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INCIDENCE OF CONGENITAL MALFORMATIONS IN THE REGIONS OF ENGLAND AND WALES

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SLIGHT attention was paid to the epidemiology of congenital malformations before the discovery that exposure of the mother to infection by rubella during early pregnancy could affect the development of the fetus (Gregg, 1941; Swan, Moore, Mayo and Black, 1943). Most malformations had been looked upon as inevitable happenings due to faults of development which were outside the scope of preventive medicine. Increasing use of *X* rays during pregnancy and studies of background radiation then suggested that these might be concerned in initiating malformations, and in 1959 a study was published associating their incidence in parts of New York State with natural radiation from the ground (Gentry, Parkhurst and Bulin, 1959). Subsequent work has not, however, so far established the existence of any significant association with background radiation arising from either soil or water supply.

In 1968 Laurence, Carter and David reported a thorough investigation of the possible factors which might be concerned in the incidence of 835 cases of congenital malformation of the central nervous system discovered among births occurring during 1956–62 in the mining valleys of Glamorgan and Monmouth and the Vale of Glamorgan. Local variations in the incidence rates of such malformations were compared with geological features, water supplies, rainfall, sunshine, background radiation, radioactive fall-out and population density but none of these factors seemed to account for the differences. The only pregnancy factor with evident significance was an increased incidence of influenza.

The incidence rate per 1,000 live and stillbirths found in this South Wales survey for anencephaly, spina bifida and hydrocephalus malformations was 8·1, similar to that found in Liverpool (7·4) by Smithells (1962) and in Belfast (8·3) by Stevenson and Warnock (1959). Lower incidence rates had been found in population surveys elsewhere.

A nation-wide survey of perinatal mortality resulting from 7,117 singleton births and comprising deaths in the first four weeks of life and stillbirths, which occurred in Great Britain in March to May 1958, was carried out by the National Birthday Trust (Butler and Bonham, 1963). This yielded some 500 congenital malformations of all kinds, but the total was insufficient for assessment of significant differences in incidence in the separate regions.

By the registration of causes of stillbirth based on certification according to the International List it becomes possible to bring together for each sex in 1963–66 the prenatal deaths from each kind of neural-tube malformation (rubrics Y 38·0 anencephaly, Y 38·1 hydrocephalus, Y 38·2 spina bifida), with all other congenital malformations (Y 38·3—Y 38·7) and postnatal deaths from corresponding causes at ages under 1 year and at 1–4 years in categories 750–752 and 753–759. In 1963–66 there were 24,458 stillbirths and deaths at 0–1 year assigned to these numbers arising from three and a half million live and stillbirths in all, and the various rates for each sex have been calculated in the present paper for each Hospital Region in the hope that geographical variations will provide some clue to the causes of malformations, particularly those of the neural tube. The total incidence of malformations in infants is not fully revealed by the deaths classified to them as underlying cause, since some affected children die of concomitant causes and others continue to live with the disability, but within England and Wales, where the rules and procedure of certification are tolerably constant, one can assume that regional rates compounded of prenatal and postnatal deaths are comparable with each other though lower than total incidence rates derived from surveys.

In the final section of the paper the various regional distributions are compared with those for mortality of females from cardiovascular diseases, and other conditions for which there are indications of a 'water factor' apparently related to hardness of local water supplies (Morris, Crawford and Heady, 1961; Crawford, Gardner and Morris, 1968).

Sex Ratios in Death Rates from Congenital Malformations in 25 Countries

Before examining regional distributions of malformations in England and Wales there are some features of their geographical distribution in other countries which merit attention. The World Health Organisation has kindly supplemented their published data of death rates at 0–1 and 1–4 years of age per 1,000 live births for 1961–64 (W.H.O., 1967) by furnishing also the rates in 1965, making it possible to show in Table I average annual rates for 25 countries. Although the death rates are subject to doubts as to precise comparability owing to differences in procedures of certification and selection of the underlying cause of death when other diseases were present, such differences would affect the two sexes in the same way and would not invalidate comparisons between the sex ratios recorded by the various countries.

In Fig. 1 the countries have been ranked in order of the female/male sex ratio of rates at 0–1 year, and the ratios at 0–4 years have also been shown alongside. The ratios range from 1·096 in Northern Ireland to 0·806 in Sweden, and it is noteworthy that the countries with ratios over 0·95 are the four parts of the British Isles and the Netherlands, whereas the four Scandinavian countries have ratios below 0·86. The most likely cause of a high female/male ratio in the death rates from all malformations at 0–1 year is a high proportion of those malformations of the central nervous system which affect females more than males, namely categories 750–752 in the International List. Table I shows that this proportion was 42% in Northern Ireland, about 39% in Eire and Scotland, about 30% in England and Wales and Canada, and 27% in Germany and the Netherlands, with lower levels in other countries The correlation coefficient between this proportion and the sex ratio at 0–1 year is 0·82, and, as will be seen in the next section, when prenatal and postnatal deaths are compounded in the regions of England and Wales it is 0·72.

