrisant and Llantwit	Agricultural	5	15	3,501	1·5	4·3
Penybont	Partly agricultural	3	34	5,053	1·0	6·7
Ogmore Vale	Industrial and villages in valleys	3	21	2,594	1·2	8·1
Maesteg		3	18	2,626	3·2	6·9
Blaenavon		12	9	879	1·8	10·2
Abertillery		11	31	2,419	3·9	12·8
Rhondda Fach		6	17	3,227	4·6	5·3
Rhondda Fawr		6	27	2,958	2·7	9·2

Fawr. The narrower valleys (Ogmore Vale, Rhondda, and some of the Monmouthshire valleys) tend to have a somewhat higher incidence than the wider valleys (Maesteg, Aberdare, and Merthyr). This is, however, far from consistent. Population densities are not meaningful here as large tracts of surrounding hilly countryside are nearly always included.

Some of these mining valleys are so narrow and deep that sunshine amounts are considerably reduced in the trough where most of the housing is situated. Persistence of mist and fog, air pollutants, and temperature reversals tend also to be appreciable. However, although there is some relationship between the high malformation incidence and the steepness of the valleys in Monmouthshire and in the Ogmore Vale and Maesteg, this is not so in the Rhondda and in Aberdare, where the steeper portions have, in fact, a lower incidence than the wider ones of the same valleys. However, relatively small numbers of cases are involved when broken down into small areas, making statistical evaluation difficult.

DISCUSSION

Epidemiological investigations of malformations tend to be of three kinds, each with its own advantages and problems (Leck and Smithells, 1963). The large scale, often national, surveys such as the National Perinatal Mortality Survey of 1958 (Butler and Bonham, 1963), the Ministry of Health survey into malformations with particular reference to Thalidomide (Ministry of Health, 1962), and some of those carried out in the United States usually require the help of government agencies and then invariably tend to involve many investigators, to be slow and incomplete, and sometimes to be inexact, but they have the advantage of large numbers for analysis. Several prospective surveys are of this kind.

TABLE

CENTRAL NERVOUS SYSTEM MALFORMATIONS REPORTED

Centre		South Wales	Liverpool	Belfast	Southampton	Birmingham	Northampton	Charleston
Type of Investigation		P	P	P	P	P	P	P
Years		1956–62	1960–64	1957	1958–62	1950–52	1944–57	1946–55
Births		102,786	91,176	8,519	14,907	56,760	62,224	55,156
Incidence per 1,000 Total Births	Anencephaly	3·5	3·1	4·6	1·9	(*a*) 2·0 (*b*) 2·0	1·0	W 1·2 N 0·2
	Spina Bifida	4·1	3·7	2·2	3·2	(*a*) 2·8 (*b*) 3·0	1·9	W 1·5 N 0·6
	Hydrocephalus	0·5	0·5	1·5	0·9	(*a*) 1·8 (*b*) 2·6	0·6	W 0·8 N 1·1
	Total	8·1	7·4	8·3	6·0	(*a*) 6·6 (*b*) 7·6	3·5	W 3·5 N 1·9
Reference		Laurence, Carter and David, 1968	Smithells, 1967	Stevenson and Warnock, 1959	Williamson, 1965	McKeown and Record, 1960	Pleydell, 1960	Alter, 1962

P = Population R = Records H = Hospital

Purely local and hospital surveys, of which that from Dublin by Coffey and Jessop (1955) is an example, generally concern a selected group, tend to be small and retrospective, and to involve the cases from many years before sufficient numbers are available. They have the advantage of being able to be carried out easily by one investigator trying to find a specific but limited answer to his problem. Regional investigations, such as the Malformations Survey in Liverpool (Smithells, 1962) and that in South Wales (Lowe and Richards, 1967) on the other hand, lend themselves both to retrospective and prospective surveys and can usually be in the hands of one investigator with the consequent consistency that this gives. A large enough area can be included, so that a sufficient population is investigated to yield enough cases for analysis. Generally such an investigation can be completed relatively speedily. The present investigation is one of this last group, where the whole of the population in a limited area was investigated by one small team and every effort was made to obtain complete ascertainment and assign the cases to their correct category.

