GENETIC AND OTHER FACTORS

IN THE

AETIOLOGY OF SCOLIOSIS

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GENETIC AND OTHER FACTORS IN THE AETIOLOGY OF SCOLIOSIS

Scoliosis is defined as a lateral curvature of the spine, and may be non-structural or structural. Postural and compensatory scoliosis (resulting, for example, from a short leg) are non-structural, that is, totally correctable. They are not serious curves, their importance lying chiefly in differential diagnosis from structural scoliosis, with which this thesis is concerned.

Structural scoliosis is a lateral curvature of the spine accompanied by rotation of the vertebrae and is a fixed, non-correctable deformity. It ranges from a mild or even transient curve to one of the most severe progressive deformities known, causing death from cor pulmonale in early middle age.

The reason for the development of a structural fixed curve is often obscure, and the basic pathological error is not the same in all cases. The major known aetiologies are:

(1) Poliomyelitis, the scoliosis resulting from assymetrical paralysis of intercostal and trunk muscles in childhood.

(2) Congenital scoliosis, resulting from congenital vertebral anomalies - the scoliosis itself may be present at birth or develop later as the child grows. There may, indeed, be no spinal curvature at all if anomalies on left and right sides balance one another.

(3) Rare disorders, many of them of unifactorial inheritance, including the muscular dystrophies, Marfan's syndrome, homocystinuria, syringomyelia, osteogenesis imperfecta and neurofibromatosis. The pathological reason for the development of scoliosis is sometimes clearer in this group than in the next one, being often associated

with a demonstrable muscle, nerve or bone lesion. There are now over forty conditions described (many of them extremely rare), in which scoliosis may be a feature.

(4) Idiopathic scoliosis. This, the commonest of all types of scoliosis, is put last because the diagnosis can only be made after careful clinical and radiological examination excludes all other known causes of scoliosis.

This thesis deals exclusively with the two common types of structural scoliosis, idiopathic and congenital, which, now that poliomyelitis is almost unknown in Britain, together account for the vast majority of all cases.

The method of research has been by family studies, in order to determine the family incidence in comparison with the general population incidence; to note any pattern of inheritance; to assess the significance of associated anomalies and the role of environmental factors.

I D I O P A T H I C S C O L I O S I S

Introduction. Studies of idiopathic scoliosis from this and other centres have established that there is a high family incidence of the same deformity compared with the frequency in the general population, but the precise nature of any genetic factor has not been determined, nor the role of such environmental factors as regional distribution, social class, pregnancy and birth history.

The aim of this present investigation was to obtain larger numbers of patients than in a previous Edinburgh survey (Wynne-Davies, 1968), in order to establish:

1) The frequency of idiopathic scoliosis in the family compared with the general population incidence.
2) The pattern of inheritance.
3) Clues relating to disordered tissue(s).
4) The role of environmental factors.

This latter point, environmental factors, was felt to be particularly important in view of the fact that in North America there are practically no reports of idiopathic scoliosis occurring in infants from birth to three years of age, although scoliosis occurring around the age of 10 - 15 years appears to be as common as in Britain and Europe.

Since genetic factors are likely to be very similar on both sides of the Atlantic, the difference in frequency (if confirmed) would point to some environmental factor present in Britain but absent in North America.

Following the 1968 Edinburgh survey, a similar study had been planned and carried out in Wilmington, Delaware, and another in Boston, Massachusetts -

this latter one being planned jointly with myself and the subsequent analysis being done in Edinburgh (vide infra). One of the aims of the current Edinburgh survey, therefore, was to compare findings with these two new American studies.

Previous literature

Early literature on idiopathic scoliosis is confused, particularly in relation to rickets and to neurofibromatosis. Clinical data relating to idiopathic scoliosis as a separate entity has only been available for about twenty years (Ponseti and Friedman 1950, James, 1951 and 1954).

In Britain and Europe there are two peaks of incidence in the age of onset of the curve: in infancy (birth to three years) and in adolescence (ten years to the end of growth), with rather fewer new cases appearing in the middle years of childhood (four to nine years). There are certain curious clinical differences between the three age groups, (infants, juveniles, and adolescents) summarised in Table 1.

Table 1.
Clinical Types of Idiopathic Scoliosis

Type	Age of onset	Sex ratio	Convexity of curve
Infantile	Birth - 3 years	3 male: 2 female	4/5 left
Juvenile	4 - 9 years	Equal	Left & right equal
Adolescent	10 years to end of growth	6-8 females:1 male	4/5 right

It will be seen that in infants there is a preponderance of left sided curves, and the deformity is more common in males; in juveniles, left and right sided curves occur equally, and the sex ratio is equal; whereas in adolescents, a high proportion of curves occur in girls, and are right-sided.

There are references to what is probably hereditary idiopathic scoliosis in the European literature of the last century but the first definite reports of inheritance in this condition in the English literature were in 1934 (Garland, 1934 and Rutherford, 1934). The first large family survey was carried out in Germany by Faber (1936) of a condition which he termed 'rachitic scoliosis', which was almost certainly adolescent idiopathic scoliosis: he himself came to the conclusion that rickets was not the true aetiology in his cases. This was a remarkable survey in that he traced 660 index patients, examined most of them personally, carrying out radiography on parents and sibs. He found 26.4 per cent of families with another individual affected, (7 per cent of sibs and 13.5 per cent of parents), several pedigrees illustrating full dominant inheritance. It is probable, though not certain, that we are discussing the same condition.

DeGeorge and Fisher (1967) conducted a survey from New York City, using medical records and tracing patients and relatives by means of a questionnaire. They concluded there was no evidence in support of a simple genetic basis for idiopathic scoliosis, though there was a familial concentration of cases. However, this is a difficult condition to diagnose accurately. There are probably some fifty different aetiologies of scoliosis and as the relatives in their survey were not examined by clinicians experienced in the problem, their figures cannot be seriously considered.

The first survey adequate by modern standards was conducted from 1962 - 1965 in Edinburgh, and first fully reported in 1968 (Wynne-Davies, 1968) when 114 index patients were studied and 27.2 per cent of families with more than one affected individual was noted, including 3 per cent of parents, 5 per cent of sibs and 5 per cent of the children of index patients. The screening of relatives in this survey was initially by clinical examination and subsequently the diagnosis was confirmed by more detailed examination and radiography.

Cowell, Nelson Hall and MacEwen (1969) reported on seventy-five cases from Wilmington, Delaware, and noted a high familial concentration of affected individuals. Parents and sibs all had a radiographic examination and approximately one-third of them were found to have a curve of more than 10 degrees. They suggested the disorder was of X-linked dominant inheritance in view of the excess of females and absence of inheritance from father to son in their survey. A survey from the U.S.S.R. (Abal'masova et al, 1970) also noted a strong familial concentration of cases with probable dominant inheritance. Filho and Thompson (1971) in Toronto analysed 201 families with idiopathic scoliosis, noting 7.2 per cent of sibs and 5.7 per cent of parents affected, and they concluded that multifactorial inheritance was probable.

The most recent report (Riseborough and Wynne-Davies, 1973) is the one previously referred to from Boston, Massachusetts. This survey confirmed the almost complete absence of infantile scoliosis in North America - an impression long held by orthopaedic surgeons on both sides of the Atlantic. The report is of 208 index patients with examination, including radiography, of nearly all their first degree relatives. 11.1 per cent of first degree relatives with a curve over 20 degrees were noted, and 2.4 and 1.4 per cent of second and third degree relatives respectively. The authors concluded that multifactorial inheritance was probable.

Infantile idiopathic scoliosis

The first large group of patients with infantile idiopathic scoliosis was described by James (1951), and a further group by him in 1954. He noted two forms, resolving and progressive scoliosis. The curve was rarely present (or noticed) at birth but tended to develop during the first few months of life, with the characteristic high proportion of males and of left-sided curves (James, Lloyd-Roberts and Pilcher, 1959). The 1968 Edinburgh survey noted that 50 per cent of infants attending the Edinburgh Scoliosis Clinic with idiopathic scoliosis were of the resolving type and 50 per cent progressive. All had plagiocephaly, with the 'recessed' side of the head always the same side as the convexity of the curve. However, the true proportion of resolving curves was probably higher, as many of them would not be referred to hospital and might not even be noticed. Lloyd-Roberts and Pilcher (1965) estimated that 90 per cent of infantile idiopathic curves resolved.

Preliminary work by Hay (1971) in investigating the plasticity of the infant axial skeleton, noted that plagiocephaly was not apparent in normal infants at birth but developed during the first few weeks of life. He thought that its onset was related to the side of habitual lying of an infant, this perhaps being aggravated if the child was bundled up with clothes and unable to move. He speculated that this habitual posture could be a possible cause of idiopathic scoliosis in this age group.

There had been speculation for many years before, particularly by Browne (1956), that posture in utero could cause infantile scoliosis. More recently, Dunn (1969) and Watson (1971) have considered the problem of infantile 'postural' deformities, and concluded that in utero pressures are likely to be one cause of 'positional' deformities such as scoliosis,

torticollis, clubfoot and congenital dislocation of the hip. However, it is difficult to account for the fact that scoliosis (like plagiocephaly) is not seen at birth, or only very rarely so. It is during the first few weeks or months of life that they both become apparent.

A significantly high proportion of mothers over the age of thirty years at the time of the birth of children who subsequently developed adolescent scoliosis was noted in three surveys: (deGeorge and Fisher, 1967, Wynne-Davies, 1968, Riseborough and Wynne-Davies, 1973).

Various developmental anomalies associated with idiopathic scoliosis have been reported, the commonest being mental retardation, congenital dislocation of the hip, congenital heart defects and structural anomalies of the upper limb (Wynne-Davies, 1968, Conner, 1969). It is, however, usually noted that the majority of patients with adolescent idiopathic scoliosis are completely normal in all other respects. There has been speculation as to whether patients with idiopathic scoliosis and mental retardation were unsuspected cases of homocystinuria, but an investigation carried out in Edinburgh (Brenton, Dow, James, Hay and Wynne-Davies, 1972) showed that this was not the case.

MATERIAL

An attempt was made to include all patients with idiopathic scoliosis who had attended the Edinburgh Scoliosis Clinic (both private and National Health Service patients) since its beginning in October 1958 to the end of December 1968. The total number of patients was 267, of whom 200 were traced and form the index patients of this survey.

The reasons for failing to include the remaining sixty-seven were as follows:

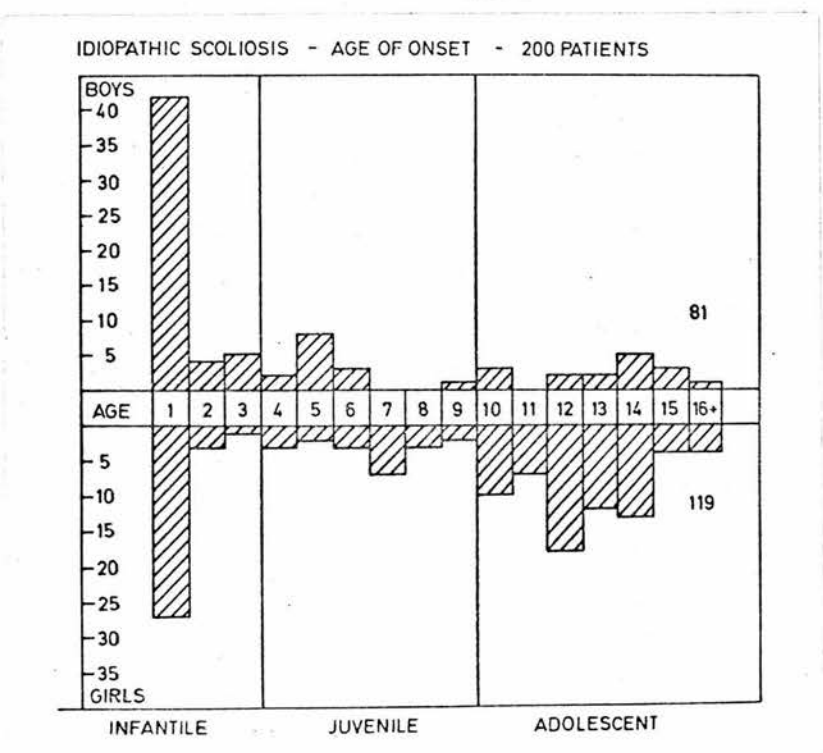
3 foster children with no family data
1 dead
21 overseas
12 discharged patients now living a long distance from Edinburgh
23 not traced
7 refused to co-operate

The very small number (7 of 267, 2.6 per cent) refusing to take part in the survey is noteworthy.

The 200 index patients came chiefly from Edinburgh, Fife and the Lothians, but since this is a specialist clinic, some attended from other parts of Scotland, Northern England and there were a few referrals from further afield. For certain epidemiological aspects of the survey only data from the sixty-nine patients living within the city of Edinburgh was analysed.

The numbers of patients divided according to sex and age of onset are shown in Figure 1.

Fig. 1



There were eighty-two infants, eighty-four adolescents and thirty-four juvenile patients.

During the survey it became apparent that more information was needed for the group with infantile idiopathic scoliosis, particularly in relation to the season of onset of the curve, social class and side of lying during early infancy. A further fifty-two patients (twenty-eight male, twenty-four female) were therefore added, all of whom first attended the Edinburgh Scoliosis Clinic after December 1968.

At the beginning of the current Edinburgh survey it was suspected that the association between mental retardation and idiopathic scoliosis was significant, and an investigation of the inmates of a large mental hospital near Edinburgh was carried out. A total of 698 mentally retarded individuals were examined (396 males, 302 females, nearly all of them adult).

Some figures obtained from the scoliosis survey required comparison with those from a normal population and the following material and sources have been used:

1) The Registrar General for Scotland; Annual Reports, 1939-67.
2) The Edinburgh Register of the Newborn, 1964-68. 692 normal newborn children with data relating to pregnancy and birth history, social class, parental age, parity and month of birth.
3) A survey of Edinburgh Schools and Infant Clinics carried out by myself in order to determine the population incidence of idiopathic scoliosis in normal children (Wynne-Davies, 1968). 11,087 individuals were examined (5,442 males, 5,645 females).

4) 223 normal infants between the ages of two weeks and six months were examined in the postnatal clinics of a maternity hospital and in the City Infant Clinics to determine the incidence, age and season of development and social class of plagiocephaly. (116 of these had been examined during the 1968 Edinburgh survey).

METHOD.

In the main group of 200 Edinburgh index patients the method of research was by family studies, the principles being:

1) to establish the proportions of the relatives of the index patients with idiopathic scoliosis, note any genetic pattern of inheritance, and compare the family figures with the incidence of idiopathic scoliosis in the general population,
2) to note any associated developmental anomalies in both index patients and relatives,
3) to note any possible environmental factors acting during pregnancy, birth or post-natally.

1. Proportions of affected relatives. The aim was to visit all families in their homes and to examine clinically all first degree relatives (parents, sibs and children). If asymmetry of the back was apparent, then these individuals were brought to hospital for further examination and radiography to establish the diagnosis by excluding other known causes of scoliosis.

A large number of second and third degree relatives were also visited and, when indicated, subsequently taken to a nearby hospital for

further examination and radiography. Hearsay evidence of scoliosis was not accepted.

In view of reports from Wilmington, Delaware, that their survey of relatives showed a high proportion of minor curves which were not easily detected clinically but apparent on radiology, it was decided routinely to radiograph all parents of those index patients living within the City of Edinburgh, whether or not a curve was suspected. 68 families took part in this aspect of the survey.

2. Associated developmental anomalies in index patient and relatives.

Enquiries were made relating to any congenital or developmental anomalies and if a positive history was obtained, then every effort was made to confirm the diagnosis by obtaining adequate medical records and visiting the patient at home. Hearsay evidence of abnormality was not accepted.

3. Environmental factors. A detailed history was obtained, usually from the mothers of index patients, relating to:

a) Maternal obstetric and gynaecological history

b) Illness during pregnancy

c) Parental age at the time of the birth of the index patient and parity of index patient

d) Birth history - gestation length, presentation, delivery and complications, birth weight of index patient and sibs

e) Seasonal variation

f) Father's occupation (as an index of social class)

g) Preference as to side of lying in the first few months of life of the patients with infantile scoliosis

The figures obtained from (a) to (f) were compared with those of the 'control' group of 692 normal children from the Edinburgh Register of the Newborn, 1964-68, or with the figures from the Annual Reports of the Registrar General for Scotland.

ADDITIONAL SURVEYS

Two subsidiary surveys were carried out in Edinburgh, one relating to mental retardation and one to plagiocephaly.

The methods were as follows:

1) Survey of a mental hospital. An examination was made of the 698 inmates of a large mental hospital near Edinburgh, in order to determine the incidence of idiopathic scoliosis among this selected group of mentally retarded individuals. The examination initially was clinical, and those in whom a curve was suspected were brought to the Edinburgh Scoliosis Clinic for further examination and radiography.