The last column of Table I shows only slight variation by country in the sex ratio between female and male rates at 0–1 year for all other kinds of malformation, namely those in categories 753–759. The range for these is from 0·82 to 0·70 whereas for the neural-tube malformations it is from 1·67 to 0·90, with ranking of the countries similar to that for all malformations (1·10 to 0·81) but more pronounced. Thus the parts of Britain, the Netherlands and Austria show ratios exceeding 1·34, Canada,

Table I

DEATH RATES FROM CONGENITAL MALFORMATIONS AT 0–1 YEAR PER 1,000 LIVE BIRTHS, AND SEX RATIOS IN 25 COUNTRIES, 1961–65. NUMBERS AND PROPORTIONS OF DEATHS DUE TO CENTRAL NERVOUS SYSTEM AND OTHER KINDS OF MALFORMATION, WITH SEX RATIOS*

Country	Rate under 1 year per 1,000 Live Births		Ratio of Female to Male Rate	Analysis of Deaths at 0–1 yr. in 1961–64				
				No. classed to		C.N.S. % of All	Sex-Ratios of Rates (F/M)	
	M	F		C.N.S. 750–752 †	Other 753–759		C.N.S.	Other
Northern Ireland	582	638	1·096	343	477	41·8	1·67	0·74
Scotland	586	613	1·045	846	1,368	38·1	1·35	0·73
Ireland (Eire)	695	709	1·020	711	1,102	39·2	1·51	0·73
Netherlands	408	400	0·979	1,096	3,018	26·6	1·45	0·77
England and Wales	435	415	0·955	4,501	10,159	30·7	1·47	0·73
Canada	461	438	0·949	2,748	5,711	32·5	1·25	0·75
Hungary	676	627	0·927	—	—	—	—	—
Germany F.R.	476	435	0·914	5,082	13,744	27·0	1·22	0·77
Belgium	488	438	0·898	742	2,076	25·4	1·09	0·81
Italy	369	330	0·894	3,295	11,307	22·6	1·14	0·74
Czechoslovakia	470	419	0·889	840	3,108	21·3	1·11	0·79
Israel	517	458	0·886	156	739	17·4	0·09	0·82
U.S.A.	379	334	0·881	—	—	—	—	—
Australia	395	345	0·873	778	2,781	21·9	1·16	0·74
Greece	352	306	0·869	282	1,695	14·2	0·92	0·77
Switzerland	434	376	0·867	428	1,344	24·2	1·09	0·76
Denmark	454	396	0·856	268	1,081	19·9	1·18	0·75
Japan	215	184	0·855	1,101	12,072	8·4	0·95	0·80
Norway	364	310	0·852	179	682	20·8	0·99	0·74
Austria	469	398	0·850	450	1,874	19·4	1·43	0·70
Venezuela	196	166	0·848	536	1,950	21·3	1·08	0·76
Finland	403	338	0·844	336	932	16·5	1·13	0·77
France	399	317	0.815	1,631	10,746	13·2	0·95	0·72
New Zealand	409	303	0·812	210	752	21·8	1·19	0·70
Sweden	362	292	0·806	319	1,165	21·5	0·98	0·70

*Calculated from date tabulated by W.H.O. (1967)
†Anencephaly, spina bifida, hydrocephalus groups only

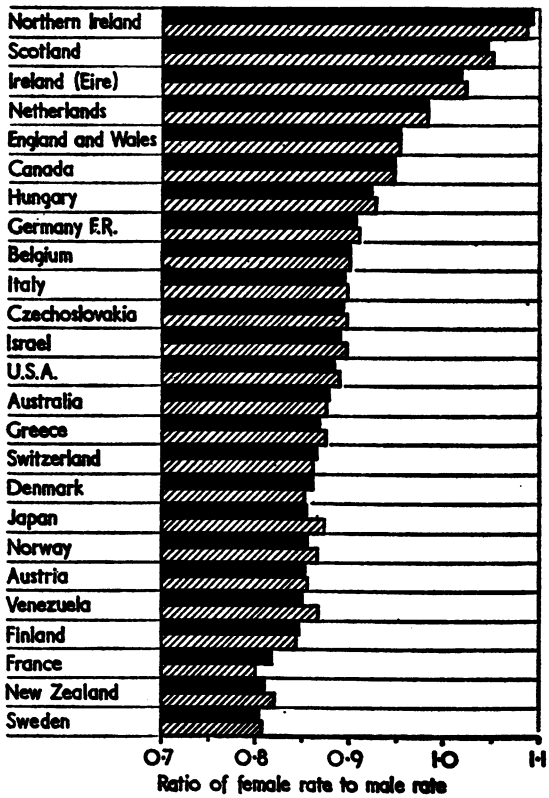

FIG. 1. Ratio of female to male mortality from congenital malformations at 0–1 and 0–4 years of age in 25 countries, 1957–66, based on numbers of live births of the sex in question.
0–1 years ■■■ 0–4 years //////

Australia, New Zealand, Germany and Denmark give ratios from 1·25 to 1·18, whilst Norway, Sweden, France, Japan, Greece and Israel have ratios below unity. The variations in ratios in the third and last two columns of the table cannot be explained by accidental factors such as differences in recording and classifying. Prenatal deaths could not be taken into account in this table owing to lack of data for most countries, but comparison with Table IV for England and Wales shows that inclusion of the stillborn increases the sex ratio for the central nervous system from 1·47 to 1·83 and for all malformations combined from 0·95 to 1·20. This is due to a higher proportion of fetal deaths among females affected by nervous system malformations than among males so affected, and this probably occurs in all countries. The remarkable feature is that the female excess among the liveborn infants with neural-tube anomalies is so much greater in the British Isles, the Netherlands and Canada than in Scandinavian countries.

The main conclusion from Table I is that there must be some factor at work in the British Isles, and perhaps in the Netherlands, Canada and Germany, which tends to increase the incidence of congenital malformations of the neural tube among female infants, and this will be investigated further in the next sections where regional variations within England and Wales are considered.