The South Wales incidence of central nervous system malformations is strictly comparable with few figures published from other centres (Table IX). For instance, the figures from Rhode Island published by MacMahon, Pugh, and Ingalls (1953), from Melbourne by Collman and Stoller (1962), from Liverpool by Malpas (1937), and Alexandria by Stevenson and others (1966) are all based on hospital series and thus could possibly be biased towards a greater number of abnormal cases with complications of pregnancy such as unstable lie or hydramnios predisposing to hospital admission. The data from Birmingham (Record and McKeown, 1949) and Scotland (Edwards, 1958) are based on death certification only and are also likely to include cases wrongly categorized. Those from New York by Gittelsohn and Milham (1962) and Erhardt and Nelson (1964) based on birth certificates with recording of malformations present are also likely to be inaccurate and incomplete. Those from Belfast (Stevenson and Warnock, 1959), Liverpool (Smithells, 1967), Southampton (Williamson, 1965), and the several smaller series from Exeter (Ward and Irvine, 1961), Leicester (Moss, 1964), Northamptonshire (Pleydell, 1960), and Reading (Griffin and Sorrie, 1964) amongst others are based like the South Wales investigation on population surveys, and the figures can therefore be compared.

There is evidence from family studies including the present one (Williamson, 1965; Carter, Laurence, and David, 1967; Carter, David, and Laurence, 1968) that congenital hydrocephalus without associated spina bifida is probably not part of the dysraphic syndrome. The inclusion of hydrocephalus, therefore, with anencephaly and spina bifida in a study into possible aetiological factors of craniovertebral dysraphia, is perhaps a mistake as it would tend to obscure any correlations. Fortunately there are only small numbers of hydrocephalics in this study. It is interesting to note that the investigations relying upon records only report a particularly high incidence of hydrocephalus, possibly because of misreporting and the inclusion of "acquired cases". This latter is almost certainly the reason why the "revised" rate at 5 years for Birmingham (McKeown and Record, 1960) is so much higher than the rate computed from birth and neonatal records. In fact, congenital hydrocephalus without associated spina bifida is a rare malformation, and it could be argued

IX
FROM VARIOUS CENTRES BETWEEN 1949 AND 1968

Japan	Liverpool	Alexandria	Rhode Island	Melbourne	Belfast	Dublin	Scotland	Birmingham
P	H	H	H	H	H	H	R	R
1948–54	1923–32		1936–52	1942–57		1953–54	1939–45	1940–47
64,570	13,964	10,401	168,654	160,400	29,215	12,552	655,892	154,307
0·6	3·6	3·6	1·9	0·7	4·1	5·0	2·5	2·3
0·3	2·8	2·0	2·5	0·5	4·0	4·2	2·3	2·5
0·3	4·2	2·0	0·9	0·6	1·2	3·5	2·1	1·0
1·2	10·6	7·6	5·3	1·8	9·3	12·7	6·9	5·8
Neel, 1958	Malpas, 1937	Stevenson et al., 1966	MacMahon et al., 1953	Collmann and Stotter, 1962	Stevenson et al., 1966	Coffey and Jessop, 1955	Record and McKeown, 1949	Record and McKeown, 1949

W=White N=Non-white (*a*)=Birth (*b*)=5 years

that the number of hydrocephalics included in an epidemiological study can be taken as an index as to how carefully the information has been recorded and collected.

The South Wales incidence of central nervous system malformations is one of the highest so far reported, exceeded only by that from Belfast (Stevenson and Warnock, 1959) of the population surveys. The rate for spina bifida is certainly the highest so far recorded if it is accepted that the Dublin series (Coffey and Jessop, 1955) is likely to be a selected one.

Marked geographical variations in the incidence of central nervous system malformations exist even after allowances are made for under-reporting in some surveys such as those relying on certification, and for high figures in others because of inevitably selected hospital series. The Chinese and Japanese and other Far-Eastern races seem to have a low incidence (Neel, 1958; Searle, 1959). The same seems to be true for the Negroes in North America (Alter, 1962) and also possibly in Africa as well. On the other hand, Europeans and probably to a lesser extent Indians, together with communities which have descended from them, seem to have a much greater predisposition to produce offspring with these malformations. Within Europe the Western European people and especially those living in the western part of the British Isles have the highest incidence rates. The high rate reported from Alexandria (Stevenson and others, 1966) is one of the more notable exceptions and will need further inquiry. These community differences must to some extent be due to genetic differences in susceptibility. However, it is questionable whether the marked local differences recorded for a hospital survey of anencephaly in France (Frézal, Kelley, Guillemot, and Lamy, 1964) and for central nervous system malformations in various parts of England, in Scotland (Edwards, 1958), and now in Wales, can be explained on genetic grounds alone.