Care was taken to exclude mentally retarded patients with cerebral palsy or any other neurological condition which in itself could cause scoliosis.

2) Plagiocephaly in infants. It had been established in the 1968 Edinburgh survey that all infants with idiopathic scoliosis had plagiocephaly, with recession of the same side of the head as the convexity of the spinal curve. A limited survey was carried out on 107 normal infants between the ages of two weeks and six months attending the post-natal clinic of a maternity hospital. Material was also used from the previous control survey (116) in order to determine the age of onset of plagiocephaly, its incidence in normal children, the side affected, and its relationship to the season of the year and the social class of the family.

RESULTS

TRACING OF RELATIVES.

An attempt was made to trace and examine all first degree relatives, and only those individuals actually seen by us are included in the analysis. The proportions seen were as follows:

160 of 200 fathers	(15	dead,	20	not	traced	or	overseas,	5	refused	to	cooperate)
192 of 200 mothers	(4	"	1	"	"	"	"	3	"	"	")
156 of 211 brothers	(8	"	45	"	"	"	"	2	"	"	")
173 of 214 sisters	(7	"	32	"	"	"	"	2	"	"	")

(All 32 sons and daughters of index patients were seen)

Of these first degree relatives, only twelve of the 725 (1.7 per cent) who were available for visiting refused to help with the survey.

Second and third degree relatives were seen and examined only if within easy reach of Edinburgh, but information obtained from the 1968 Edinburgh survey has been included in this analysis, since some patients were in both surveys. (All first degree relatives, however, were re-visited for the current survey).

CLINICAL DATA.

(Findings only are noted in this section, their possible significance is discussed pp. 50-57).

Sex ratio. The figures showed the expected differences between infantile and adolescent groups, with boys being more frequently affected in infancy and girls at the later age. The juvenile group was intermediate in type (Table 2).

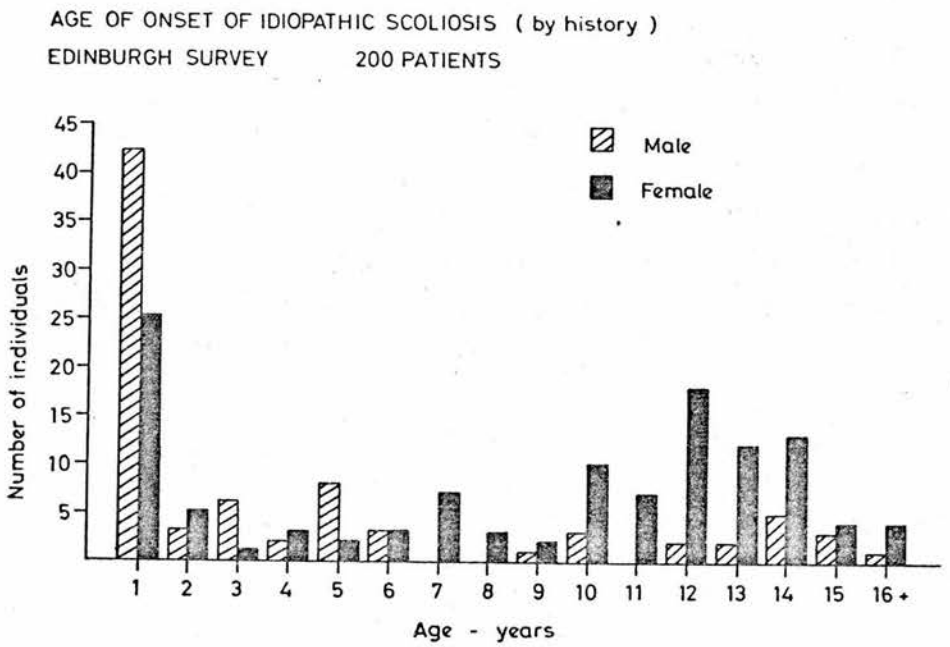
Table 2.

Edinburgh Survey - Sex Ratios

Edinburgh index patients	Males	Females	Sex ratio
Infantile scoliosis	51	31	1.6 (3 boys to 2 girls)
Juvenile "	14	20	0.70 (2 boys to 3 girls)
Adolescent "	16	68	0.24 (girls x 4)

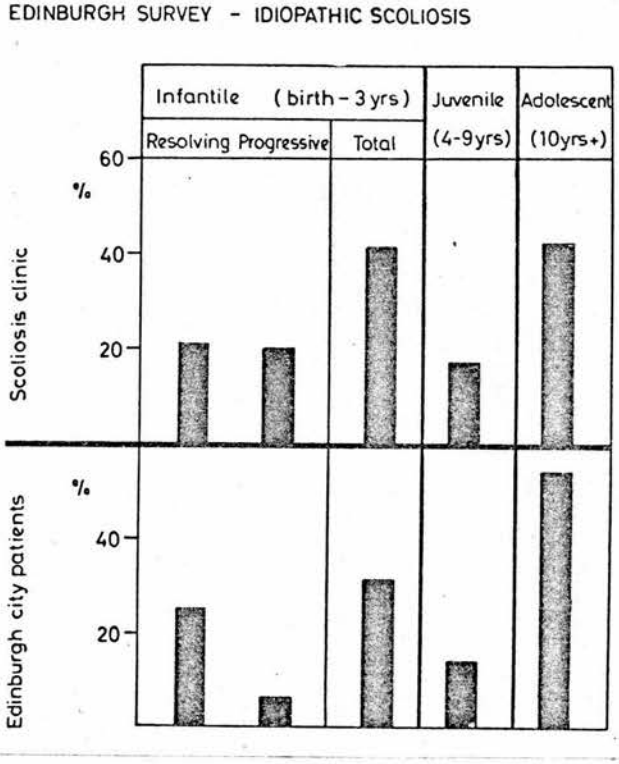
Age of onset. The survey showed the age distribution noted in the previous 1968 survey and in other British surveys with two peaks of incidence, one in infancy and the other in adolescence. (Fig. 2).

Fig. 2



41 per cent of the patients presented during infancy (birth to three years) and approximately half of these resolved and half progressed. However, since the Edinburgh Scoliosis Clinic is a specialist clinic to which the more severe and difficult cases are referred, the true incidence of resolving compared with progressive curves was likely to be different. The figures, therefore for those patients living within the City of Edinburgh were extracted (Fig. 3).

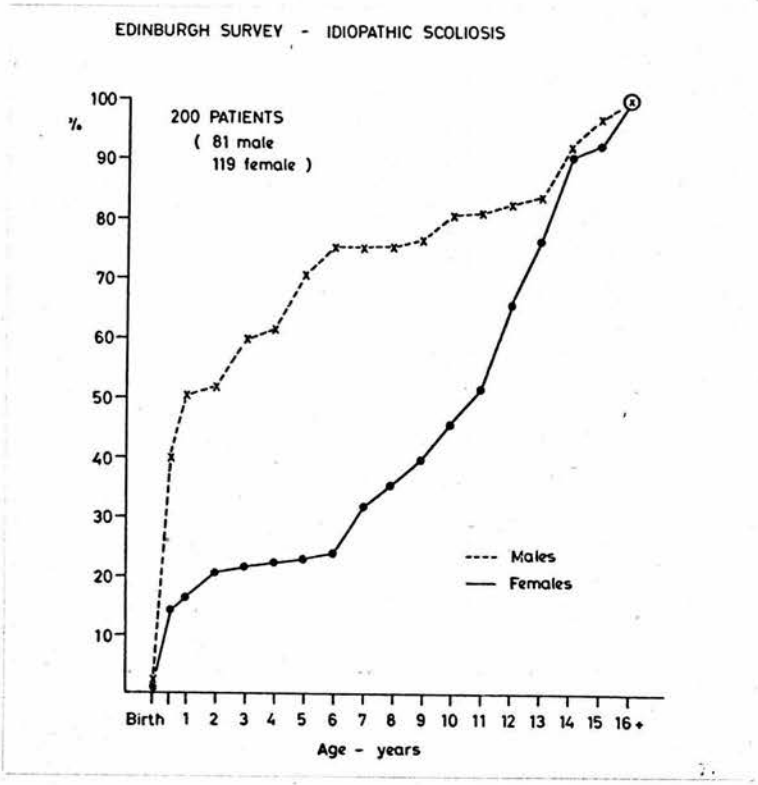
Fig. 3



Twenty-eight of sixty-one (45.9 per cent) of the total eighty-nine Edinburgh City patients presented during infancy, and of these, twenty-two resolved and only six progressed.

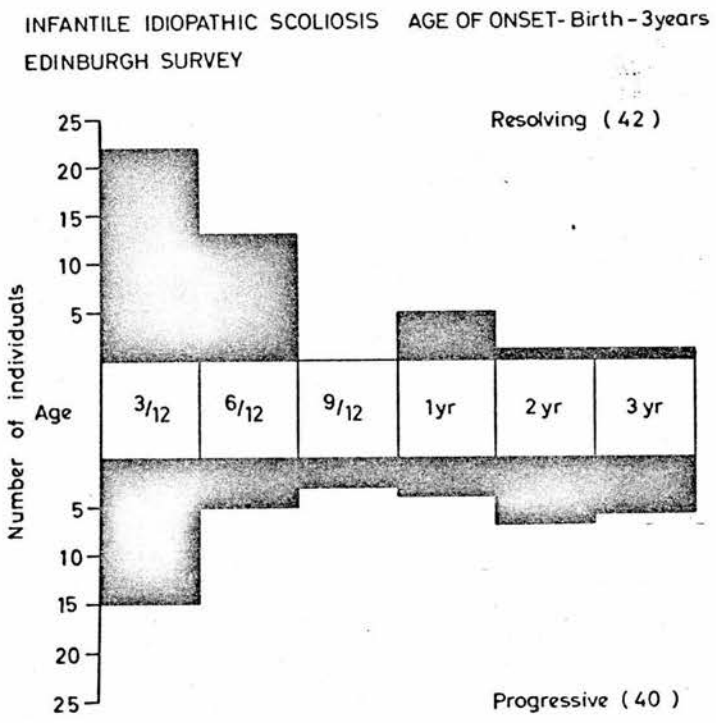
The cumulative totals of males and females attending the Scoliosis Clinic is shown for each year of age in Figure 4.

Fig. 4



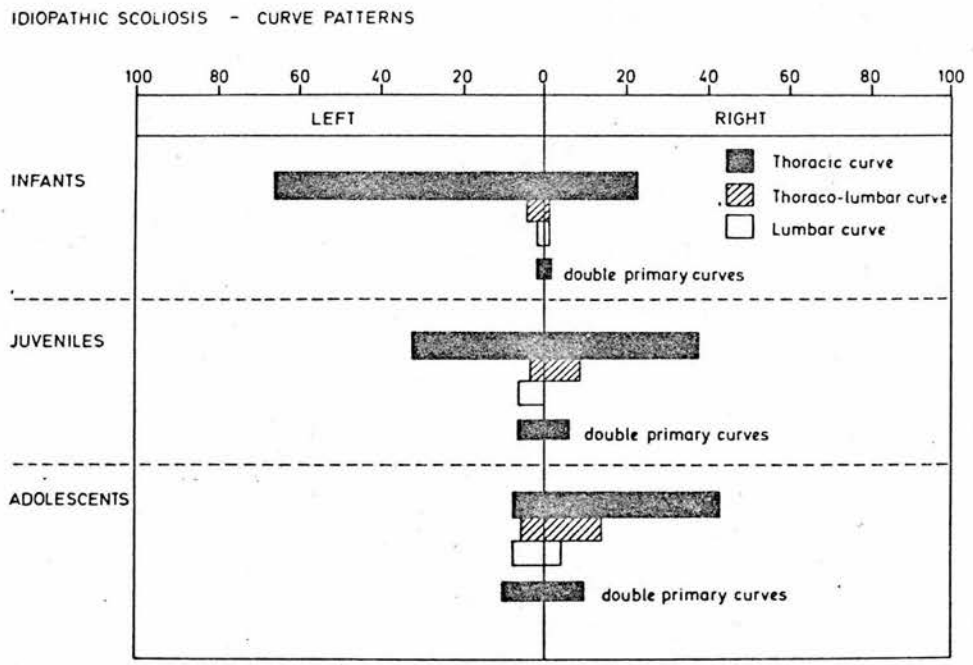
67 per cent of infants with idiopathic scoliosis developed the curve by six months of age. 83 per cent of all resolving curves presented by this age, though only 50 per cent of progressive curves (Fig. 5).

Fig. 5



Side and site of curve. The survey showed the expected preponderance of infants with left-sided thoracic curves, and a preponderance of adolescents with right-sided thoracic curves (Fig. 6), with almost equal left and right sided curves developing during the middle years of childhood. Double primary (or triple) curves were rare in infancy (2.4 per cent) but commoner in the older children (11.9 per cent of adolescents).

Fig. 6



Associated Anomalies. The commonest associated anomalies found in the index patients were as follows:

		Approximate frequency in the general population
Mental retardation	8% (males 13% females 6%)	1% ?
Congenital dislocation of the hip	3.5%	0.1 - 0.4%
Congenital heart disease (1 patent ductus 4 ventricular septal defects)	2.5%	0.4%
Inguinal hernia	7.4% of males	0.9% males (to 15 years of age)

No child with resolving scoliosis was mentally retarded, (Table 3).

Table 3

IDIOPATHIC SCOLIOSIS SURVEY
EDINBURGH

MENTAL RETARDATION

	Males	Females	Total
Infantile resolving	0	0	0
Infantile progressive	13%	0	7.5%
Juvenile	14%	15%	15%
Adolescent	13%	4%	6%
Total	13%	6%	8%

There was (with the exception of inguinal herniae) no excess of these associated anomalies amongst the relatives of index patients. There was a history of inguinal hernia occurring under the age of forty-five years in 6.5 per cent of fathers, 3.5 per cent of mothers and in 2.4 per cent of brothers.

(Plagiocephaly: see page 38).

PROPORTIONS OF AFFECTED RELATIVES

First degree relatives *

Twins In all cases twin pairs were discordant, only one affected with scoliosis. There were no monozygotic twins in this survey.

Infantile	idiopathic	scoliosis:	one male with twin sister one male with a dyzygotic twin brother
Juvenile	"	"	no twins
Adolescent	"	"	one female with dyzygotic twin sister one male with dyzygotic twin brother two females with twin brothers

Parents, sibs and children Since spinal curvature can develop at any age up to fifteen or sixteen years, it was necessary to devise a method of age correction for younger sibs who cannot, as it were, count their full weight. The graph of cumulative totals was used (Fig. 4), showing the percentage of males and females attending the clinic at each age. In correcting for age a young sister of six years, for example, only counts as 0.24 of a person, because at this age only 24 per cent of girls who will develop scoliosis have already done so. Thus the total number of sibs when corrected for age is less than the actual number of individuals seen.

The proportions of first degree relatives affected with the same deformity is shown in Table 4.

* Details of families with at least one affected first degree relative are in the appendix (page 109).

Table 4.

Edinburgh Survey

Proportions of affected 1st degree relatives
(Age corrected for sibs)

Index Patients	Fathers	Mothers	Brothers	Sisters	Total	
INFANTS						
Male (51)	2/43	2/49	0/29 (38)*	1/32 (40)	5/153 (78)	3.3%
Female (31)	0/24	1/31	0/25 (31)	0/20 (35)	1/100 (66)	1.0%
Total (82)	2/67	3/80	0/54 (69)	1/52 (75)	6/253 (144)	2.4%
JUVENILES						
Male (14)	0/13	0/14	0/10 (20)	0/9 (19)	0/46 (39)	-
Female (20)	1/17	3/20	0/8 (18)	1/8 (19)	5/53 (37)	9.4%
Total (34)	1/30	3/34	0/18 (38)	1/17 (38)	5/99 (76)	5.1%
ADOLESCENTS						
Male (16)	1/12	1/14	0/10 (14)	0/12 (14)	2/48 (28)	4.2%
Female (68)	2/51	5/64	1/25 (35)	4/34 (46)	12/174 (81)	6.9%
Total (84)	3/63	6/78	1/35 (49)	4/46 (60)	14/222 (109)	6.3%
ALL MALES (81)	3/68 (4.4%)	3/77 (3.9%)	0/49 (72) -	1/53 (73) (1.9%)	7/247 (145)	2.8%
ALL FEMALES (119)	3/92	9/115	1/58 (84)	5/62 (100)	18/327 (184)	5.5%
GRAND TOTAL (200)	6/160 (3.8%)	12/192 (6.3%)	1/107 (156) (0.9%)	6/115 (173) (5.2%)	25/574 (329)	4.4%

*The figure in brackets is the total number of sibs seen.
The figure preceding it is age-corrected.

The overall figures for affected parents, sibs and children are shown in Table 5.

Table 5.