Regional Distribution of Congenital Malformations in England and Wales

The Registrar General uses two systems of division into regions: (1) Standard regions of which there were 11 in 1957–64 and 10 in 1965–66, of which 5 were subdivided into the conurbations and the remainder of the region (see footnote to Table II); (2) Hospital regions of which there are 15, with boundaries more suitable for hospital administration. Both systems have been used in the present

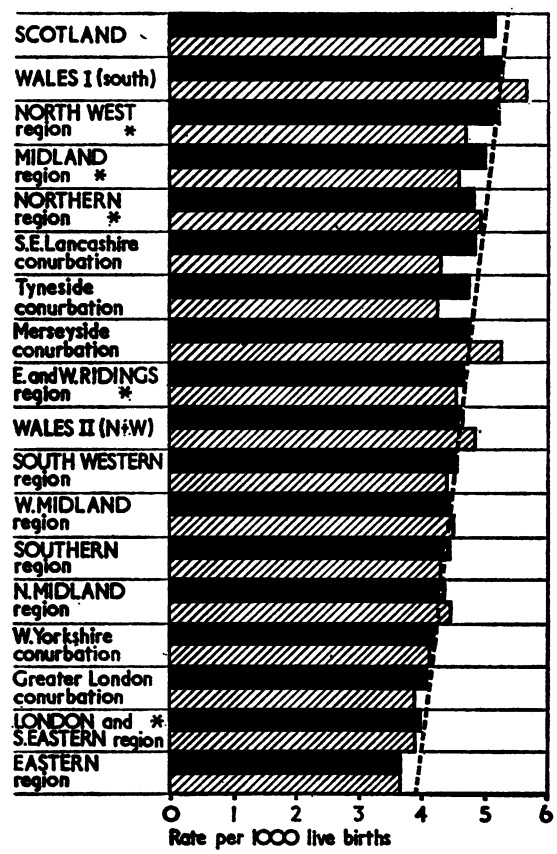

FIG. 2. Infant mortality of males and females attributed to congenital malformations in standard regions and conurbations of England and Wales, 1957–66, and in Scotland, 1963–66. (*Standard region excluding conurbations within it.)
Males ■■■ Females //////

TABLE II

MEAN ANNUAL DEATHS FROM CONGENITAL MALFORMATIONS IN MALES AND FEMALES AT AGES 0–1 AND 1–4 AND RATES PER 1,000 LIVE BIRTHS IN STANDARD REGIONS AND CONURBATIONS, 1957–66*

Standard Region	Malformation Deaths at Age-period 0–1 year		Rates per 1,000 Live Births at 0–1 year		No. of Deaths at 1–4 years		Addition to Rate at 0–1 year		Sex Ratio of Female/Male Rate at Age	
	M	F	M	F	M	F	M	F	0–1 year	0–4 years
Conurbations										
Tyneside	874	325	4·69	4·32	30	20	0·38	0·26	0·92	0·90
South East Lancashire	1,079	905	4·78	4·25	93	81	0·42	0·38	0·89	0·89
Merseyside	680	709	4·68	5·23	72	48	0·49	0·24	1·12	1·14
West Yorkshire	641	597	4·20	4·13	70	61	0·43	0·43	0·98	0·96
West Midland	989	938	4·41	4·45	100	87	0·45	0·41	1·01	1·00
Greater London	2,258	2,054	4·06	3·86	248	213	0·44	0·38	0·95	0·95
*Standard region**										
South-Western	1,274	1,158	4·42	4·37	114	153	0·40	0·20	0·99	0·99
Southern	917	850	4·37	4·25	103	90	0·49	0·47	0·97	0·96
London and South-Eastern†	737	697	3·96	3.93	90	91	0·48	0·57	0·99	1·01
Eastern	1,057	920	3·63	3·61	124	104	0·43	0·41	0·99	0·99
Northern†	1,082	1,038	4·79	4·88	78	77	0·34	0·36	1·01	1·02
Midland†	1,128	986	4·98	4·59	103	118	0·45	0·32	0·92	0·94
Wales I (south-east)	865	841	5·19	5·31	67	80	0·40	0·50	1·02	1·04
Wales II (rest)	290	252	4·63	4·33	26	23	0·42	0·39	0·93	0·93
North-Western†	1,235	1,064	5.13	4.70	121	98	0·57	0·43	0·92	0·91
East and West Ridings†	821	761	4·64	4·54	61	63	0·34	0·37	0·98	0·96
North Midland	1,156	1,109	4·34	4·45	122	96	0·48	0·38	1·02	1·01
Scotland	1,076	989	5·12	4·97					0·97	

* In 1965–66 some regions were altered and the above refer to the regions as defined in 1957–64. It was not possible to obtain figures for 1965–66 for the Southern, London and South Eastern, Eastern, East and West Ridings and North Midland regions nor for Greater London, and the data in the table are for 1957–64 for those areas. Comparability of the mean annual rates and of the sex ratios is not affected appreciably.
† Excluding conurbations

study but the relevant data for the standard regions and conurbations are limited to the deaths by sex and age from total congenital malformations and the total live and stillbirths by sex, and these have been aggregated for the 10 years 1957–66. Since the numbers of stillborn with malformations are not tabulated for this series of regions by the Registrar General for the whole period, the rates at ages 0–1 and 1–4 in Table II represent deaths registered at those ages per 1000 live births for the sex in question.

For the Hospital Regions in 1963–66 more information has been obtained, including supplementary data by sex and separate cause for stillbirths (furnished by the Registrar General), making possible the calculation of rates per 1000 live and stillbirths shown in Tables III and IV.

Table II shows that the mean annual death rates of male infants from all congenital malformations in the six conurbations were highest in the northern areas of south-east Lancashire (4·78), Tyneside (4·69) and Merseyside (4·68), lower in the West Midlands (4·41) and West Yorkshire (4·20) conurbations and lowest in Greater London (4·06). In the standard regions excluding conurbations the male rates were highest in South Wales (Wales I) with 5.19, and the North West (5·13), followed by the Midlands, Northern, East and West Ridings of Yorkshire and the rest of Wales. This is made clear in Fig. 2 which also shows that Scotland had a rate of about 5 as in the North West and Wales I. Male rates below 4·4 occur in the whole of the Eastern, South-Eastern and Southern regions, as well as in the North Midlands.