The secular trends, such as the marked fall in the incidence in New York State between 1945 and 1959 (Gittelsohn and Milham, 1962), and the steady fluctuation which has taken place in Birmingham over the last 25 years (Leck, 1966), do not seem to have taken place in South Wales. In any case no explanation has yet been put forward for any secular trends, though they must surely have some environmental basis.

Various geographical factors have been incriminated from time to time. In Holland there seems to be a positive relationship between rainfall and anencephaly and a negative one with sunshine (Rootselaar and Beks, 1967). In South Wales neither of these factors seems to explain the variations. Although irradiation is one of the most potent methods of producing central nervous system malformations experimentally, and background radiation has been suspected as an aetiological factor (Gentry, Parkhurst, and Bulin, 1959), several investigations in North America (Grahn and Kratchman, 1963; Segall, MacMahon, and Hannigan, 1964) and the evidence from South Wales do not support this idea. The same is true for radioactive fall-out, which could not have been a factor before the second world war, but has been incriminated elsewhere (le Vann, 1963, 1965).

The urban/rural gradient noted by Edwards (1958) for spina bifida only is quite marked for total central nervous system malformations in South Wales. What factor in these variations is responsible in South Wales has not been identified. Although the people themselves and the mode of life appear to be different in the rural areas, they seem to come from the same stock and they seem to have a fairly similar social class structure. Housing density could in some way possibly be a factor. This, however, is a difficult matter to investigate in an area where much of the population lives in straggling semi-industrial "villages" often in intimate contact with agricultural communities. Whether density of population, sunshine, air temperature, air pollution, and the like play any part in this should be further investigated.

The West/East upward gradient in incidence, which seems to stand up to several different statistical tests, would appear to be highly significant. So far no satisfactory geographical explanation has emerged. Nor does there appear to be a convincing ethnic, sociological, or economic basis for it (Laurence, Carter, and David, 1968). It is, of course, always possible that the explanation may lie in some epidemiological quirk which may become exposed by time.

Summary

This is an investigation into as complete as possible an ascertainment of cases of anencephaly, spina bifida cystica (and encephalocoele), and congenital hydrocephalus born between 1956 and 1962 in the mining valleys of Glamorganshire, east of Neath and of Monmouthshire, and in the Vale of Glamorgan, in a population of 850,000 with 102,786 total births.

Methods of ascertainment whereby 835 cases (364 anencephaly, 425 spina bifida, and 46 hydrocephalus) were found, partly retrospectively and in part prospectively, are discussed. The incidence of total central nervous system malformations of 8·1 per 1,000 births is one of the highest recorded and that for spina bifida (4·1 per 1,000 births) the highest in a total population.

No secular trend was found, but local variation in the incidence was considerable, with a marked West/East upward gradient of both the total malformations and the two main groups separately. The local variations are discussed in the light of the geological background, various water supplies, rainfall, and sunshine, background radiation, and radioactive fall-out, and population density and urban/rural areas, none of which seems to explain the local differences.

This investigation could not have been carried out without the unstinting help of our hospital colleagues, the Local Health Authorities and the local general practitioners, but we are particularly indebted to Dr W. E. Thomas, County Medical Officer of Health for Glamorgan, Dr G. Rocyn-Jones, County Medical Officer of Health for Monmouthshire, and Dr T. H. Stephens, Medical Officer of Health for Merthyr Borough, their Divisional Medical Officers, Health Visitors, and Midwives, and to the Medical Records Officers of the various hospitals in the area. We should also like to thank the Registrar General for his help with case-finding, and the Local Executive Councils, the Central National Health Service Register of the Ministry of Health, and the International Investigation Department of the Salvation Army for their help in tracing families, and Miss J. V. Dunscombe who helped us throughout and for a period as research assistant. We are grateful to Prof. C. R. Lowe, Prof. A. L. Cochrane, and Prof. A. G. Watkins of the Welsh National School of Medicine for their advice, to Dr H. Campbell and Mr P. M. Sweetman of the Medical Statistical Department of the Welsh National School of Medicine for their constant statistical help, to Prof. J. S. Webb of Imperial College, London, for carrying out the geochemical investigations, to Dr D. Bassett of the National Museum of Wales and Prof. J. Oliver of Swansea University College for geological and geographical information, and to Dr J. F. Loutit of the Medical Research Council's Radiobiological Research Unit for help with Strontium 90 assays, and we are indebted to Mr T. J. H. Cooke for the preparation of the illustrations.

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