Edinburgh Survey

Proportions of affected parents, sibs and children (10 degree curves and over)

Index patients	Parents	Sibs	Children
Infantile resolving (42)	2/74 (2.7%)	0/50	0
" progressive (40)	1/73 (1.4%)	1/56 (1.8%)	0/1*
Juvenile (34)	4/64 (6.3%)	1/35 (2.9%)	0/5*
Adolescent (84)	9/141 (6.4%)	5/81 (6.2%)	0/26*

*all under 6 years of age.

Taking the whole group of 200 index patients, approximately 5 per cent of parents and 3 per cent of sibs were affected. There was no significant difference between any of the age groups of index patients, though the infantile group had fewer affected relatives than the adolescent group.

The figures for male first degree relatives (fathers and brothers) and females (mothers and sisters) are shown in Table 6.

Table 6

EDINBURGH IDIOPATHIC SCOLIOSIS FAMILY SURVEY

1972

Proportion of 1st degree relatives with scoliosis

(10^{o} and over, age corrected)

Index patients	Males	Females	Total
	Fathers and brothers	Mothers and sisters	
200	7 of 267 (2.6%)	18 of 307 (5.7%)	25 of 574 (4.3%)

There were two instances of male index patients with an affected father - one patient had infantile resolving scoliosis and the other was of the adolescent type. Both fathers had curves of over 20 degrees, and in the case of the adolescent male patient, a paternal aunt was also affected.

If only curves of 20 degrees and over are considered, the proportions of affected relatives drops markedly (parents 0.75 per cent, sibs 1.6 per cent).

Comparison with frequency in general population The family figures were all obtained from clinical examination of patients' relatives followed by radiographic examination if a curve was suspected. The population survey conducted in Edinburgh in 1968 was carried out in the same manner, and thus the two sets of figures may be compared. The overall figure for the general population was 1.8 per 1,000, the lowest group being adolescent males (0.3 per 1,000) and the highest, adolescent females (3.9 per 1,000). Infants with scoliosis were approximately 1 per 1,000. The family figures are all significantly in excess of these.

The parents of the sixty-eight patients living within the City of Edinburgh were examined routinely by radiography, whether or not a curve was suspected. Results are shown in Table 7, where it is seen that the proportions affected are considerably higher than those found on clinical examination alone.

Table 7

EDINBURGH IDIOPATHIC SCOLIOSIS FAMILY SURVEY

1972

Proportion of parents with scoliosis on radiography

(10^{o} curves and over, Edinburgh City only)

Index patients	Fathers	Mothers	Total
68	11.9%	23.9%	17.9%

When curves of under 10 degrees were included, the proportions of first degree relatives affected was higher again, (19 per cent of fathers and 48.9 per cent of mothers). However, diagnosis of idiopathic scoliosis is doubtful in these very minor cases.

Second and third degree relatives Detailed figures of the proportions of second and third degree relatives with scoliosis are shown in Tables 8 and 9.

Table 8.

Edinburgh Survey

Proportions of 2nd degree relatives with scoliosis

Index patients	Male relatives	Female relatives	Total
Infantile - resolving (42)	0/177	1/201	1/378 (0.26%)
" - progressive (40)	1/241	1/247	2/488 (0.41%)
Juvenile (34)	4/183	2/196	6/379 (1.6%)
Adolescent (84)	2/456	3/484	5/940 (0.53%)
Total (200)	7/1,057	7/1128	14/2,185 (0.64%)

Table 9.

Edinburgh Survey

Proportions of 3rd degree relatives with scoliosis

Index patients	Male relatives	Female relatives	Total
Infantile resolving (42)	1/181	2/178	3/359 (0.84%)
" progressive (40)	1/301	0/261	1/562 (0.18%)
Juvenile (34)	1/239	2/209	3/448 (0.67%)
Adolescent (84)	0/500	2/489	2/989 (0.20%)
Total (200)	3/1,221	6/1,137	9/2,358 (0.38%)

The overall figures for second degree relatives was 0.64 per cent and for third degree, 0.38 per cent.

There was no significant difference between the proportions of affected relatives of male and female index patients, or between affected male and female relatives. Also there was no significant difference between paternal and maternal sides of the family.

CONSANGUINOUS PARENTS

In none of all 200 index patients were there any related parents.

SURVEY OF EDINBURGH MENTAL HOSPITAL.

A total of 698 inmates of a mental hospital were examined for idiopathic scoliosis, those identified on initial clinical examination were subsequently brought to the Princess Margaret Rose Orthopaedic Hospital for a more detailed examination and radiography. Results are shown in Table 10.

Table 10

SURVEY OF MENTAL HOSPITAL
EDINBURGH
Patients with idiopathic scoliosis

Males	Females	Total
14 of 342 (4.1%)	9 of 256 (3.5%)	23 of 598 (3.8%)

* Excluding 43 mongols and 57 patients with neurological disorders

An attempt was made to carry out family studies of the twenty-three mentally retarded scoliotic patients, and seventeen families were traced. Failure in six cases was due to:-

3 - no living relatives known
2 - only living relatives also mentally retarded
3 - failure to trace

A total of forty-seven first degree relatives were traced, only one of whom (a brother) had a very slight (10 degree) thoracic curve.

In the nineteen families for whom medical records were available, there was a history of mental retardation in:

1 father
3 mothers
5 of 16 brothers
5 of 11 sisters

That is, in 14 of 65 first degree relatives (21.5 per cent), which is much in excess of a general population frequency of perhaps 1 or 2 per cent.

EPIDEMIOLOGICAL DATA - ENVIRONMENTAL FACTORS

(a) Maternal obstetric and gynaecological history

There were no significant findings in the data collected:

Numbers of abortions and stillbirths
Age of starting menstruation
Length and regularity of menstrual cycle
Dysmenorrhoea
Age of menopause

(b) Maternal illness during pregnancy of index patient

There were no significant findings.

(c) Parental age and parity

A maternal age effect was found amongst the infantile progressive, the juvenile and the adolescent groups. There was a significant number of

the mothers over the age of thirty years at the time of birth of the index patient, when compared with the expected figures obtained from the Registrar General's reports (Tables 11 and 12 and Fig. 7).

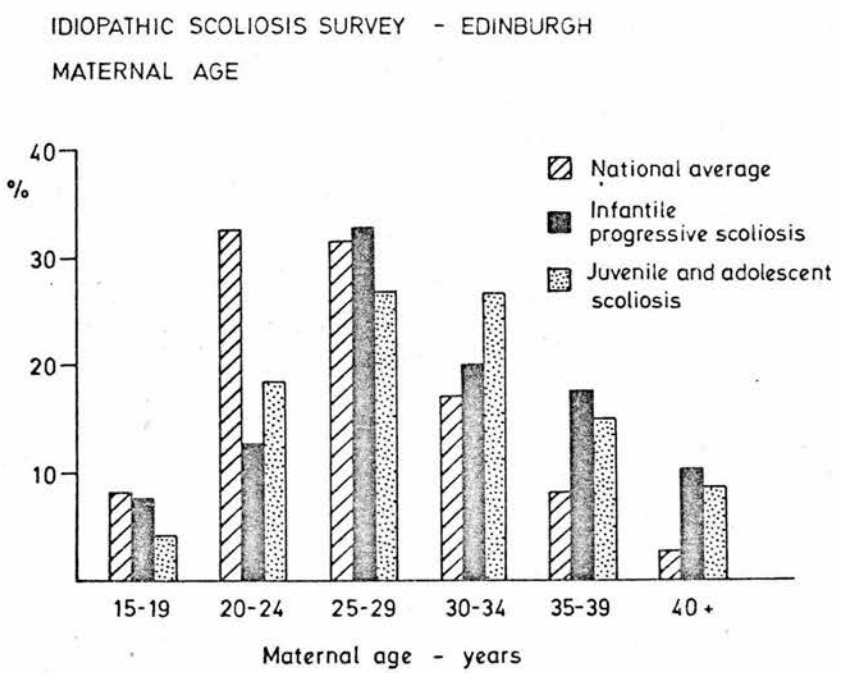
Table 11.
Maternal age
Infantile Progressive Scoliosis

Maternal age (yrs)	15-19	20-24	25-29	30-34	35-40	40+	Total
Observed	3	5	13	8	7	4	40
Expected	3.19	13.14	12.65	6.80	3.27	0.95	40
$x^2_{(2)} = 9.9$	$0.01 > p > 0.001$ Difference Significant						

Table 12.
Maternal age
Juvenile and adolescent scoliosis

Maternal age (yrs)	15-19	20-24	25-29	30-34	35-39	40+	Total
Observed	5	22	32	31	18	10	118
Expected	9.42	38.76	37.31	20.06	9.65	2.80	118
$x^2_{(4)} = 35.5$	$p < 0.001$ Difference Highly Significant						

Fig. 7



The 'expected' number of mothers over the age of thirty years is 28 per cent, but amongst the mothers of index patients with scoliosis, approximately 50 per cent were over this age. This effect was not apparent in the mothers of infants with resolving scoliosis.

The age difference between fathers and mothers showed a slight but significant difference from the national average in the group of adolescent girls with scoliosis - the fathers averaging 3.4 years older than the mothers, compared with the expected figure of 2.3 years. This figure of approximately three years older remained the same whether sporadic index cases were considered or cases in which there were affected relatives in the family.

A parity effect was shown amongst the adolescent group, in that there was a significant excess of first born children compared with the expected figure (Table 13).

Table 13.

Parity - Adolescent Scoliosis

	Parity			
	0	1	2+	Total
Observed	42	22	20	84
Expected	30.65	26.24	27.11	84
$x^2_{(2)} = 6.75$	0.05>p>0.02 Difference Significant			

(d) Birth history

For this aspect of the survey, those children presenting with scoliosis in the first six months of life were considered separately (fifty-five index patients) because there were significant findings relating to length of gestation, presentation and birth weight amongst this group, though not amongst those developing scoliosis from seven months of age onwards. This group is referred to as "early onset scoliosis". Control data for this analysis was obtained both from sibs of the index patients and from the Edinburgh Register of the Newborn.

Length of gestation and birth weight. There was a significant excess of males born prematurely (two weeks and more) who were also significantly underweight. Females were normal both in regard to gestation length and birth weight, (Tables 14 and 15).

Table 14

EARLY ONSET IDIOPATHIC SCOLIOSIS

PREMATURITY
(2 weeks and over)

Males	Females
10 of 35	2 of 20
(29%)	(10%)
(Controls 14%)	(Controls 16%)

Table 15.
Early Onset Scoliosis - Birth Weight
Male index patients

	Under Term	Others	Significance of Difference bet."under term" & "others"
Resolving	6lb 7oz ± 1.25lbs	7lb 14oz ± 1.18lbs	0.05>p>0.01 Significant
Progressive	5lb 4oz ± 1.02lbs	7lb 15oz ± 0.66lbs	0.05>p>0.01 Significant

In the whole survey there were only six patients in whom scoliosis was noticed at, or very soon after, birth, three males and three females. Each of the three males and one of the females were premature (four weeks, five weeks, ten weeks and one with dates not known, but the birth weight was under three pounds). (Table 16).

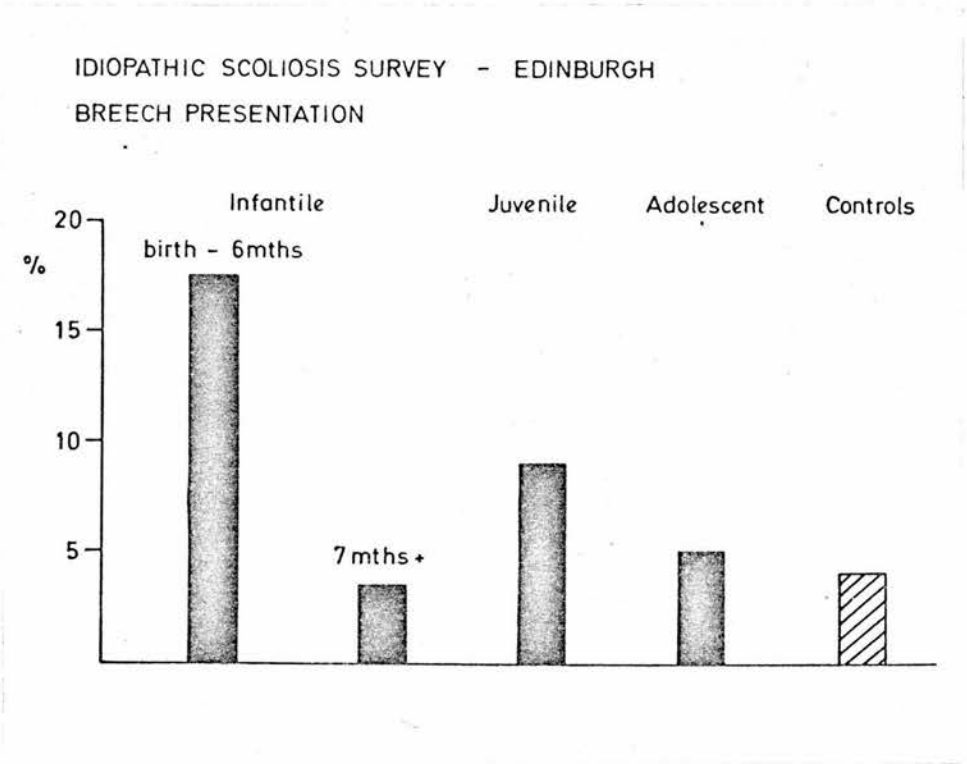
Table 16

INFANTILE IDIOPATHIC SCOLIOSIS SURVEY
EDINBURGH
6 patients diagnosed at birth

Birth history	Resolving or Progressive	Associated Anomaly
4 weeks prem Twin	Res. (M)	Large umbilical hernia
Normal	Pro. (F)	Joint laxity (14 yrs) Finger contractures
5 weeks prem. Breech	Res. (F)	Neonatal C.D.H.
10 weeks prem. Placenta praevia	Pro. (M)	-
Mother 46 years Prem. (2 lbs 12 oz)	Pro. (M)	M.D. Bilateral herniae
Normal	Res. (F)	C.D.H. (9/12)

Presentation. There was a significant excess of breech presentations in babies developing scoliosis in the first six months of life, but not thereafter (Fig. 8).

Fig. 8



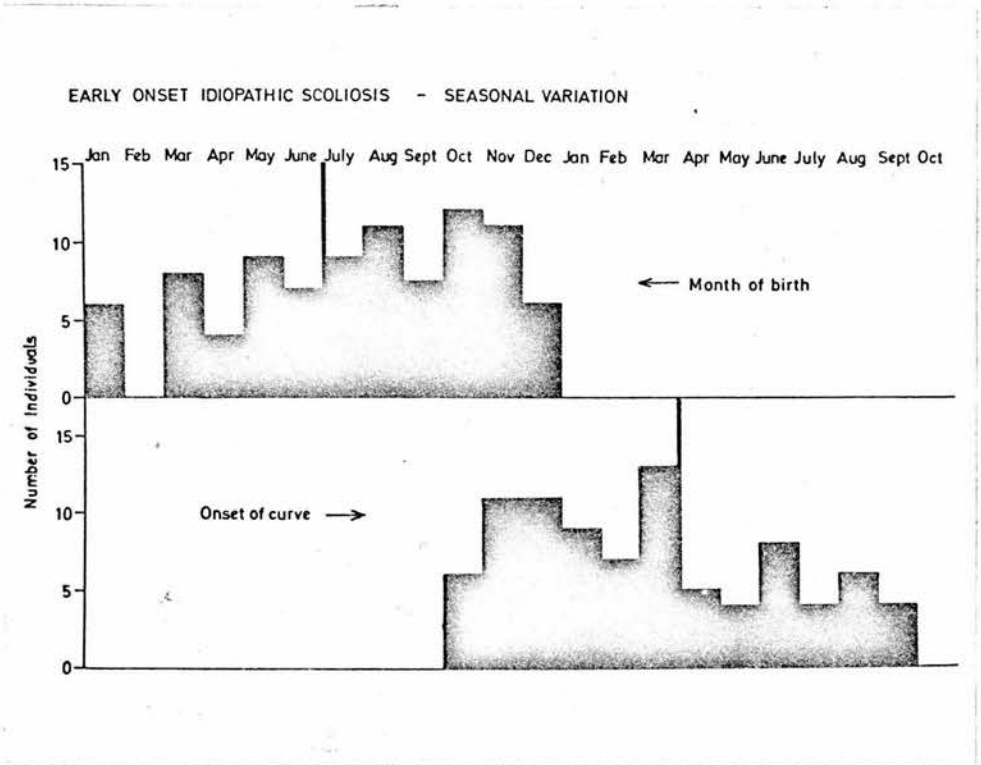
For the remaining investigation of environmental factors the number of infants was increased by fifty-two, all of whom attended the Edinburgh Scoliosis Clinic subsequent to 1968, thus making 134 infants in all, ninety of whom developed scoliosis in the first six months of life.