The rates for female infants have a similar distribution, exceeding 5 in Merseyside and South Wales and less than 4 in the Eastern and South-Eastern regions. Figure 2 shows that the female rate is much below that of males in South-East Lancashire and Tyneside conurbations and in the North-West and Midland regions, but the distribution is similar to that for males. The sex ratio of female to male mortality at 0–1 year exceeds unity in Northern England, South Wales, North Midland regions and in Merseyside and West Midland conurbations, and is under 0·95 in the rest of Wales and in Tyneside conurbation and Midland and North-Western regions. As noted in the last section, the most likely reason for a high female excess would be a higher proportion than average of malformations of the neural tube. This possibility can be examined by analysing the hospital regional data for 1963–66 where combined live and stillbirth rates have been calculated.

Table III shows the mean annual death rates in 1963–66 in the 15 Hospital Regions (which incorporate the conurbations within those areas) based on the prenatal deaths occurring after the 28th week of pregnancy and postnatal deaths at 0–1 year for

TABLE III

MEAN ANNUAL RATES OF MORTALITY BETWEEN THE 28th WEEK OF PREGNANCY AND 1 YEAR OF AGE PER 1,000 LIVE AND STILLBIRTHS CLASSED TO CONGENITAL MALFORMATIONS OF THE CENTRAL NERVOUS SYSTEM AND OTHER PARTS OF THE BODY FOR EACH SEX IN HOSPITAL REGIONS, 1963–66

Hospital Region	Males Mean annual rates, 1963–66*					Females Mean annual rates, 1963–66				
	A	B	C	A–C	Other	A	B	C	A–C	Other
Liverpool	1·58	1·31	0·71	3·60	3·82	3·95	1·97	0·85	6·77	2·79
Welsh	1·09	1·81	0·84	3·67	3·63	4·54	2·50	0·73	7.77	2·63
Manchester	1·48	1·18	0·74	3·40	3·65	3·52	1·55	0·68	5·75	2·65
Newcastle	1·23	0·82	1·06	3·21	3·73	3·28	1·79	0·88	5·95	3·02
Wessex	1·12	1·04	0·73	2·89	3·67	2·44	1·13	0·51	4·08	3·27
Birmingham	1·14	0·79	0·81	2·74	3·77	2·81	1·38	0·58	4·77	2·53
Leeds	1·08	0·77	0·60	2·45	4·05	3·08	1·09	0·58	4·75	2·78
Sheffield	1·11	0·57	0·69	2·37	4·01	3·09	1·36	0·65	5·03	2·92
North-East Metropolitan	0·94	0·60	0·69	2·23	4·08	1·90	1·24	0·43	3·57	2·98
South-Western	1·00	0·78	0·59	2·37	3·94	2·75	1·29	0·56	4·60	2·96
South-East Metropolitan	0·93	0·53	0·56	2·02	3·96	2·16	0·90	0·45	3·51	3·07
East Anglia	0·71	0·49	0·71	1.91	3·94	2·42	1·05	0·53	4·00	3·36
Oxford	0·91	0·77	0·45	2·15	3·24	2·74	1·35	0·44	4·53	2·58
South-West Metropolitan	0·71	0·53	0·33	1·57	3·76	1·93	0·55	0·43	2·91	2·64
North-West Metropolitan	0·80	0·46	0·52	1·78	3·52	1·82	0·96	0·49	3·27	2·67
England and Wales	1·11	0·81	0·68	2·60	3·73	2·77	1·35	0·59	4·70	2·91

A = Anencephaly (Y 38·0, 750)
B = Spina bifida (Y 38·2, 751)
C = Hydrocephalus (Y 38·1, 752)
Other = Remaining malformation groups (Y 38·3, 753, other nervous system and sense organs; Y 38·4–7, 754–9, other systems)
For totals of all congenital malformations, see first columns of Table IV

each sex per 1000 live and stillbirths. The malformations have been divided by cause into those due to the neural-tube anomalies—anencephaly, spina bifida and hydrocephalus (stillbirth rubrics Y 38·0, Y 38·2, Y 38·1 and infant mortality categories 750, 751, 752)—and those due to other forms of malformation (Y 38·3 to Y 38·7 and 753–759). Table IV expresses the groups as percentages of all malformations and shows the sex ratios for each of the two groups.

The regions are ranked in order of the total rate for males, as also in Figure 3 where the excess of female over male rates arising from inclusion of the prenatal deaths is seen in every region. The male rate is over 6·85 per 1000 live and stillbirths in Scotland and in the Liverpool, Welsh, Manchester and Newcastle regions, and rates under 5·85 occur in the Western Metropolitan regions and in Oxford. For females the geographical distribution is similar, with high rates of 8·4 or more in the Northern areas,

TABLE IV

RATES OF MORTALITY FROM ALL CONGENITAL MALFORMATIONS PER 1,000 LIVE AND STILLBIRTHS FOR EACH SEX, PROPORTIONS AFFECTING THE CENTRAL NERVOUS AND OTHER SYSTEMS, WITH SEX RATIOS OF FEMALE TO MALE RATE, IN HOSPITAL REGIONS, 1963–66