(e) Seasonal variation

Of the ninety infants who developed scoliosis in the first six months of life, 64 per cent were born during the second half of the year, July to December, and exactly the same proportion, 64 per cent, developed scoliosis during the two winter quarters (October to March), (Fig. 9). The ratio in each case was 1.8:1, whereas the expected ratio for normal babies born in the

first half of the year compared with the second half, is 1:1 (327:326, Edinburgh Register of the Newborn, Controls).

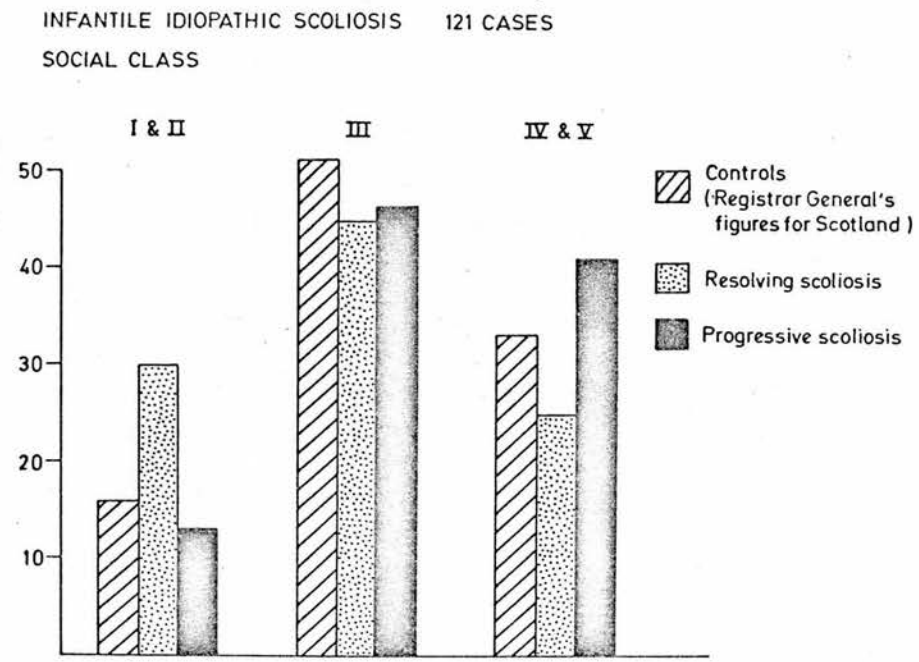
Fig. 9



(f) Social class

Data showed no statistically significant variation from the expected figures in any of the scoliosis groups. However, in the 121 cases of infantile scoliosis where information relating to the fathers' occupation was available, there was a difference which almost reached significance at the 5 per cent level between patients with resolving and progressive scoliosis. A higher proportion of the former were in the upper social classes, 1 and 2, and the latter in the lower socio-economic groups, 4 and 5 (Fig. 10).

Fig. 10



(g) Side of lying in early infancy

The mothers of ninety-one children developing scoliosis in infancy were questioned as to the child's preference in the first few months of life for lying on one side or the other, on his back, or prone. Retrospective history taking is notoriously unreliable, and the investigation proved to be equivocal. That is, infants with left-sided or right-sided curves were equally likely to lie on the concavity or the convexity of the curve - or on their backs.

However, the survey did establish that only 3 of 91 infants habitually lay prone. All three had resolving scoliosis.

PLAGIOCEPHALY.

Findings of the 1968 Edinburgh survey were confirmed in that all infants with idiopathic scoliosis also had plagiocephaly. That is, one whole side of the head appeared to have 'flowed backwards' resulting in asymmetry of the skull and face. The 'receding' side of the head corresponded always with the side of the convexity of the curve.

Examination of 223 normal infants between the ages of two weeks and six months (116 from the 1968 Edinburgh survey and 107 in 1969-70) showed that 28 per cent had a mild to moderate degree of plagiocephaly, the sexes being equally affected. There was a preponderance of left sided deformities (83 per sent) and one half of the children were in the lower social classes (4 and 5), compared to only one-quarter from the upper social classes 1 and 2.

It was also noted that, of those infants examined in the winter months (October - March), 30 per cent were affected, but of those examined in the summer months, only 8 per cent showed the deformity.

COMPARISON OF EDINBURGH, BOSTON AND WILMINGTON SURVEYS

Two visits of two weeks were made by me to the U.S.A. in 1971 and 1972, in order to examine material from scoliosis clinics and from family surveys completed in Boston, Massachusetts and the Alfred I du Pont Institute, Wilmington, Delaware.

Clinical features and the proportions of relatives affected with scoliosis were compared with the Edinburgh survey. The total number of index patients investigated is shown in Table 17.

Table 17

IDIOPATHIC SCOLIOSIS SURVEYS

NUMBER OF PATIENTS

	EDINBURGH	BOSTON	WILMINGTON	Total
Infantile	82	1	(2)	83
Juvenile	34	22	15	71
Adolescent	84	185	119	388
Total	200	208	134	542

Method

1) Boston. The initial planning of this survey had been carried out jointly with Dr. E.J. Riseborough. The clinical and family investigations were conducted from his scoliosis clinic, and the subsequent analysis done in Edinburgh. The aim, in addition to comparing clinical types on each side of the Atlantic, was to determine familial incidence of idiopathic scoliosis in

first, second and third degree relatives, to note any associated anomalies and to determine the parental age effect. All first degree relatives (parents and sibs only) were seen by him and radiographic examination carried out. Second degree relatives (grandparents, uncles and aunts) and third degree relatives (first cousins only) wherever possible were seen and examined. In the case of those living at a distance from Boston, diagnosis was made on radiographic examination only. It is probable, therefore, that figures for second and third degree relatives are less accurate than for first degree. However, it is unlikely that the diagnosis would be missed on radiography, only that too many would be wrongly included because of other aetiologies of scoliosis - thus proportions of second and third degree relatives found with a curve are likely to be too high. Analysis was based on 208 index patients and 2,662 relatives, (Riseborough and Wynne-Davies, 1973).

2) Wilmington. This survey had been completed by the time the current Edinburgh one started (Cowell, Nelson Hall and MacEwen, 1969), but the only difference between this and the Boston survey was that, by intention, only first degree relatives were included and any patient with an associated anomaly had been excluded. The examination of 134 index patients and 572 of their first degree relatives had been conducted essentially in the same manner as in Boston. That is, all index patients were seen personally by the authors, and first degree relatives were examined both clinically and radiographically for evidence of a curve.

Radiographs of all patients and relatives were seen by me in Wilmington, ensuring that the same criteria of diagnosis had been used as in Edinburgh and Boston. It was also possible to note from hospital records covering the period of the Wilmington survey, if any infant patients had

attended with idiopathic scoliosis together with associated anomalies - there were in fact two, both male. One had scoliosis and talipes equino-varus and the other had scoliosis with congenital heart disease and mental retardation.

Age of onset and sex ratio

The age of onset of spinal curvature in the two American surveys differed from the Edinburgh one in the virtual absence of idiopathic scoliosis under the age of six years, (Figs. 11 and 12).

Fig. 11

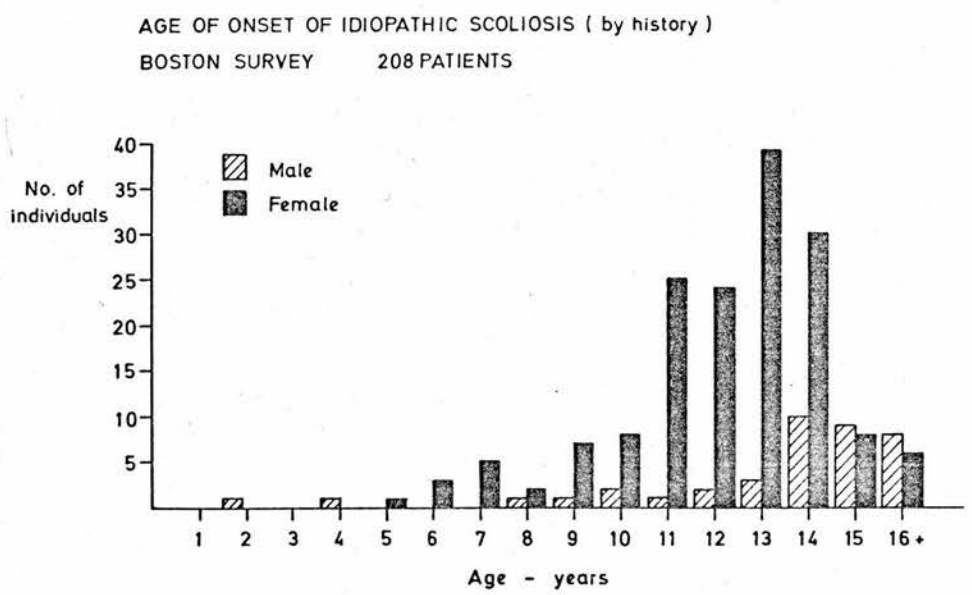
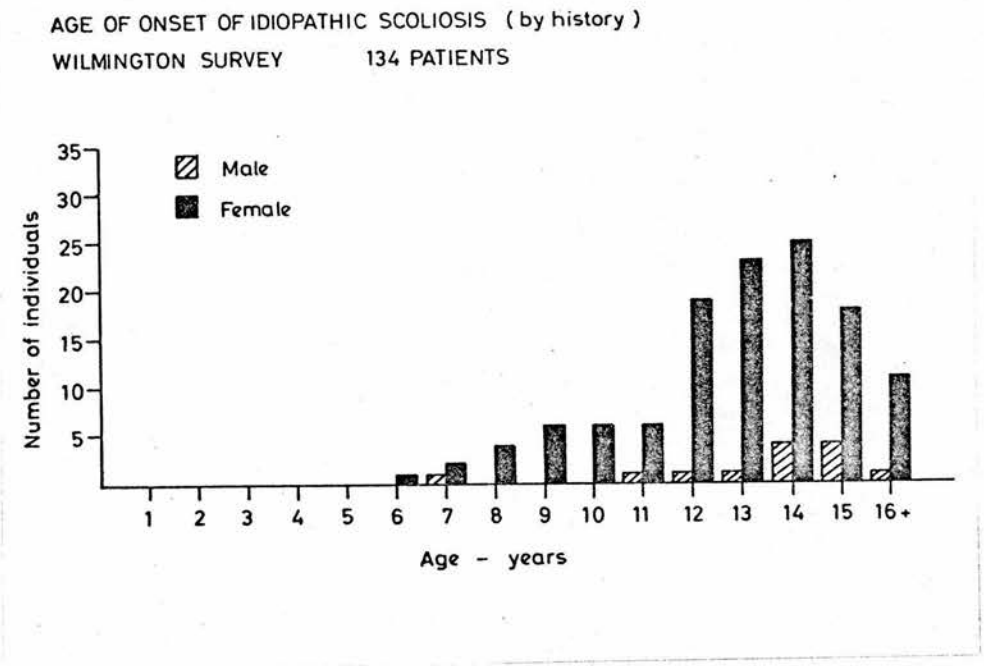


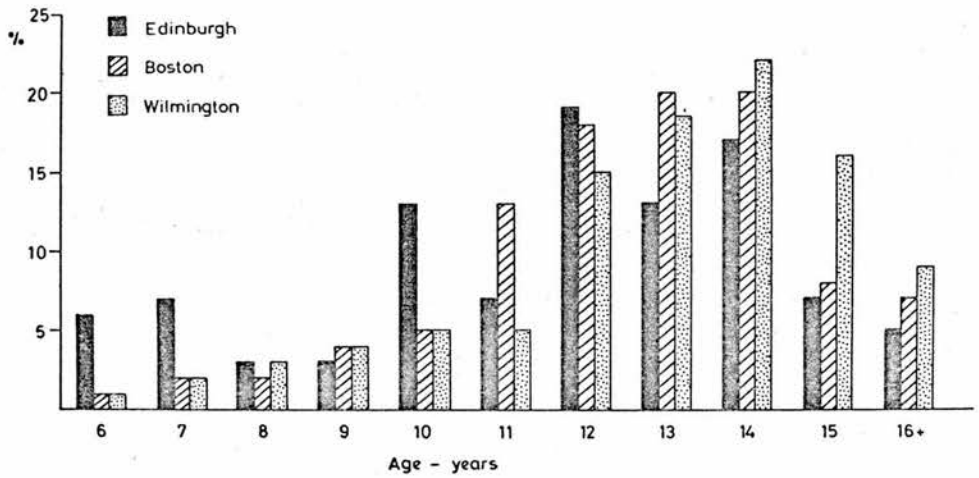
Fig. 12



If all patients in the Edinburgh survey under the age of six years are removed, the age distribution of all three surveys becomes very similar, (Fig. 13).

Fig. 13

AGE OF ONSET OF IDIOPATHIC SCOLIOSIS (by history) – 6 YEARS AND OVER
EDINBURGH , BOSTON & WILMINGTON SURVEYS 442 PATIENTS



The sex ratios of all three surveys was similar for adolescent cases, but there were more American girls with scoliosis in the juvenile group than in Edinburgh, (Table 18).

Table 18.

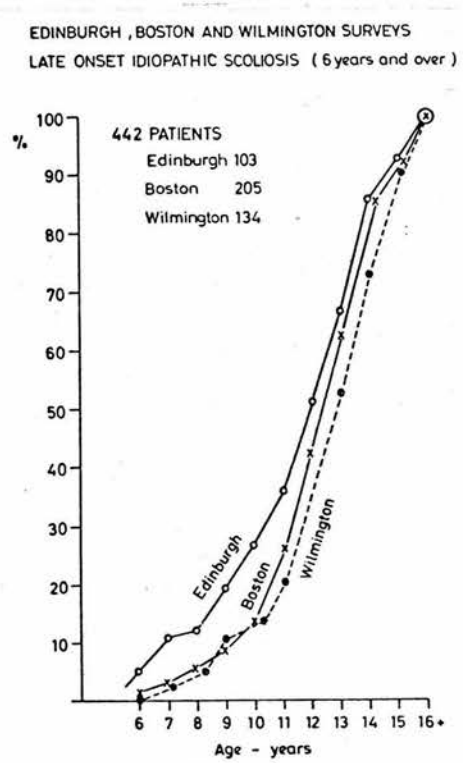
American Surveys - Sex Ratios

Boston index patients	Males	Females	Sex ratio
Juvenile scoliosis	3	19	0.16 (girls x 6)
Adolescent "	35	150	0.23 (girls x 4)
Wilmington index patients			
Juvenile scoliosis	1	14	0.07 (girls x 14)
Adolescent "	11	108	0.10 (girls x 10)

However, in the Edinburgh survey the juveniles included a number of males with onset age under six years - a group which does not appear to exist in the U.S.A. If, then, Edinburgh index patients of only six years and over are included, the sex ratio becomes similar to the American one (0.27, or four girls to one boy).

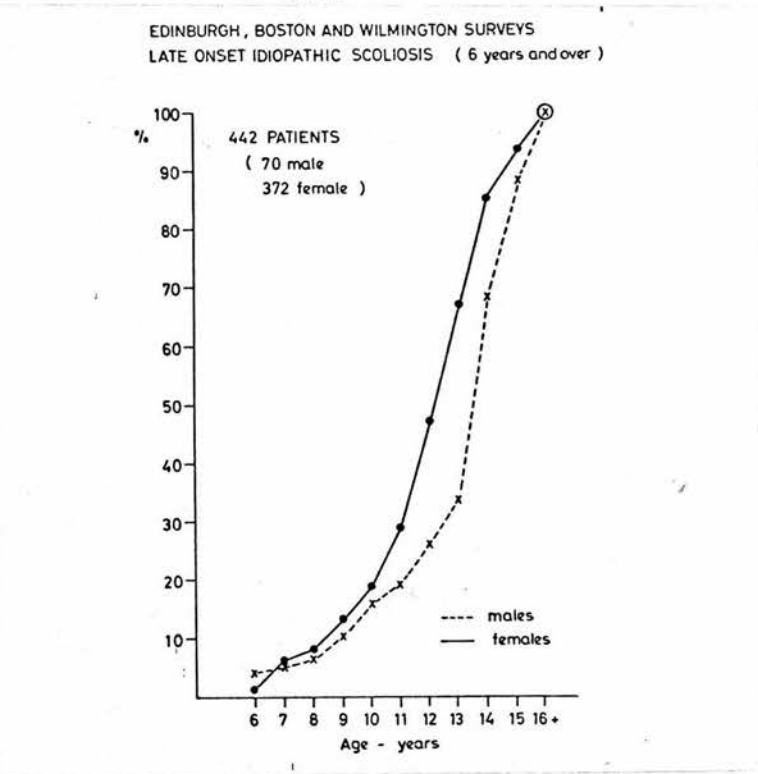
The graph of the cumulative totals for each year of age is seen to be very similar in the three surveys, (Fig. 14), though the Edinburgh patients present a little earlier.

Fig. 14



If the figures for Edinburgh, Boston and Wilmington are added, but divided for males and females (Fig. 15), it can be seen that there is a tendency for the males to present at a later age than females.

Fig. 15



Proportion of affected relatives

(1) Boston Survey. The proportions of first degree relatives with scoliosis of at least 10 degrees (all of whom were radiographed) are shown in Table 19. The only child with infantile scoliosis, who also had talipes equino-varus, was excluded, leaving 207 index patients.

Table 19.

Boston Survey

Proportions of 1st degree relatives with idiopathic scoliosis (10 degree curves and over)

Index patients	Fathers	Mothers	Brothers	Sisters	Total
Male (38)	1/26	4/28	3/11	6/16	14/81 (17.3%)
Female (169)	3/129	34/134	5/92	31/116	73/471 (15.5%)
Total (207)	4/155 (2.6%)	38/162 (23.5%)	8/103 (7.8%)	37/132 (28.0%)	87/552 (15.8%)

The figures for parents and sibs were respectively 13.2 and 19.1 per cent. If the smallest curve allowed is 20 degrees, the figures were:

Fathers 2.6 per cent
Mothers 18.5 per cent
Brothers 3.9 per cent
Sisters 17.4 per cent

The proportions of affected second degree relatives were 2.4 per cent and third degree, 1.4 per cent.

It was noted that the proportions of affected female relatives was always three - five times higher than that of affected male relatives, mirroring the sex ratio of index patients with adolescent scoliosis. This was not a feature of the Edinburgh and Wilmington surveys.

(2) Wilmington Survey. This included the radiographic examination of first degree relatives only and results for 20 degrees and over curves are shown in Table 20.

Table 20.

Wilmington Survey

Proportions of 1st degree relatives with scoliosis
(20 degree curves and over)

Index patients	Fathers	Mothers	Brothers	Sisters	Total
Male (12)	0/11	0/11	0/12	2/9	2/43 (4.7%)
Female (122)	4/112	9/121	3/68	7/80	23/381 (6.0%)
Total (134)	4/123 (3.3%)	9/132 (6.8%)	3/80 (3.8%)	9/89 (10.1%)	25/424 (5.9%)

(Parents 5.1 per cent, sibs 7.1 per cent, all first degree relatives 5.9 per cent)

The figures for 10 degree curves and over were very considerably higher (Table 21).

Table 21.

Wilmington Survey

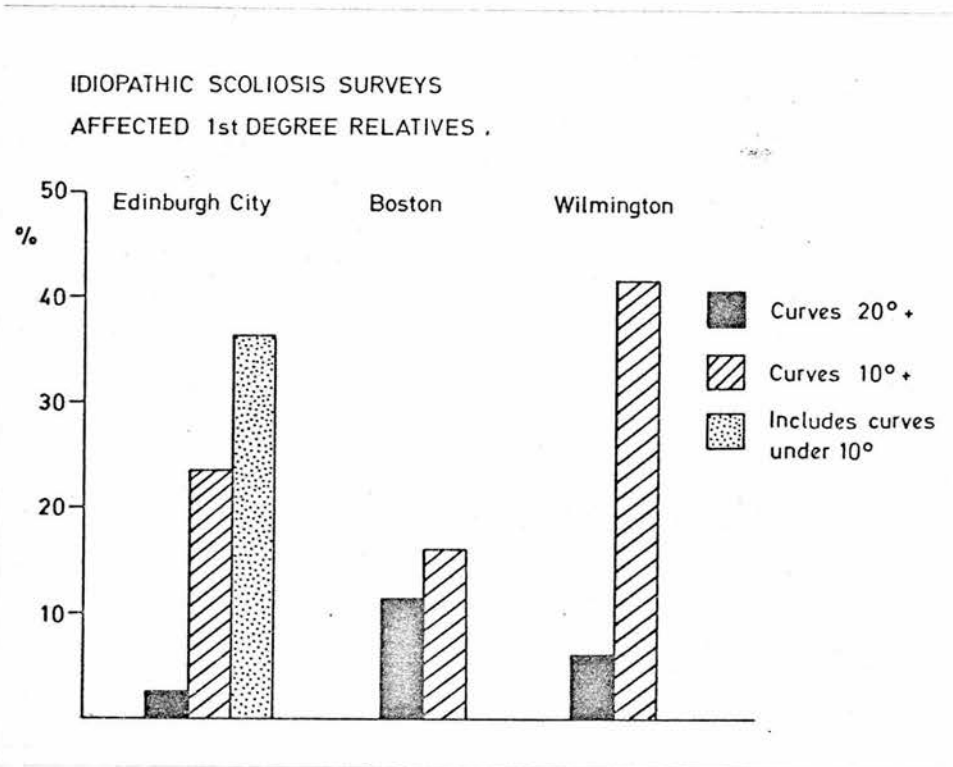
Proportions of 1st degree relatives with scoliosis
(10 degree curves and over)

Index patients	Fathers	Mothers	Brothers	Sisters	Total
Male (12)	2/11	4/11	3/12	5/9	14/43(32.6%)
Female (122)	37/112	51/121	26/68	49/80	163/381(42.8%)
Total (134)	39/123 (31.7%)	55/132 (41.7%)	29/80 (36.3%)	54/89 (60.7%)	177/424 (41.7%)

(Parents 36.9 per cent, sibs 49.1 per cent, all first degree relatives 41.7 per cent)

All these American figures are well in excess of the estimated general population incidence of 2 per 1,000, and also considerably higher than those found in the Edinburgh survey. However, for exact comparison with the two American surveys, Edinburgh City patients only were included in whom radiographic examination of the parents had been carried out. The three surveys then agreed reasonably well when 20 degree curves were considered, but the Wilmington survey had an excess of minor curves (between 10 and 20 degrees) compared with Edinburgh and Boston (Fig. 16).

Fig. 16



However, when Edinburgh relatives with curves under 10 degrees were included, the figures were similar to Wilmington. It is thought that all these variations probably indicate merely differences in measurement techniques.

It was noteworthy that the relatives with scoliosis in the Boston survey maintained the same sex ratio as in the main survey, and also the same curve pattern (an excess of females, and thoracic curves to the right in nearly all cases). Both the Edinburgh and Wilmington surveys had a higher proportion of males than expected amongst relatives, and the curve pattern was more variable, indicating perhaps the inclusion of minor scoliosis of different aetiologies in the relatives of index patients.

DISCUSSION

CLINICAL DATA.

Age of onset, sex ratio, side of curve. The main point of note from the clinical data was the virtual absence of infantile idiopathic scoliosis in the two American surveys, whereas nearly half the Edinburgh Scoliosis Clinic is made up of infant patients. The true time of onset of scoliosis can never be known for certain, since the information is only obtained from history taking. However, the discrepancy on the two sides of the Atlantic is so great that one must presume a genuine difference.

The Edinburgh and American surveys are very similar to one another if Edinburgh children under six years of age are excluded. It is from this age that the sex ratio becomes typical of 'late onset' scoliosis, that is, with an excess of girls in the ratio of about five to one. Also, it is from this age that the convexity of the curve is typically to the right.

The reason for the preponderance of left sided curves in infancy and of right sided curves after the age of six years is not clear, though one can speculate that the infant's liver is proportionately much larger than in the later years of childhood, and that any tendency to curvature in the thoracic spine would be mechanically 'easier' around the liver, that is, convex to the left.

Associated anomalies. The four associated anomalies - mental retardation, congenital heart disease, congenital dislocation of the hip and congenital-type herniae were found amongst all groups of scoliosis patients, infants to adolescents, with a higher proportion (x ten or twenty times) than would be expected from a random survey of the population.

The preponderance of mentally retarded males with scoliosis was noteworthy as was the higher proportion (14-15 per cent) of mentally retarded children (both males and females) who developed a curve during the middle years of childhood. Amongst normal children this is a rare time to develop scoliosis. There were no mentally retarded children amongst the group with resolving scoliosis, perhaps suggesting that the association of idiopathic scoliosis with mental retardation carries a worse prognosis for the curve. However, in the examination of the inmates of a mental hospital, no severe curves were found. Approximately 4 per cent of mentally retarded patients, both males and females, had scoliosis but the curves had not progressed beyond 20 - 30 degrees. The numbers affected were far in excess of the general population figures, (approximately 2 per 1,000).

The family survey of these mentally retarded patients showed 21.5 per cent of mentally retarded relatives but only one first degree relative with a doubtful scoliosis. Correspondingly, in the main scoliosis family survey, there were many cases of scoliosis but no excess of mentally retarded relatives. The same was true of congenital dislocation of the hip and of congenital heart disease - these anomalies were apparent in the index patients, but there was no excess within the families. However, the number of first degree relatives with inguinal hernia (6.5 per cent of fathers and 3.5 per cent of mothers) was significantly greater than would be expected from a random survey. 9 per 1,000 males to the age of fifteen years, and females much less than this was reported by Knox (1959). Kellmer Pringle, Butler and Davie (1966) reported 7.9 per 1,000 males and 1.3 per 1,000 females to the age of seven years.

This evidence suggests that in the case of mental retardation and congenital heart disease there is no common genetic aetiological factor leading to these associated defects and to idiopathic scoliosis. If a common factor were present, both abnormalities should be appearing in each other's families. It is possible, therefore, that mental retardation and congenital heart disease themselves predispose an individual to scoliosis.

Congenital dislocation of the hip is itself of complex aetiology, (Wynne-Davies, 1970), one feature being a connective tissue disorder evidenced by generalised joint laxity and congenital type herniae - both in patients and relatives. It is possible that genetic factors are involved in a connective tissue disorder, leading to some cases of idiopathic scoliosis, congenital dislocation of the hip and/or herniae. Certainly, scoliosis without vertebral anomalies is not uncommonly a feature of some of the single gene heritable disorders of connective tissue (e.g. Marfan's syndrome, Ehlers Danlos syndrome and Morquio's disease).

PROPORTIONS OF AFFECTED RELATIVES WITH SCOLIOSIS.

All twins in the Edinburgh survey, six pairs, were dyzygotic and discordant. Evidence from the literature, including the previous Edinburgh survey, indicated that there is a higher rate of concordance amongst MZ twins than DZ, but there have been no large scale twin surveys, and neither is it certain that the criteria for diagnosis was the same in previously reported cases.

The diagnosis of idiopathic scoliosis in relatives presents difficulties and inaccuracies in:

1) Determining how small a curvature constitutes 'scoliosis'.

2) Ignorance as to age of onset, since most relatives were unaware of having a curvature.

The method of screening relatives is clearly significant, in that larger numbers of minor curves will be found on radiological screening. However, it is not possible to know which individuals with very minor curves (under 10 degrees) are genuinely idiopathic scoliosis of a very mild nature, or are normal individuals with a minor variation of the spine. It is probable that the numbers found with 20 degree curves and over are more reliable.

In the Edinburgh survey the proportions of affected relatives were approximately equal for all groups, infants (whether resolving or progressive, onset under six months of age, or over), juvenile or adolescent. All figures were significantly in excess of the general population frequency of around 2 per 1,000.

The proportions of affected relatives from the Edinburgh and Boston surveys show a rapid fall towards the population incidence, from first to second and then to third degree relatives. This is compatible with multifactorial inheritance, (Carter, 1969).

The current Edinburgh figures for second and third degree relatives are considerably less than those found in the 1968 survey, (3.7 and 1.6 per cent compared with 0.64 and 0.38 per cent). This is due to the experience gained since then in diagnosing idiopathic scoliosis, particularly in the elderly (Vanderpool, James and Wynne-Davies, 1969). The condition, previously, was somewhat over-diagnosed.

It is unlikely that the pattern of inheritance will become any clearer while only these clinical methods of diagnosis are available. The situation is too uncertain when very minor curves are found on radiography, and it is very probable that idiopathic scoliosis, as described here in patients and relatives, does not form a homogenous group. Nevertheless, there do seem to be families in which the clinical picture is distinctive and affecting both sexes in two or more generations. That is, in some instances, the scoliosis, per se, could be of autosomal dominant inheritance, partially sex-limited to females. There is no evidence for X-linked inheritance, in that father to son inheritance does occur. However, taking the survey as a whole, rather than these few families, the aetiology is likely to be multifactorial.

Genetic counselling is difficult in view of the multiplicity of factors involved, particularly in infants, but it would appear that the risk of a major curve appearing in a subsequent sib is low. If both parents are normal, the risk is approximately 1.7 per cent. If one parent has scoliosis the risk is 6.0 per cent. The risks are higher for females (11.1 per cent) than for males (2.6 per cent).

ENVIRONMENTAL FACTORS (Particularly relating to INFANTILE SCOLIOSIS).

Apart from noting a parity effect (excess of first born children) in the adolescent group, and confirming the fact of a raised maternal age amongst the same group, positive evidence under this heading relates mainly to the group with infantile scoliosis, and more particularly to those developing a curve during the first six months of life. Amongst this latter group the special features were:

(1) 17.6 per cent with breech presentation

(2) 29 per cent premature, underweight males

(3) Seasonal variation in incidence (curve onset in the two winter quarters)

(4) At least two-thirds of the curves resolved

It is reasonable to suppose that adverse factors during pregnancy and birth could influence events during the early months of life. The excess of breech presentations has been noted in other 'positional' deformities (congenital dislocation of the hip and torticollis, for example). The reason for the excess of premature males (not females) is unclear. If these infant boys are removed from the survey, then the numbers of male and females in the infantile group are equal.

The seasonal variation shown by date of birth and onset of curve during the two winter quarters is interesting. It is possible that the infant is particularly susceptible to developing scoliosis from the age of three to nine months and that factors limiting free movement (being heavily wrapped up in the cold weather, for example) increase this tendency by retarding physical development.

Approximately two-thirds of curves resolve in the group of infants up to the age of six months. The true figure is no doubt higher than this, since some curves will never be noticed, or if they are, will be considered too minor for the child to attend for treatment.

There were several special features noted in the children with progressive scoliosis:

(1) Only half the curves which will subsequently progress have appeared (or been noticed), by the age of six months, whereas four-fifths of the curves which will resolve have developed by this age.

(2) 13 per cent of males with progressive scoliosis were mentally retarded (no females).

(3) The mothers of children with progressive scoliosis were older than average.

(4) There was some evidence of a social class effect, in that more infants with progressive scoliosis came from the lower social classes both by comparison with the normal population figures and with resolving scoliosis.

It is difficult to know whether all resolving curves are potentially progressive. The fact that progressive curves present later may mean delay in noticing and bringing for treatment (as might be expected in the lower social classes); or perhaps the mothers of lower social class children do not bother to bring resolving scoliosis to clinic.

A maternal age effect had been noted in the previous Edinburgh survey amongst adolescent patients but this is the first time the effect has been shown also amongst the mothers of children with progressive infantile scoliosis.

Evidence relating to the habitual side of lying in early infancy was equivocal, though it was established that in this country the usual is not 'prone' as it is known to be in North America. The only three infants in this survey who habitually lay prone had resolving scoliosis. There has been speculation on both sides of the Atlantic whether infant posture is significant in the development of scoliosis: whether the prone position in some way promotes physical development of the spinal muscles and corrects any tendency to scoliosis at this early age. It is clear that there must be strong environmental factors acting in infantile scoliosis since the individuals in the British and American surveys must, genetically, be very similar.

It would not be easy to prove the significance of infant posture and it is only suggested that the prone position could be relevant.

It is also difficult to know the significance of plagiocephaly in scoliosis. Certainly many otherwise completely normal children do develop, and recover from, plagiocephaly. The plagiocephaly survey showed (unlike scoliosis) an equal number of males and females affected but, (like scoliosis), some excess amongst the lower social classes and in the winter months. It is likely that whatever factors can lead to plagiocephaly can also lead, less commonly, to scoliosis, since in 100 per cent of cases of infantile idiopathic scoliosis plagiocephaly is also present. In a large proportion of cases both deformities are transitory.

However, the scoliosis infants in many cases have several additional adverse factors to contend with (prematurity, low birth weight, mental retardation, older mothers, low social class, congenital heart disease, and perhaps muscle weakness associated with undue generalised joint laxity as evidenced by congenital dislocation of the hip and herniae). That is, there are additional factors in their external or internal environment and one can speculate that these may retard movement and early physical or neurological development, perhaps leading to unequal maturation and spinal curvature.

CONCLUSION

When all the evidence is considered, it appears that idiopathic scoliosis is of complex aetiology, not all cases sharing the same causative factors.

Certainly some cases of scoliosis appear, per se, to be genetic in origin, perhaps of dominant inheritance. These are families in whom the scoliosis appears amongst several members (both sexes and two or three generations), and with no apparent associated anomaly.

Since the proportions of affected relatives were more or less similar, and much in excess of the general population incidence, whatever group of scoliosis index patients was considered, an underlying genetic tendency is probably present in all groups. What must be different at different ages, (and absent in American infants), is the environmental 'trigger'.

In infants, it is suggested that genetic and environmental factors (internal or external) can produce scoliosis. The adverse environment may be present in a normal baby, in which case, as growth proceeds the curve may resolve. If present in a child who has a genetic predisposition to scoliosis then the curve may progress. Lack of movement, for whatever reason, could lead to retarded maturation, and one can speculate that the "static" or "floppy" baby may be particularly at risk.