Hospital Regions and Scotland	Total Rates for All Malformations		Percent in Groups A, B, C (A–C) of the Nervous System			Sex Ratios of Rates			
	M	F	M	F	M+F	All Forms F/M	Group A–C F/M	Other F/M	Deaths at 0–1 F/M*
Liverpool	7·42	9·56	48·5	71·0	60·5	1·29	1·88	0·73	0·95
Welsh	7·20	10·40	51·0	74·7	67·3	1·44	2·12	0·72	1·00
Manchester	7·05	8·40	48·2	68·4	59·0	1·19	1·69	0·73	0·84
Newcastle	6·93	8·97	46·3	66·3	58·6	1·29	1·85	0·81	0·98
Wessex	6·56	7·35	44·1	55·5	50·0	1·12	1·41	0·89	0·94
Birmingham	6·51	7·30	42·1	61·2	52·7	1·20	1·74	0·67	0·95
Leeds	6·50	7·53	37·7	63·1	48·2	1·17	1·94	0·69	0·89
Sheffield	6·38	7·95	37·1	63·3	51·2	1·25	2·12	0·73	0·93
North-East Metropolitan	6·31	6·55	35·3	54·5	44·8	1·04	1·60	0·73	0·89
South-Western	6·11	7·55	38·6	60·9	50·9	1·24	1·94	0·75	0·93
South-East Metropolitan	5·98	6·58	33·4	53·3	44·3	1·10	1·74	0·77	0·88
East Anglia	5·85	7·56	32·6	54·3	44·3	1·28	2·09	0·85	0·88
Oxford	5·37	7·31	40·0	62·0	53·3	1·38	2·12	0·80	1·00
South-West Metropolitan	5·33	5·55	29·5	52·4	40·8	1·04	1·86	0·69	0·79
North-West Metropolitan	5·30	5·96	33·6	54·9	45·6	1·12	1·89	0·76	0·84
England and Wales	6·33	7·61	41·1	61·8	52·2	1·20	1·83	0·75	0·91
Scotland	7·76	10·77	46·5	66·7	57·9	1·41	1·99	0·87	0·98

*Ratio for death rates at 0–1 year per 1,000 live births (all forms of malformation)

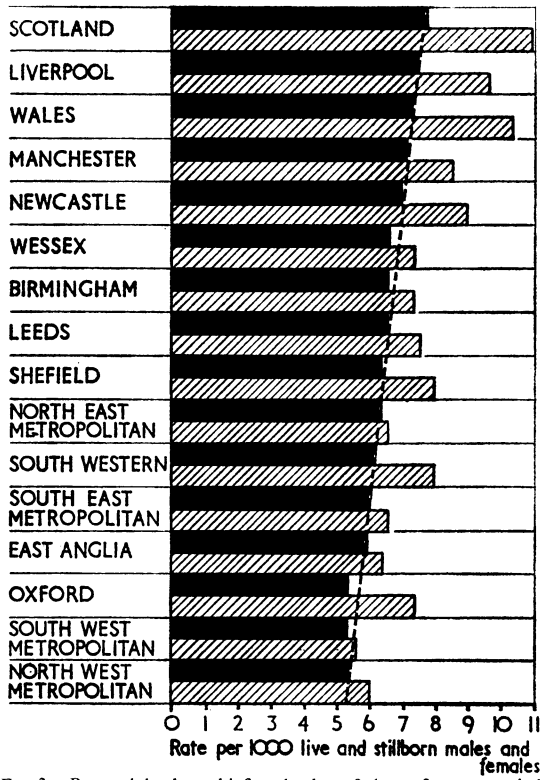

FIG. 3. Prenatal deaths and infant deaths at 0–1 year fromc ongenital malformations per 1000 live and stillborn males and females in hospital regions of England and Wales and in Scotland, 1963–66.
Males ■■■■ Females //////

Scotland and Wales and rates below 7 in the Metropolitan regions. Figure 3 shows that the largest female excess occurs in Scotland and in the Welsh, Liverpool, Newcastle, Manchester, Oxford, Sheffield and South-West regions, and in Table IV it is seen that the sex ratio between female and male rates for all malformations combined ranges from 1·44 in Wales to values from 1·04 to 1·12 in the Metropolitan regions and Wessex.

Regional Differences in Rates According to Nature of Malformation

The total prenatal and postnatal deaths in England and Wales during 1963–66 from the *various types of congenital malformation* as defined in Tables III and IV are shown in Table V.

TABLE V

	Males				Females			
	A	B	C	D	A	B	C	D
Prenatal (after 7 months)	1,645	476	935	854	4,290	738	727	707
Postnatal under 1 year)	340	981	286	5,832	445	1,561	274	5,185
Total	1,985	1,457	1,221	6,686	4,735	2,299	1,001	5,974

In Table III, where the regions are ranked in descending order of the male rate for all malformations (see the first column of Table IV) it is seen that the rates for the three divisions of the central nervous system (A, B, C) all show a ranking similar to that of the total malformations. Group A rates for males (anencephaly) are highest in the North and North-West (over 1·2) and lowest in the Metropolitan regions, East Anglia and Oxford (under 0·95), and for females they are highest in the North, North-West and Wales (over 3·2) and lowest in the Metropolitan regions (under 2·2). In group B (spina bifida) male rates are highest in the North, North-West, Wales and Wessex (over 0·9) and lowest in the Metropolitan, East Anglia and Sheffield regions (under 0·61), and female rates are highest in the North, North-West and Wales (over 3·2) and lowest in three of the Metropolitan regions and East Anglia (under 1·06). In group C (hydrocephalus) male rates are highest in the North, North-West, Wales, Birmingham and Wessex (over 0·72) and lowest in three Metropolitan regions and Oxford (under 0·57), and female rates are highest in the North, North-West and Wales (over 0·67) and lowest in the Metropolitan and Oxford regions. The three central nervous groups therefore have a strong north-west to south-east downward trend in mortality for each sex.