Why so many cases of scoliosis develop in adolescent girls is not clear - possibly the environmental trigger in this instance is present in all females, being related to the normal physiological hormonal changes at puberty.

It seems apparent that the aetiology of idiopathic scoliosis is multifactorial, with a genetic tendency to the deformity which is then 'triggered off' at different ages by different factors, some medical, some themselves genetic, and some associated with the external environment. The balance of all these factors must vary from individual to individual - thus someone with a strong genetic tendency needs very little 'triggering' action. At the other end of the scale it is possible that scoliosis can be produced in a normal infant or in a child with virtually no genetic tendency to the deformity, entirely by an adverse environment.

SUMMARY

(1) A family survey of 200 idiopathic scoliosis patients from the Edinburgh Scoliosis Clinic has been carried out.

(2) Results have been compared with two American surveys, 208 from Boston, Massachusetts and 137 from Wilmington, Delaware.

(3) Idiopathic scoliosis developing under the age of six years is almost absent from the U.S.A. surveys.

(4) The pattern of inheritance is essentially similar -

a) in all ages of Edinburgh patients

b) in all patients from Edinburgh over the age of six years when compared with the American surveys

(5) The associated anomalies of mental retardation, congenital heart disease and congenital dislocation of the hip were apparent in all age groups of index patients, but there was no excess of these disorders in their families. Inguinal hernia was often a feature both of index patients and relatives.

(6) It is suggested that:

a) mental retardation and congenital heart disease themselves predispose an individual to scoliosis

b) a genetic disorder of connective tissue underlies a tendency to some cases of idiopathic scoliosis, congenital dislocation of the hip and congenital type herniae.

(7) In infants developing scoliosis under the age of six months there was an excess of:

a) breech presentations

b) premature, underweight males

c) onset of curves in the two winter quarters of the year

(8) In infants with progressive scoliosis there was an excess of:

a) curves presenting after the age of six months
b) mentally retarded males
c) older than average mothers
d) low social class children

(9) It is suggested that, in infants, particularly those under six months of age, scoliosis can be produced by a variety of adverse environmental factors.

(10) It is concluded that there are variable underlying genetic factors in idiopathic scoliosis, and that the environmental 'trigger' needed to establish the deformity varies at different ages.

V E R T E B R A L A N O M A L I E S -
C O N G E N I T A L S C O L I O S I S

Introduction* Spinal curvature associated with congenital vertebral anomalies is the second most common type of scoliosis, and congenital anterior vertebral defects are one of the main causes of kyphoscoliosis, a deformity in which the principle element is antero-posterior angulation, (vide infra.) Errors in segmentation of the developing embryonic vertebrae are extremely variable, involving anything from one level only to multiple defects throughout the length of the spine. Spinal curvature may be apparent at birth, may develop during growth, or may never develop at all, if segmental defects on each side of the vertebral column 'balance out'. Certain groups of anomalies are described, based on anatomical types:

(1) Neural arch defects. At its most severe the posterior arch defect is total and associated with a meningocele or myelomeningocele. Hydrocephalus may or may not be present. The spinal defect is sometimes referred to as spina bifida cystica, and together with the aetiologically related anencephaly, form the neural tube defects - which are the commonest of all congenital anomalies in man.

Not infrequently, spina bifida cystica is accompanied by segmental vertebral defects and congenital scoliosis; and it is only this group of spina bifida cystica patients who are included in the present survey.

Posterior arch defects may occur without a meningocele, and can be of any grade of severity at any number of levels.

* much of this section is taken from James (1967)

Spina bifida occulta at the fifth lumbar and/or first sacral levels is extremely common in the general population - just how frequent is one of the points determined by this survey. It should probably be regarded more as an anatomical variation than a congenital defect.

(2) Lateral segmental defects. These are extremely variable in type and extent. Scoliosis is frequent, due to the asymmetrical width and depth of affected vertebrae, and to their continued unequal growth. Rib anomalies are common (absence or fusion), also Sprengel's shoulder. The formation of a rigid bar of bone in the concavity of a curve associated with several fused vertebrae, occurs in some severe cases.

When anomalous and fused vertebrae are in the cervical region and accompanied by a low hair line and webbing of the neck, the disorder is known as the Klippel Feil syndrome. Scoliosis is not usually present, and the syndrome is specifically not included in the present survey. However, there are cases included in whom upper thoracic segmental defects extend into the neck.

(3) Fusion of vertebrae. In addition to the lateral segmental defects, there may be fusions of two or more vertebral bodies, laminae or spines, or these may occur as isolated features in an almost normal vertebral column.

(4) Kyphoscoliosis. This term is used very precisely to mean the presence of a true kyphosis as well as a lateral curvature (the term is frequently used inaccurately in cases of scoliosis with lateral rotation of the vertebral bodies and a rib hump simulating kyphosis). Congenital kyphoscoliosis is caused by defects of the vertebral bodies - that is, the defect is anterior. There may be a partial or complete absence of the vertebral body, or fusion of two or three bodies, or a combination of these. It is characteristically a

localised deformity, extending over one, two or three vertebrae only, and the neural arch is usually unaffected.

It is a potentially serious anomaly because the increasing angulation of the vertebrae as the child grows causes pressure on the spinal cord and paraplegia may develop.

Previous literature

(1) Congenital scoliosis. Clinical data relating to congenital scoliosis and kyphoscoliosis has been given by many authors (James 1955 and 1967; MacEwen 1967; Winter, Moe and Eilers 1968; Winter, Moe and Wang, 1973). There are frequent reports of associated congenital anomalies such as congenital heart disease, imperforate anus, cleft lip and palate and genito-urinary tract anomalies. MacEwen, Winter and Hardy (1972) studied 231 cases of congenital scoliosis (excluding spina bifida cystica) and found on intravenous pyelogram that 18 per cent of patients had a kidney anomaly (unilateral agenesis, duplication, obstruction and so on), though most were symptomless.

There have been no family studies in congenital scoliosis, although there have been occasional reports of more than one affected member of a family. A family survey of cervical vertebral defects ('Klippel Feil syndrome') was carried out by Gunderson, Greenspan, Glaser and Lubs (1967). They investigated eleven index patients and carried out radiography of the cervical region in 121 relatives. They concluded there were a number of different genetic patterns of inheritance (including dominant and recessive types), varying with the nature of the lesion in the index patient. Some of their cases had vertebral anomalies other than cervical.

(2) Spina bifida cystica. There have been many family and epidemiological studies from different parts of the world of this condition, with or without hydrocephalus, and of the related neural tube defect, anencephaly (Record and McKeown, 1950; Edwards, 1958; Williamson, 1965; Nuggan and MacMahon, 1967; Carter and Fraser Roberts, 1967; Carter, David and Laurence, 1968; Fedrick, 1970, and Elwood, 1970, to mention only some). Some of these cases must also have had other congenital vertebral defects, but how many is not known.

The main findings of these surveys may be summarised as follows:

(i) Anencephaly and spina bifida/meningocele, with or without hydrocephalus often occur within the same kindreds and are therefore aetiologically related.

(ii) Hydrocephalus occurring alone appears to be of different aetiology (some cases are of X-linked recessive inheritance).

(iii) There are, even within the British Isles, strong regional differences in the incidence of the neural tube defects, being highest in Northern Ireland and lowest in South-east England.

(iv) Concordance in monozygous twins is low, perhaps in only 20 per cent of cases are both twins affected.

(v) The risk of a second sib being affected is approximately 5 per cent (higher in areas of high incidence); if two sibs are already affected, the risk to a third is approximately 10 per cent.

(vi) There appears to be an excess of affected relatives on the maternal side of the family, amongst the mothers' sisters' children.

(vii) The disorders are more common in the lower social classes.

(viii) Some surveys report an increased incidence in the winter months.

(ix) There is an excess of first born children, and of mothers who are older than average.

The disorders are thought to be of multifactorial inheritance, with a strong environmental element to the aetiology.

The aim of the current Edinburgh survey was to try and establish whether there was any aetiological relationship between spina bifida/meningocele and other congenital vertebral defects, that is, with congenital scoliosis. The method was by family survey, noting particularly the proportions of anencephaly, spina bifida/meningocele and other vertebral anomalies amongst the relatives of 339 index patients, and comparing this figure with the general population frequency. Data was also collected relating to the pregnancy, birth history, parental age and parity, season of birth, social class and regional distribution of the index patients.

POPULATION INCIDENCE.

The incidence of the neural tube defects has been well established from many surveys, and ranges in Britain from approximately 1 - 5 per 1,000 births. The figure for Edinburgh City from the Register of the Newborn, (1964 - 1968) was 2.2 per 1,000 births for anencephaly and spina bifida/ meningocele.

These defects, however, are immediately apparent at birth. There is a great deal more difficulty in establishing a population incidence for other congenital vertebral anomalies which are very probably not apparent at birth, and perhaps not discovered for many years, or certainly in some cases not at all, (one patient in this survey was not diagnosed until the age of 44 years). The following information is available:

(1) In a study of 15,000 minifilms of the chest from the State of Delaware, U.S.A., Shands and Eisberg (1955) noted seven cases of congenital scoliosis with definite vertebral anomalies. This gives an incidence of 0.5 per 1,000 but would exclude anomalies in the lumbar region, since they studied only chest x-rays.

(2) In the Edinburgh Scoliosis Clinic between 1958 and 1968 (the period of this survey) there were seventy-two patients with congenital scoliosis who came from Edinburgh City, the Lothians and Fife. Over the same period and from the same area, there were 118 patients with idiopathic scoliosis. That is, idiopathic scoliosis was 1.6 times more common. The general population incidence for idiopathic scoliosis was established in Edinburgh as approximately 2 per 1,000, and so a figure of

1 per 1,000 for congenital vertebral anomalies is a reasonable guess: it is not too dissimilar from Shands and Eisberg's figure, which is clearly too low an estimate.

The frequency of very minor vertebral anomalies is impossible to assess since there will be no reason for individuals to attend hospital for treatment, and even if radiographs were taken of a large population, only some of such defects would be apparent.

However, an additional survey was carried out in order to determine the frequency of spina bifida occulta at the 5th lumbar/1st sacral level. It was thought to be very common in the general population, though no reliable figures were available, and it was hoped to assess the significance of relatives who might be so affected. Lorber and Levick (1967) noted 20 per cent of parents with spina bifida occulta and only 5 per cent of controls - though some anatomy text books refer to 5 - 10 per cent. In view of the uncertainty of visualising this minor anomaly on any one radiograph, a series was examined from scoliosis patients, 162 idiopathic and fifty-nine paralytic, due to previous poliomyelitis. These two groups were chosen because each individual had dozens of vertebral column radiographs, taken at intervals throughout the growing period, perhaps from three months to sixteen years of age. There was, therefore, a greater chance of observing a minor vertebral anomaly.

FREQUENCY OF SPINA BIFIDA OCCULTA.

The material used for this additional survey was radiographs from 162 patients with idiopathic scoliosis and fifty-nine with paralytic scoliosis (usually resulting from poliomyelitis). The actual number of radiographs studied was not recorded, but any one patient might have as many as twenty or thirty.

Results were as follows:

Spina bifida occulta	Idiopathic scoliosis (162 patients)	Paralytic scoliosis (59 patients)	Total (221 patients)
4th lumbar	3	0	3
5th lumbar (alone)	17	0	17
1st sacral (alone)	72	23	95
L.5 and S.1	83	26	109

Almost exactly half of all individuals had a spina bifida occulta of the 5th lumbar/1st sacral region.

There were four more cases with spina bifida occulta at other levels (thoracic 10 and 11; thoracic 7, 8, 9 and 10; thoracic 1, 2, 3 and 4; thoracic 3 and 6, with lumbar 3). All four of these patients had spina bifida occulta of the first sacral segment also.

These results are quite unequivocal - at least half the general population has spina bifida occulta and this must still be a minimum figure since this was only a radiographic survey.

The reason for failing to observe a minor neural arch defect on any one x-ray is that the two sides of the arch instead of meeting and fusing, over-ride one another and it will not necessarily be apparent on radiography that a defect is present.

In view of the high proportion of the general population with spina

bifida occulta at the lower end of the vertebral column, the deformity has been ignored both in index patients and their relatives.

MATERIAL FOR THE FAMILY SURVEY.

An attempt was made to include all patients with congenital scoliosis who had attended:

(1) The Edinburgh Scoliosis Clinic from October 1958 - December 1968.

(2) The Royal National Orthopaedic Hospital Scoliosis Clinic, London, from January 1948 - December 1968.

The total number of patients was 470 (160 Edinburgh, 310 London) of whom 339 were traced and form the index patients of this survey (Table 22).

Table 22.
Congenital Scoliosis

	Edinburgh	London	Total
Males	36	67	103
Females	93	143	236
Total	129	210	339

There was more difficulty in tracing patients, particularly from the London area, than was experienced in the idiopathic scoliosis survey which was

entirely based on Edinburgh. Also the period of study for this survey extended back to 1948 and older patients who had married and changed their names were particularly difficult to find.

The reason for failing to include 131 patients were:

4 foster children with no family data
7 dead
6 overseas
91 not traced
23 refused to co-operate

Only a small proportion (6.8 per cent) refused to take part in the survey.

There were 129 patients from the Edinburgh Clinic, 72 of them from the City, the Lothians and Fife. This group alone is considered for certain epidemiological aspects of the survey, since they would normally attend Edinburgh hospitals and the group thus provides a truer picture of the size of the congenital scoliosis problem. All scoliosis in the district is treated by Professor James at the Scoliosis Clinic, and so these seventy-two index patients are likely to be the total number in the area. Many of the Royal National Orthopaedic Hospital patients and the remaining fifty-seven from Edinburgh came from long distances away specifically in order to attend a specialist clinic.

All types of congenital vertebral defects were included in this survey, but patients with spina bifida/meningocele as a solitary defect were excluded, as were anomalies above the first thoracic and below the first sacral segments. Cervical vertebral anomalies (including the Klippel Feil syndrome) are frequently present without scoliosis, and there were too few patients in either clinic to make their analysis feasible. There were, however, a number of patients included in the survey with vertebral anomalies extending from the upper thoracic levels into the cervical region.

The same sources as for the idiopathic scoliosis survey were used for comparison with certain epidemiological features (The Registrar General's Annual Reports and the Edinburgh Register of the Newborn).

METHOD.

The method of family survey research was essentially the same as for idiopathic scoliosis, though in this instance a large number of sibs with anencephaly or spina bifida cystica had been stillborn or died in infancy, and therefore could not be examined. In all cases medical records, including post mortem examination reports, were sought and hearsay evidence was not accepted. Living relatives with clinical evidence of a vertebral anomaly were brought to hospital for further examination and radiography.

All Edinburgh patients and the case records of all London patients were studied by me and all radiographs examined in order to determine, as far as possible, the anatomical nature and levels of the vertebral defects.

The parents of the first twenty-four Edinburgh patients indexed (forty-eight individuals) had routine radiographic examination of the vertebral column, but results being entirely negative, it was thought unjustifiable to proceed with this investigation further. It is possible there are more relatives with minor vertebral anomalies than are here reported; this survey can give only a minimum figure for the proportions affected. However, radiographic examination of relatives is by no means a complete answer. Minor vertebral anomalies might or might not be visible, even if the quality of radiographic technique was good. The only sure way to diagnose them is to see them - either during an operative procedure or at post mortem examination.

Major vertebral anomalies are nearly always clinically apparent, and anencephaly and spina bifida cystica, of course, always so.

RESULTS

TRACING OF RELATIVES.

All 339 families taking part in the survey were visited at home, and a total of 924 first degree relatives seen. A history, usually from the mother, was taken relating to all first and second degree relatives, and to first cousins (third degree). As stated above, many affected relatives were stillbirths or perinatal deaths, and the diagnosis could only be confirmed from medical records, not by examination.

CLINICAL DATA.

A clinical assessment of these patients was not the primary aim of the survey, (this would be a major project in itself), but it became apparent that certain clinical types of congenital scoliosis formed aetiological groups. Also, various other features which could have been relevant to aetiology were noted during the course of the survey and are briefly reported here.

Clinical types.* The 339 index patients were divided into four groups:

(1) 118 patients with anomalies which included a neural arch defect:

39 with meningocele
39 with wide, extensive spina bifida, but no meningocele
40 with spina bifida occulta (excluding the 5th lumbar and 1st sacral segments, see page 69).

(2) 118 patients with multiple vertebral anomalies, without any apparent neural arch defect:

This was a somewhat unsatisfactory group, including some patients without adequate radiographs, (e.g. x-rays taken at too late an age for an exact diagnosis ever to be possible). A few cases may well belong to the previous group, with neural arch defects. However, they were quite clearly delineated from group (3) -

* See plates 1-4, page 107a.

(3) 101 patients with localised or minor vertebral anomalies:

40 with kyphoscoliosis, (that is, absence or fusion of the vertebral body only over one, two or three adjacent segments).

45 with isolated hemivertebrae.

16 with minor anomalies such as narrowing of disc spaces or fused vertebrae only.

(4) Two patients with hydrocephalus and an "idiopathic" type scoliosis, with no congenital vertebral anomalies observed at all.

Hydrocephalus occurring alone is probably of different (unifactorial) aetiology, and these two cases were discarded from the survey.

For the remainder of the thesis, 337 patients in three large groups are considered:

(1) Spina bifida group (118)

(2) Multiple vertebral anomalies group (118)

(3) Localised " " " (101)

Sex ratio. Females were more common in each of the three groups (Table 23), though the sex ratio was nearly equal in index patients with localised anomalies.

Table 23.

Vertebral Anomalies - Sex Ratios

	Spina Bifida Group	Multiple Vertebral Anomalies	Localised Vertebral Anomalies
Males	32	28	41
Females	86	90	60
Ratio	0.37	0.31	0.68
	Females x 2.7	Females x 3.2	Females x 1.5

Age of diagnosis. Patients with a meningocele were, of course, diagnosed at birth but excluding these, the age at which the vertebral defect became apparent was very variable. Some presented with scoliosis at the time of birth, in some a curve developed as the child grew, and in some the vertebral anomalies were found by chance when, for example, a chest x-ray was taken. (Table 24).

Table 24.

Age of diagnosis of vertebral anomalies

	Mean	Range
Spina bifida group (excluding meningocele)	2.1 years	Birth to 14 years
Multiple vertebral anomalies	4.3 years	Birth to 44 years
Localised vertebral anomalies	6.3 years	Birth to 21 years

There was no typical pattern of age distribution, a feature so characteristic of idiopathic scoliosis.

Side of curve. There were almost equal numbers of right and left curves:

Right	-	45 per cent
Left	-	40 per cent
Double primary curves*	-	8 per cent
No scoliosis	-	6 per cent

There was no preponderance of left-sided curves in infants and right-sided in adolescents, as in idiopathic scoliosis.

* that is, two structural, fixed curves.

Level of curve. The site of scoliosis in the 94 per cent of patients who had a curve was as follows:

High thoracic (above the 6th thoracic vertebra)	- 29	(9 per cent)
Thoracic	- 156	(50 per cent)
Thoraco-lumbar	- 71	(23 per cent)
Lumbar	- 33	(10 per cent)
Double primary curves	- 26	(8 per cent)

With the exception of the high thoracic curves, a type unknown in idiopathic scoliosis, the distribution was similar to that of idiopathic curves.

Skin signs overlying the vertebral anomalies. The most usual sign was a hairy patch, or hair with a pigmented area, but hair with a lipoma, haemangiomata, and lipomata without hair were recorded. Some form of skin sign was present in:

Spina bifida group	-	22 per cent
Multiple vertebral anomalies	-	4 per cent
Localised vertebral anomalies	-	3 per cent

These skin signs were not apparent in any of the forty patients with kyphoscoliosis.

Sprengel's shoulder. The presence of an undescended scapula accompanying the vertebral anomalies was recorded in 12 per cent of all cases, though only in 1 per cent of the group with localised vertebral anomalies.

Neurological signs and diastematomyelia.

(1) Positive neurological signs present at birth, or non-progressive signs, were present in:

Spina bifida group	- 60 of 118	(51 per cent)
Multiple vertebral anomalies	- 3 of 118	(0.8 per cent)
Localised vertebral anomalies	- none of 101	

(2) Diastematomyelia was probably present in nineteen patients, all in the spina bifida group, (16 per cent), but the diagnosis was only completely certain in the six who developed signs of paraplegia and the bony spur was removed at operation.

(3) Paraplegia developed during growth in twenty patients: 11 with kyphoscoliosis, 6 with diastematomylia, 2 with multiple vertebral anomalies, and 1 with a solitary hemivertebra in the upper thoracic region.

NO VERTEBRAL ANOMALIES IN THE CURVE

There was a group of twenty-three patients in whom vertebral anomalies were present but these were either above or below the curve and not directly causing it. The group was considered separately in order to try and determine if these were cases of idiopathic scoliosis occurring coincidentally with congenital vertebral anomalies. Clinical details were as follows:

Age of onset

Infants (birth - 3 years)	- 16 (4 males, 12 females)
Juveniles (4 - 9 years)	- 3 (1 male, 2 females)
Adolescents (10 years to the end of growth)	- 4 (2 males, 2 females)

There was the same number of left and right sided curves; all were in the thoracic region. The group is small, but even so, it does not show the characteristic sex ratio or side of curve characteristic of idiopathic scoliosis, (pages 14 and 19).

ASSOCIATED ANOMALIES.

Under this heading are noted structural or developmental anomalies unrelated to the vertebral column/spinal cord defect. Such deformities as talipes equino-varus and congenital dislocation of the hip would nearly always be paralytic in nature, secondary to the neurological defect. Two index

patients with spondylolisthesis related to lower lumbar vertebral anomalies were noted.

The main associated anomalies in index patients were as follows:

Spina bifida group (118 patients)

5 herniae (2 inguinal, 1 hiatus, 1 lumbar, 1 femoral)
2 congenital heart defects (1 dextracardia, 1 ventricular septal defect)
1 hypoplastic thumb
1 syndactyly of toes (2nd and 3rd)

(Total 7.6 per cent)

Multiple vertebral anomalies (118 patients)

3 herniae (1 inguinal, 1 femoral, 1 lumbar)
2 congenital heart defects (1 Fallot's tetralogy, 1 dextracardia and ventricular septal defect)
4 thumb anomalies (absence or hypoplasia)
3 accessory breasts
2 congenital contracture of fingers
1 cleft lip and palate
1 imperforate anus
1 branchial cyst
1 slipped upper femoral epiphysis (aged 12 years)
1 Perthes' disease (6 years)

(Total 16.1 per cent)

Localised vertebral anomalies (101 patients)

5 herniae (all inguinal)
3 congenital heart defects (2 Fallot's tetralogy, 1 aortic stenosis)
2 congenital dislocation of the hip (without evidence of paralysis)
1 cleft lip and palate
1 duplication of small intestine (causing neonatal intestinal obstruction)
1 imperforate anus
1 absent lung
1 femoral dysplasia
1 polydactyly of foot (pre-axial)

(Total 15.8 per cent)

In the spina bifida group, one patient had a lumbar teratoma associated with her meningocele. In the localised vertebral anomalies group, one patient had a dermoid cyst in the region of the curve.

No congenital defects of the genito-urinary tract were noted in these patients, but no special investigations had been carried out.

There was no particular pattern of associated developmental anomalies, but there was a far higher proportion of index patients with some other defect than would be expected from a random survey of the general population (perhaps 2 - 3 per cent, compared with 8 and 16 per cent in this survey).

Associated developmental anomalies were noted for relatives, but again, it was not possible to detect any particular pattern.

First degree relatives

Spina bifida group (489 first degree relatives)

2 congenital heart defects (both atrio-septal defects, 1 mother, 1 brother)
2 idiopathic scoliosis (2 sisters of one index patient)
1 oesophageal atresia (brother)
1 Scheuermann's disease (brother)
1 congenital dislocation of the hip (brother)
1 syndactyly of toes (2nd and 3rd - sister)

(Total 1.6 per cent, which is close to the expected figure of 2 per cent)

Multiple vertebral anomalies (488 first degree relatives)

1 inguinal hernia (father)
1 congenital heart defect (coarctation of the aorta - brother)
1 microcephalic (sister)
1 pituitary dwarf (brother)
1 thyroid cyst (sister)
1 pelvic kidney (sister)
1 bifid thumb (father)
1 talipes equino-varus (father)

(Total 1.6 per cent)

Localised vertebral anomalies (467 first degree relatives)

6 inguinal herniae (2 fathers, 3 brothers, 1 sister)
4 congenital heart defects (1 patent ductus, 3 septal defects)
2 idiopathic scoliosis (mother and MZ twin of one index patient)
1 hemihypertrophy (brother)
1 congenital dislocation of the hip (daughter)
1 slipped upper femoral epiphysis (daughter)
1 severe coxa vara (brother)
1 Perthes' disease (brother)

(The total was 3.7 per cent, which is rather above the expected figure of 2 per cent for the general population).

Second degree relatives (half-sibs, nephews and nieces only)

The findings here are unlikely to be accurate for the older second degree relatives (grandparents, uncles and aunts), and so associated developmental anomalies are described only for half-sibs, nephews and nieces in whom the information is thought to be complete.

Spina bifida group (94 second degree relatives)

1 double ureter (half-sister)
1 congenital short leg (nephew)

(Total 2.1 per cent)

Multiple vertebral anomalies (146 second degree relatives)

1 inguinal hernia (nephew)
1 talipes equino-varus (nephew)

(Total 1.4 per cent)

Localised vertebral anomalies (142 second degree relatives)

2 congenital dislocations of the hip (nieces)
1 congenital heart defect (ventricular septal defect - nephew)
1 hypospadias (nephew)
1 pyloric stenosis (nephew)
1 degenerative encephalitis (niece)

(Total 4.2 per cent)

Again, no pattern emerges but there are proportionately more relatives with structural or developmental anomalies in the group of index patients with localised vertebral defects, when compared with the other two groups, and with an estimated 2 per cent for the general population.

Third degree relatives (first cousins only)

There was more difficulty collecting information relating to these more distant relatives, but the following anomalies were noted:

Spina bifida group (1,288 third degree relatives)

1 arthrogryposis
1 cleft lip and palate, with a teratoma of the palate
1 embryonal sarcoma
1 Perthes' disease
1 talipes equino-varus and absent second toe

(5 of 1,288 third degree relatives, 0.4 per cent)

Multiple vertebral anomalies (1,460 third degree relatives)

3 chromosome anomalies (1 Turner's syndrome, also with an atrio-septal defect, 1 Trisomy D, 1 Trisomy 21)
2 congenital dislocations of the hip (one with inguinal hernia)
2 talipes equino-varus (1 with syndactyly of the fingers and cleft palate)
1 coarctation of the aorta
1 absent fibula
2 renal agenesis
2 stenosis of ureter and hydronephrosis (1 with duodenal atresia)

One further child was investigated for a "cyst in the spine"; its nature was uncertain but it was stated to be non-progressive.

(14 of 1460 third degree relatives, 1.0 per cent)

Localised vertebral anomalies (944 third degree relatives)

2 talipes equino-varus
2 coeliac disease
1 phenylketonuria
1 congenital heart defect (type unknown)
1 ileal atresia
1 stenosis of ureter
1 cleft lip and palate

(9 of 944 third degree relatives, 1.0 per cent)

PROPORTIONS OF AFFECTED RELATIVES.

The proportions of relatives with: (1) anencephaly, (2) spina bifida and meningocele, with or without hydrocephalus, (3) Vertebral anomalies, other than spina bifida and meningocele, are noted separately. No more precise grading was possible since many of these individuals were dead and more details of the vertebral column defect were not available.

The three groups of congenital scoliosis index patients are noted separately and compared:

(1) Spina bifida group
(2) Multiple vertebral anomalies group (without spina bifida)
(3) Localised vertebral anomalies group

FIRST DEGREE RELATIVES.*

Triplets and twins.

All were discordant.

(1) Spina bifida group	- 1 male with monozygous twin - 1 female with dyzygous twin sister
(2) Multiple vertebral anomalies	- 1 male of triplets, with two dyzygous sisters - 1 female with monozygous twin - 1 female with dyzygous twin sister - 1 male with dyzygous twin brother - 1 female with twin brother
(3) Localised vertebral anomalies	- 1 male with dyzygous twin brother

The index patients reported as having a monozygous twin had no special investigations carried out, the diagnosis was thought probable on clinical grounds.

* Details of families with at least one affected first degree relative are in the appendix (page 103).

Parents, sibs and children

Proportions of affected relatives in the tables are for sibs only, since, clearly, no parent can be anencephalic and very few spina bifida cystica patients have as yet had families. There were, however, two parents with vertebral anomalies, one mother and one father. Both index patients were female in the multiple vertebral anomalies group. Both parents also had multiple vertebral anomalies. Routine radiography of forty-eight parents proved entirely negative.

The proportions of sibs with anencephaly, spina bifida/meningocele, and with other vertebral anomalies are noted in Tables, 25, 26 and 27.

Table 25.

118 INDEX PATIENTS WITH VERTEBRAL ANOMALIES INCLUDING SPINA BIFIDA/MENINGOCELE

Proportions of Affected Sibs (including stillbirths) with Anencephaly, Spina Bifida & Other Vertebral Anomalies

Index patients		Edinburgh Clinic Brothers	Sisters	Total	Index patients		London Clinic Brothers	Sisters	Total	Index patients		Total Brothers	Sisters	Total
	A*	-	-	-		A	-	1	1		A	-	1	1
Males (12)	S*	2/10	1/7	3/17	(20)	S	-/26	-/24	-/50	(32)	S	2/36	1/31	3/67
	V*	-	-	-		V	-	-	-		V	-	-	-
	A	3	3	6		A	1	-	1		A	4	3	7
Females (46)	S	1/65	-/48	1/113	(40)	S	-/36	1/26	1/62	(86)	S	1/101	1/74	2/175
	V	2	1	3		V	1	-	1		V	3	1	4
	A	3	3	6		A	1	1	2		A	4	4	8
Total (58)	S	3/75	1/55	4/130	(60)	S	-/62	1/50	1/112	(118)	S	3/137	2/105	5/242
	V	2	1	3		V	1	-	1		V	3	1	4

*A = Anencephaly; S = Spina bifida ± meningocele ± hydrocephalus; V = Other vertebral anomalies.

Table 26.

118 INDEX PATIENTS WITH MULTIPLE VERTEBRAL ANOMALIES
(WITHOUT SPINA-BIFIDA/MENINGOCELE)

Proportions of Affected Sibs (including stillbirths)
with
Anencephaly, Spina Bifida & Other Vertebral Anomalies

	Edinburgh Clinic				London Clinic					Total				
Index Patients		Brothers	Sisters	Total	Index Patients		Brothers	Sisters	Total	Index Patients		Brothers	Sisters	Total
	A*	-	-	-		A	-	-	-		A	-	-	-
Male (7)	S*	1/12	-/7	1/19	(21)	S	1/29	1/17	2/46	(28)	S	2/41	1/24	3/65
	V*	-	2	2		V	-	3	3		V	-	5	5
	A	1	-	1		A	-	-	-		A	1	-	1
Female (30)	S	-/34	1/33	1/67	(60)	S	1/54	1/54	2/108	(90)	S	1/88	2/87	3/175
	V	1	-	1		V	1	-	1		V	2	-	2
	A	1	-	1		A	-	-	-		A	1	-	1
Total (37)	S	1/46	1/40	2/86	(81)	S	2/83	2/71	4/154	(118)	S	3/129	3/111	6/240
	V	1	2	3		V	1	3	4		V	2	5	7

*A = Anencephaly; S = Spina bifida ± meningocele ± hydrocephalus; V = Other vertebral anomalies.

Table 27.

101 INDEX PATIENTS WITH MINOR OR LOCALISED VERTEBRAL ANOMALIES

Proportions of Affected Sibs (including stillbirths) with Anencephaly, Spina Bifida & Other Vertebral Anomalies

Index patients		Edinburgh Clinic Brothers	Sisters	Total	Index patients		London Clinic Brothers	Sisters	Total	Index patients		Total Brothers	Sisters	Total
	A*	-	-	-		A	-	-	-		A	-	-	-
Males (15)	S*	-/28	-/11	-/39	(26)	S	-/30	-/30	-/60	(41)	S	-/58	-/41	-/99
	V*	-	-	-		V	-	-	-		V	-	-	-
	A	-	-	-		A	-	-	-		A	-	-	-
Females (17)	S	-/27	-/23	-/50	(43)	S	1/48	-/48	1/96	(60)	S	1/75	-/71	1/146
	V	-	-	-		V	-	-	-		V	-	-	-
	A	-	-	-		A	-	-	-		A	-	-	-
Total (32)	S	-/55	-/34	-/89	(69)	S	1/78	-/78	1/156	(101)	S	1/133	-/112	1/245
	V	-	-	-		V	-	-	-		V	-	-	-

*A = Anencephaly; S = Spina bifida ± meningocele ± hydrocephalus; V = Other vertebral anomalies.

The figures for Edinburgh and London were noted separately because the general population frequency of the neural tube defects is known to be higher in South East Scotland than in South East England. It is clear from the figures shown that there are fewer affected sibs amongst patients from the London scoliosis clinic.

The overall proportions of affected sibs are shown in Table 28, expressed as percentages.

Table 28.