In contrast to this the group of all other congenital malformations shows no variation in regional rates which could not be explained by chance. Thus, for the first four regions in the table the average rates are 3·68 for males and 2·77 for females, and for the last four they are 3·62 for males and 2·82 for females. It can be concluded from this that the factors responsible for the regional distribution in Fig. 3 *affect only malformations of the central nervous system and not other forms.*

Table IV also shows that the percentage of groups A–C (neural tube) in the total malformations of both sexes ranged from 67 in Wales and about 59 in the North and North-West to less than 45 in the Metropolitan regions and East Anglia. The ranking of the percentages agrees rather closely with that of the sex ratio of death rates at 0–1 year from all forms of malformation, the correlation coefficient being + 0·72. Almost the same correlation (+ 0·71) was found between the percentage of central nervous groups (750–752) among the deaths from all malformations at 0–1 year and the sex ratio of the total death rate (for groups 750–759) in 23 countries as already noted.

Factors Underlying the Differences in Regional Incidence of Malformations

The regional distribution of the rates of combined prenatal and postnatal mortality (under 1 year) from congenital malformations of the central nervous system, shown in Fig. 4 as the mean rates for males and females, divides the country into a high-rate area in the North, North-West and Wales, a low-rate area south and east of a line from the Wash to the Bristol Channel and an intermediate midland zone together with Leeds. Table IV shows that this applies to rates for the central nervous defects in groups A–C but *not* to other malformations which exhibit no significant regional differences. There must be some factor or factors to account for this contrast and a point to notice is that distributions closely resembling Fig. 4 are found for cardiovascular diseases, and, though the correspondence is not so close, for nephritis, bronchitis and stomach cancer also.

In early studies of geographical pathology climatic factors were blamed for the northerly excess of mortality in general in England, and later air pollution was implicated for respiratory diseases, but these would not account for the high rates for many causes in Wales unless high rainfall was a factor. Epidemiological studies of cancer drew attention to the high incidence of gastric cancer in Wales and to the possibility that some constituents of water supplies might be responsible (Stocks, 1947, 1950). The geological map sketched in Fig. 5 helps to explain why hardness of water tends to be

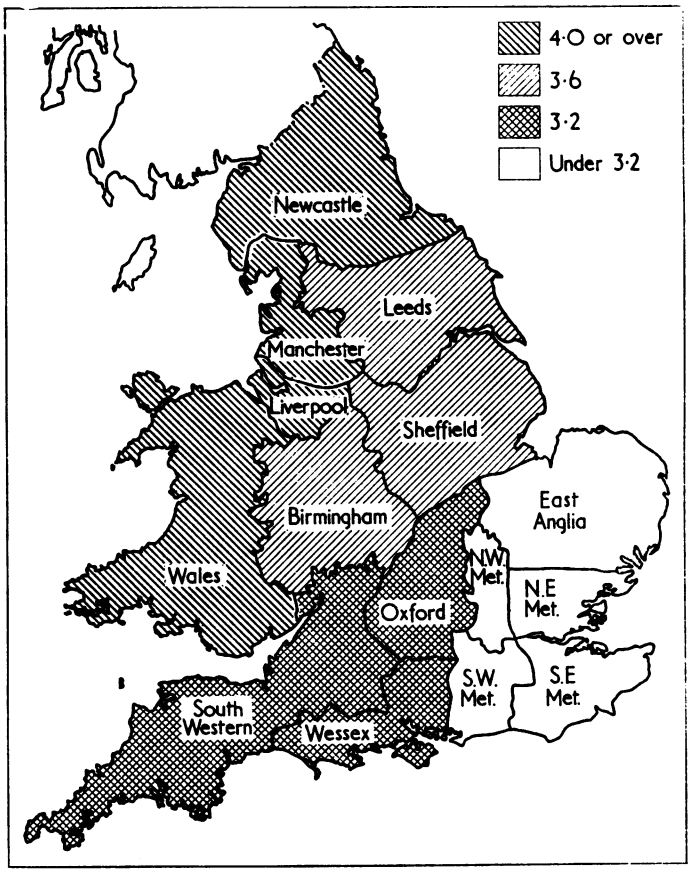

FIG. 4. Map of hospital regions of England and Wales showing distribution of mortality between the 28th week of pregnancy and 1 year of age per 1000 live and stillbirths classed to congenital malformations of the central nervous system (groups A–C) 1963–66. (Mean of rates for males and females.)

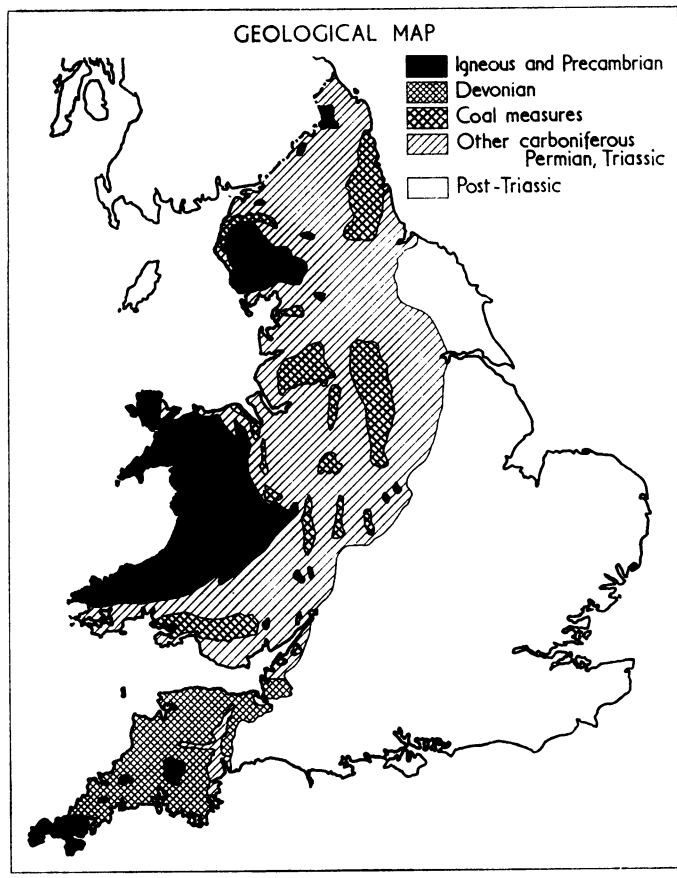

FIG. 5. Geological map showing general distribution of outcropping strata according to age.

TABLE VI

DEATH RATES OF FEMALES AGED 25–54 IN 1963–66 FROM CARDIOVASCULAR DISEASES, NEPHRITIS, STOMACH CANCER, BRONCHITIS AND ALL OTHER CAUSES IN HOSPITAL REGIONS OF ENGLAND AND WALES

Hospital Regions (ranked by malformation rates of males as in Table IV)	Mean Annual Rates per Million in 1963–66							
	Chronic Rheumatic Heart	Coronary Disease	Other Heart Disease	Vascular Lesions of C.N. S.	Nephritis and Nephrosis	Stomach Cancer	Bronchitis	All Other Causes
Liverpool	188	228	92	216	27	61	69	168
Welsh	179	213	86	228	36	50	52	166
Manchester	174	234	87	253	28	59	82	176
Newcastle	152	236	72	226	32	65	73	168
Wessex	82	122	68	165	23	48	29	162
Birmingham	115	146	74	213	30	50	54	169
Leeds	141	190	53	192	28	56	67	167
Sheffield	139	159	72	191	32	51	63	155
North-East Metropolitan	114	141	46	161	24	51	37	156
South-Western	97	139	59	210	29	42	35	167
South-East Metropolitan	92	130	71	167	22	36	37	175
East Anglia	57	113	57	167	21	38	31	152
Oxford	77	120	60	154	18	49	29	147
South-West Metropolitan	90	123	45	166	24	41	35	174
North-West Metropolitan	89	128	49	155	20	41	34	175
Mean regional rates	119	161	66	191	26	49	49	165

greater in the south and east than in the north and west and Morris *et al.* (1961, 1962), and more recently Crawford *et al.* (1968), demonstrated the surprising fact that mortality from most cardiovascular diseases in the county boroughs was strongly associated with softness of their water supplies and negatively correlated with the amounts of calcium present. A very careful search was made for other social and chemical factors which might account for this but nothing definite emerged except the 'water factor' and an ill-defined 'latitude' factor. Calculation of water indices characterizing whole regions would be difficult owing to the number of local sources involved, and it is only possible to postulate that differences between such indices in respect of the amount of one constituent might account for the curious distributions of mortality.

In Table VI the mean annual death rates of women aged 25–54 during 1963–66 are given for causes of death whose regional frequency pattern resembles that for congenital malformations of the central nervous system in Figure 4. Such causes fall into the following groups comprising the international categories shown in parentheses:

Cardiovascular
- Chronic rheumatic heart disease (410–416)
- Coronary disease (420)
- Other degenerative, hypertensive and ill-defined heart disease (421–443)
- Vascular disease of central nervous system (330–334)

Other diseases
- Nephritis and nephrosis (590–594)
- Cancer of stomach (151)
- Bronchitis (500–502)

In the final column are the rates for all other causes of death at 25–54 years.

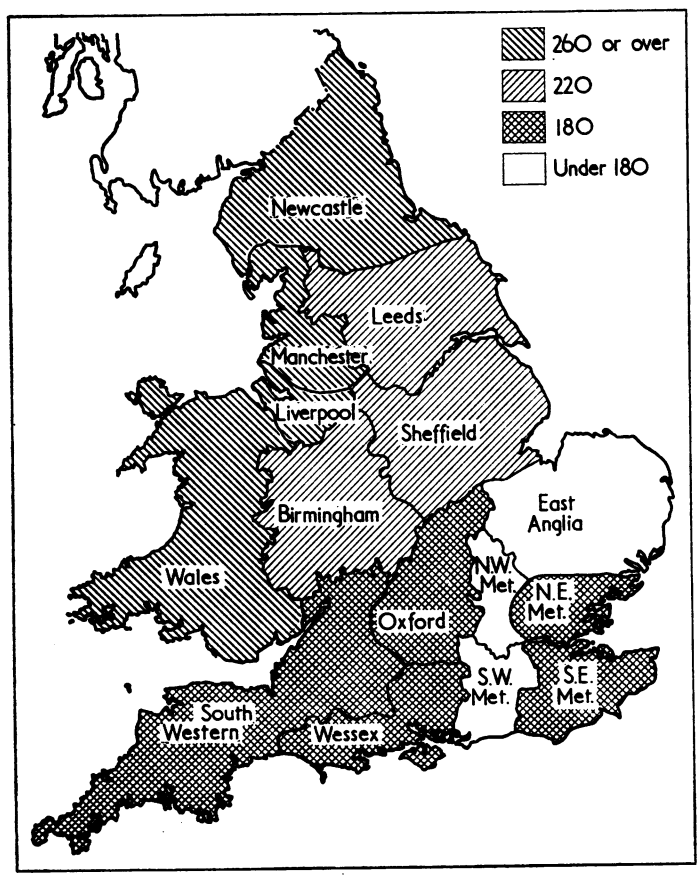

FIG. 6. Map of hospital regions of England and Wales showing distribution of death rates per million women aged 25–54 from all non-rheumatic heart disease, 1963–66.

For clarity the 15 regions are ranked in descending order of the male rates for all congenital malformations as given in the first column of Table IV. The cardiovascular groups have highest rates in the first four regions of the North, North-West and Wales (the only exception being Birmingham for 'other heart'), and they have lowest rates in the last four regions and Wessex (exceptions being the North-East Metropolitan region for 'stroke' and 'other heart' and Leeds and the South-West regions for 'other heart'). A map for any of these causes would be hardly distinguishable from Fig. 4. This point is illustrated in Fig. 6 which shows the distribution of mortality due to non-rheumatic heart disease. Stomach cancer shows a similar distribution, being highest in the North and North-West (and in Wales at more advanced ages) and lowest in the last six regions and Wessex. For nephritis and bronchitis the correspondence with the malformation rates is less pronounced though for both causes the rates are above average in the first four regions and below average in the last four. For the group of all other causes no regional pattern is evident.

Evidence that some regional factor accounts for the correspondence between the frequencies of congenital malformation in infants and of certain diseases in the adult population would be strengthened if the correspondence appeared for specific types of malformation and not for the others. In Table VII correlation coefficients have been calculated between the regional rates for malformations of the central nervous system (groups A–C in Table III) and the deaths rates of women aged 25–54 from the causes identified in Table VI; and corresponding coefficients are shown for all other forms of congenital malformations. The outcome of the extensive calculations required for Table VII is unexpected and astonishing, for a very clear-cut difference appears between the right- and left-hand parts of the table. Malformations of the neural tube (A–C) correlate very closely with mortality of women from each of the cardiovascular disease groups with coefficients all exceeding +0·8 whereas other malformations produce only insignificant negative coefficients. With nephritis, cancer of the stomach and bronchitis the coefficients with the nervous system malformations are between +0·62 and +0·75 whereas with other malformations they are negative or insignificant. The residual group of all other causes of death in women produces no correlations with either group of malformations except a small but not significant negative coefficient with 'other' malformations in female infants. It is to be noted that the size of the coefficients with the neural-tube malformations differs little between the sexes of the infants.

The conclusion to be drawn from these findings seems to be that whatever may be the environmental or genetic factors responsible for the regional mortality pattern shown by cardiovascular diseases, with a falling trend of rates from north-west to south-east, some of the same factors also have pronounced effects on the incidence of congenital malformations of the central nervous system but not on other forms of malformation. In lesser degree this seems to apply also to nephritis, stomach cancer and bronchitis. The nature of the regional factors remains in doubt, but the findings of Morris and his co-workers on soft water as a factor tending to increase mortality from cardiovascular diseases in the large towns point to a water factor as being probably important, and it is conceivable that differing calcium contents of water supplies might account for the regional variations of C.N.S. malformations in Tables III and IV.

TABLE VII

CORRELATION COEFFICIENTS BETWEEN PRENATAL AND INFANT MORTALITY FROM CONGENITAL MALFORMATIONS OF EACH SEX AND DEATH RATES OF WOMEN AGED 25–54 FROM CERTAIN CAUSES IN THE 15 HOSPITAL REGIONS DURING 1963–66, DISTINGUISHING CENTRAL NERVOUS FROM OTHER MALFORMATIONS

Causes of Death of Women aged 25–54 (rates of dying in the same regions)	Congenital Malformations, Prenatal and Under 1 year			
	Of Central Nervous System		Of Other Parts of Body	
	Males	Females	Males	Females
Chronic rheumatic heart disease (410–6)	+0·845	+0·871	0·000	–0·361
Coronary disease (420)	+0·844	+0·828	+0·033	–0·250
Other degenerative and hypertensive and ill-defined heart (421–443)	+0·867	+0·803	–0·174	–0·167
Vascular lesions of central nervous system (330–334)	+0·840	+0·908	–0·111	–0·311
Nephritis and nephrosis (590–594)	+0·620	+0·747	+0·159	+0·003
Cancer of stomach (151)	+0·747	+0·708	–0·052	–0·067
Bronchitis (500–502)	+0·678	+0·650	+0·123	–0·267
All other causes	+0·174	+0·017	+0·050	–0·310

SUMMARY

In 25 countries during 1961–65 the sex ratios of female to male rates of infant mortality attributed to congenital malformations were higher in Ireland, Scotland, England and Wales, the Netherlands and Canada than in any other country and were low in Scandinavia. Analysis according to the part of the body affected showed that the high rates arose from larger proportions of deaths from malformations of the neural tube and a greater excess of females in that group.

When England and Wales were divided into standard regions and conurbations the infant mortality of males in 1957–66 from all malformations combined were highest in the North and North-West and in Wales, and lowest in the East, South-East and South. Female rates exceeded those of males in Northern and North Midland regions, and South Wales and in the Merseyside and West Midland conurbations.

When prenatal deaths were combined with postnatal deaths at 0–1 year the rates per 1000 live and stillbirths in the Hospital Regions during 1963–66 were highest for both sexes in the Liverpool, Welsh, Manchester and Newcastle regions, and lowest for males in the western Metropolitan areas and Oxford, and for females in the Metropolitan areas. The downward trend in incidence from north-west to south-east is even more striking for the neural-tube malformations, and the sex ratio for these ranged from 1·4 to 2·4. No regional trend appears, however, for other congenital malformations.

Death rates of women aged 25–54 from each group of cardiovascular diseases show a closely similar regional distribution to that for the neural-tube malformations, with correlation coefficients exceeding 0·8; nephritis, stomach cancer and bronchitis also show a similar pattern with correlations over 0·6. None of these causes shows any association with other kinds of malformation. Rates from all other diseases of women show no correlation with any form of malformation. It is concluded that there must be some factor, genetic or environmental, which affects at the same time the incidence of congenital malformations of the central nervous system and mortality of women from the diseases mentioned.

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