Proportions of Sibs with Anencephaly, Spina Bifida or Other Vertebral Anomalies
Percentages

Index patients	Sibs	Edinburgh	London	Total
Spina bifida group (118)	Anencephaly	4.8)	1.9)	3.4)
	Spina bifida	)7.7	)2.7	)5.4
	Vertebral anomalies	3.2)	0.9)	2.1)
		2.4	0.9	1.7
	Total	10.0	3.6	7.0
Multiple vertebral anomalies (118)	Anencephaly	1.3)	-)	0.4)
	Spina bifida	)3.5	)2.6	)2.9
	Vertebral anomalies	2.5)	2.6)	2.6)
		3.8	2.6	3.0
	Total	7.5	5.2	5.8
Localised vertebral anomalies (101)	Anencephaly	-	-	-
	Spina bifida	-	0.7	0.4
	Vertebral anomalies	-	-	-
	Total	-	0.7	0.4

These figures are much in excess of the general population incidence estimated as between 0.1 and 0.4 per cent for anencephaly and spina bifida/meningocele and 0.1 per cent for congenital vertebral anomalies.

There was a great similarity between the first two groups of congenital scoliosis index patients (spina bifida group and multiple vertebral anomalies group), although there were fewer anencephalic sibs amongst the latter. The overall percentages of affected sibs were 7.3 per cent and 4.7 per cent. The thirty-nine index patients with a meningocele were analysed

separately, and gave a similar result (2 anencephalics, 3 spina bifida cystica and 1 other vertebral anomaly amongst 69 sibs - 8.7 per cent).

The difference between these groups and the index patients with localised vertebral anomalies is very striking - in all 245 sibs there was only one case of spina bifida/meningocele, (0.4 per cent, which is close to the general population frequency). This one case is probably coincidental.

It was also noted that in no case did a relative with a vertebral anomaly have a localised defect. All cases came from the first two groups and all had multiple defects.

Many of the index patients in this survey were adult, not severely deformed, and had had children of their own. There were no cases of anencephaly, spina bifida/meningocele or vertebral anomalies amongst them, and only one child, a daughter, had a developmental anomaly (congenital dislocation of the hip, which was definitely not of the paralytic type). Details of the children, abortions and stillbirths of index patients are shown in Table 29. (Maternal abortions and stillbirths are noted on pages 96 and 97).

Table 29.

Adult Index Patients - Children

	Sons	Daughters	Abortions	Stillbirths
Spina bifida group	7	13	4	-
Multiple vertebral anomalies	8	11	1	-
Localised vertebral anomalies	7	13*	4	1

* 1 with congenital dislocation of the hip.

There was no excess of abortions or stillbirths when compared with the expected figures from a normal population (approximately 14 per cent abortions and 1.5 per cent stillbirths).

One additional point was noted amongst the first degree relatives: there were fewer than the expected number of sisters amongst the sibs (including stillbirths). This was apparent throughout the whole survey:

	Brothers	Sisters
Spina bifida group	137	105
Multiple vertebral anomalies	129	111
Localised vertebral anomalies	133	112
Total:	399	328

Seventy-one fewer girls in these families is remarkable. It may be that the true sex ratio of congenital scoliosis is even more unequal than has been reported here (1.5 - 3 times as many girls), and that some severely affected females are aborted early in pregnancy.

Affected relatives of index patients with no vertebral anomaly in the curve.

The twenty-three patients without vertebral anomalies in the curve were analysed separately because of the possibility that they might belong to the idiopathic scoliosis group, the vertebral anomalies being only coincidental.

There was a total of forty-six parents and forty-six sibs, or ninety-two first degree relatives. Not one of these relatives had an idiopathic curve; 3 of 46 sibs (6.5 per cent) had a congenital vertebral defect (2 with and 1 without spina bifida). There were no anencephalics.

This evidence would suggest that these patients belong, aetiologically, to the congenital scoliosis group, not to the idiopathic.

Second and third degree relatives

Detailed figures of the proportions of second and third degree relatives with anencephaly, spina bifida/meningocele and vertebral anomalies are shown in Tables 30a and 30b and the proportions summarised as percentages in Table 31.

Table 30a

Proportions of Affected 2nd Degree Relatives
with
Anencephaly, Spina Bifida & Other Vertebral Anomalies

Index Patients		2nd Degree Relatives									
		Paternal		Maternal		Brothers' children		Sisters' children		Half brothers	Half sisters	
		Uncles	Aunts	Uncles	Aunts	Nephews	Nieces	Nephews	Nieces	Maternal	Paternal	Maternal
Vertebral anomalies including spina bifida/meningocele (118)	A*	-	-	-	-	-	-	-	1/	-		-
	S*	- 212	- 197	- 196	- 196	- 21	- 20	1/23	- 23	- 3	-	- 4
	V*	-	-	1/	-	-	-	-	-	-		-
Multiple vertebral anomalies without spina bifida/ meningocele (118)	A	-	-	-	-	-	-	-	-	-	-	-
	S	- 215	- 232	- 228	1/201	- 36	- 32	- 30	- 31	- 4	- 3	- 10
	V	-	-	-	-	-	-	-	-	-	-	-
Minor or localised vertebral anomalies (101)	A	-	-	-	-	-	-	-	-	-		-
	S	- 164	- 148	- 173	- 185	- 34	- 22	- 45	- 38	- 1	-	- 2
	V	-	-	-	-	-	-	-	-	-		-

*A = Anencephaly; S = Spina bifida ± meningocele ± hydrocephalus; V = Other vertebral anomalies.

Table 30b

Proportions of Affected 3rd Degree Relatives
with
Anencephaly, Spina Bifida & Other Vertebral Anomalies

Index Patients		3rd Degree Relatives							
		Paternal Cousins				Maternal Cousins			
		Uncles'		Aunts'		Uncles'		Aunts'	
		Male	Female	Male	Female	Male	Female	Male	Female
Vertebral anomalies including spina bifida/meningocele (118)	A*	-	-	-	-	1/	-	1/	-
	S*	- 181	- 161	- 166	- 164	- 126	- 124	- 171	3/ 195
	V*	-	-	-	-	-	-	-	-
Multiple vertebral anomalies without spina bifida/ meningocele (118)	A	-	1/	-	-	-	-	-	-
	S	- 183	1/ 174	1/213	- 192	- 197	- 156	- 171	- 174
	V	-	-	-	-	-	-	-	-
			(Also one half-brother's son with spina bifida)						
Minor or localised vertebral anomalies (101)	A	-	-	-	-	-	-	-	-
	S	- 116	- 106	- 106	- 102	- 106	- 112	1/156	- 140
	V	-	-	-	-	-	-	-	-

*A = Anencephaly; S = Spina bifida ± meningocele ± hydrocephalus; V = Other vertebral anomalies.

Table 31.

Proportions of Second & Third Degree Relatives with Anencephaly, Spina Bifida, or Other Vertebral Anomalies

Index Patients	Second degree relatives (Half sibs, nephews & nieces only)			Third degree relatives (First cousins only)		
Spina bifida group (118)	A*	1	(1%)	A	2	0.2%
	S*	1/94	(1%)	S	3/1,188	0.3%
	V*	-	-	V	-	-
Multiple vertebral anomalies (118)	A	-	-	A	1	0.1%
	S	-/146	-	S	3/1,461	0.2%
	V	-	-	V	-	-
Localised vertebral anomalies	A	-	-	A	-	-
	S	-/142	-	S	1/944	0.1%
	V	-	-	V	-	-

*A = Anencephaly; S = Spina bifida ± meningocele ± hydrocephalus; V = Other vertebral anomalies.

Only the percentages for half-sibs, nephews and nieces are noted in Table 31, since these are likely to be the most reliable. The proportions show a rapid fall towards the expected figure for the normal population (0.1 - 0.4 per cent). None of the more distant third degree relatives had vertebral anomalies other than spina bifida cystica.

In this, as in many previous surveys relating to the neural tube defects, a higher proportion of affected relatives was noted on the maternal side of the family, among the mothers' sisters' children. The figures for first cousins in the spina bifida group were:

Paternal cousins	Nil of 572	
Maternal cousins	5 of 616	(2 anencephalic, 3 spina bifida) (0.8 per cent)

Four of the five affected cousins were maternal aunts' children (4 of 366, 1.1 per cent). However, it was only in the spina bifida group that this distribution was apparent. Amongst the cousins of index patients with multiple vertebral anomalies the figures were as follows:

Paternal cousins	3 of 762	(2 anencephalic, 1 spina bifida)
Maternal cousins	Nil of 698	

Two of 357 (0.7 per cent) were paternal uncles' children, and one of 405 (0.2 per cent) a paternal aunt's child.

In the group of index patients with localised vertebral anomalies there was only one cousin with spina bifida:

Paternal cousins	Nil of 430
Maternal cousins	1 of 514

(Nil of 218 maternal uncles' children, one of 296, a maternal aunt's child, 0.3 per cent).

The disparity between congenital scoliosis index patients with and without spina bifida is noteworthy - previously the argument has been that

mothers "only know about" their own sisters' children, hence the higher figures for neural tube defects in them. This would not seem to be borne out here since amongst the multiple vertebral anomalies index patients, only cases on the paternal side of the family were noted.

When nephews and nieces are considered, the only two affected were in the families of index patients from the spina bifida group. Both were sisters' children:

Brothers' children	Nil	of 41
Sisters' children	2	of 46 (4.3 per cent)

There were no significant findings relating to the numbers of affected sibs in other clinical groupings. There was no difference between upper and lower vertebral defects, those with and without Sprengel's shoulder, rib anomalies, diastematomyelia, or neurological defects.

The positive findings were the marked similarity between congenital scoliosis with spina bifida and the group with multiple vertebral anomalies but no spina bifida, and their differences from the localised anomalies group.

CONSANGUINOUS PARENTS.

There were two instances of related parents (first cousins), both index patients were in the localised vertebral anomalies group, one with kyphoscoliosis and the other with a simple vertebral fusion. A total of seven sibs, two sons and three daughters were all normal, as were the parents.

EPIDEMIOLOGY - ENVIRONMENTAL FACTORS

Data collected under this heading has been compared with that from normal populations, obtained from various sources:

1) The Annual Reports of the Registrar General for Scotland.
2) The Edinburgh Register of the Newborn, 1964-68 (a city register of all births with congenital anomalies, and a control series, over the same period, of 692 normal births - this latter data being used here).
3) The sibs of index patients.

MATERNAL OBSTRETRIC AND GYNAECOLOGICAL HISTORY

A history was taken from the mothers of index patients relating to menstruation, abortions and stillbirths and the data compared with similar information recorded in the Edinburgh Register of the Newborn.

Menstruation. Irregularities of the menstrual cycle are so common that it is not possible to make any very exact comparison with the small number of cases in this survey. However, it was noted that nearly half of the mothers of index patients in the spina bifida group had some "gynaecological" history, (irregularity of menstruation, long periods of infertility, menorrhagia, severe dysmenorrhoea, and so on), whereas amongst the other groups of index patients and controls rather less than one-quarter of mothers had similar complaints.

Abortions. The numbers of maternal abortions and stillbirths were recorded, and in the great majority of cases confirmation was obtained from medical records. Abortions under eight weeks gestation were not included - the majority were between 8 and 12 weeks. The overall figures were:

Spina bifida group	50 of 301 pregnancies	(16.6 per cent)
Multiple vertebral anomalies	37 of 283 "	(13.1 per cent)
Localised vertebral anomalies	34 of 279 "	(12.2 per cent)

The 'expected' figure is 15 per cent, and so all groups appeared to be within normal limits. However, when reviewed case by case, it became apparent that a large number of abortions came from very few families. In the spina bifida group of 118 cases, seven mothers between them had twenty-seven abortions - over half the total of fifty in this group. These same seven mothers between them had also: two anencephalic stillbirths, four children with spina bifida and meningocele, and three other (apparently normal) stillbirths.

This type of history was not so striking in the other two groups but only six of the 219 mothers had one-third of the seventy-one abortions recorded.

Stillbirths. The total numbers of maternal stillbirths noted were:

Spina bifida group	21 of 301 pregnancies	(7.0 per cent)
Multiple vertebral anomalies	13 of 283 "	(4.6 per cent)
Localised vertebral anomalies	7 of 279 "	(2.5 per cent)

When anencephalic and spina bifida/meningocele stillbirths are removed, the figures for the first two groups are between 3 and 4 per cent. All groups are a little higher than the 'expected' figure of 1.5 per cent.

MATERNAL ILLNESS

The only significant finding under this heading related to maternal hypertension and toxaemia of pregnancy. This is a clinical diagnosis and it is difficult to be precise in retrospective history taking, but it was possible to identify three grades of toxaemia of pregnancy in both the mothers of index patients and the control population (from the Edinburgh Register of the Newborn).

Mild - indicates a history of raised blood pressure, swollen ankles or albuminuria, not considered serious enough for admission to hospital.

Moderate - indicates admission to hospital for treatment of up to two weeks.

Severe - indicates longer than two weeks' treatment in hospital.

(There were no cases of eclamptic fits).

Using this rather rough clinical division, results are shown in Table 32:

Table 32.

Maternal Toxaemia of Pregnancy

	Mild	Moderate	Severe	Total
Controls	14	8	4	26 of 334 (7.8%)
Spina bifida group	10	7	-	17 of 118 (14.4%)
Multiple vertebral anomalies	7	7	1	15 of 118 (12.7%)
Localised vertebral anomalies	5	1	-	6 of 101 (5.9%)

The figures for mothers of index patients in the spina bifida and the multiple vertebral anomalies groups are clearly above the control figure of 8 per cent.

PARENTAL AGE

The mean ages of fathers and mothers, and the means of the paternal-maternal age differences were all significantly raised, for all groups (Table,33, see page 100).

Thus, all congenital vertebral anomalies appear to be associated with parents who are older than average though not very markedly so. A raised maternal age has previously been described for spina bifida cystica, but not for other vertebral anomalies.

PARITY

There was a significant excess of first born children in the spina bifida group and also amongst children with multiple vertebral anomalies. There was no significant finding in the localised vertebral anomalies group (Table 34).

Table 33.

Mean Parental Ages

Index patients	Father	Mother	Parental age difference
Edinburgh			
(58) Spina bifida group	30.13 ± 6.76 (p>0.05)	27.74 ± 6.25 (0.05>p>0.01)	2.5 ± 3.89 (p>0.05)
(37) Multiple vertebral anomalies	31.47 ± 8.64 (p = 0.05)	28.18 ± 6.77 (0.05>p>0.01)	3.03 ± 5.59 (p>0.05)
(32) Localised vertebral anomalies	30.59 ± 5.94 (p>0.05)	27.5 ± 5.53 (p>0.05)	2.99 ± 3.18 (p > 0.05)
London			
(60) Spina bifida group	30.86 ± 8.33 (0.05>p>0.01)	27.7 ± 6.53 (0.05>p>0.01)	3.16 ± 5.36 (0.05>p>0.01)
(81) Multiple vertebral anomalies	31.31 ± 6.55 (p<0.001)	27.92 ± 5.9 (0.01>p>0.001)	3.41 ± 3.78 (0.05>p>0.01)
(69) Localised vertebral anomalies	30.26 ± 6.73 (0.05>p>0.01)	27.79 ± 5.94 (0.01>p>0.001)	2.37 ± 3.9 (p>0.5)
Controls	28.50	25.83	2.67

Table 34.

Parity of Index Patients

Index patients		1st born	2nd born	3rd born+	Total	Significance
(118) Spina bifida group	Observed	56	24	38	118	Significant
	Expected	43.08	36.87	38.05	118	0.02>p>0.01
(118) Multiple vertebral anomalies	Observed	58	31	29	118	Significant
	Expected	43.08	36.87	38.05	118	0.02>p>0.01
(101) Localised vertebral anomalies	Observed	40	29	32	101	Not significant
	Expected	36.87	31.56	32.57	101	

BIRTH HISTORY

There were no significant findings relating to length of gestation or presentation.

The mean birth weight of index patients in all groups was significantly low compared with their sibs (Table 35).

Table 35.

Birthweight of Index Patients Compared with Sibs

	Index patients Mean weight (lbs)	Sibs Mean weight (lbs)
Edinburgh		
(58) Spina bifida group	6.81 ± 1.72	7.46 ± 1.41
	$(0.01 > p > 0.001)$	
(37) Multiple vertebral anomalies	6.85 ± 1.22	7.52 ± 1.28
	$(0.05 > p > 0.01)$	
London		
(60) Spina bifida group	6.71 ± 1.2	7.33 ± 1.14
	$(0.01 > p > 0.001)$	
(81) Multiple vertebral anomalies	6.7 ± 1.34	7.10 ± 1.16
	$(0.05 > p > 0.01)$	

SEASONAL VARIATION

There were no significant findings - there were equal numbers of births in winter and summer.

SOCIAL CLASS

It was noted that there was a highly significant proportion of index patients from the lower social classes, 4 and 5 (using the Registrar General's grading of 1 - 5). This has previously been shown in many surveys of anencephaly and spina bifida, but the effect was quite clear in this survey for all congenital vertebral anomalies (Table 36).

Table 36.

Social Class of Index Patients
(Edinburgh City, Lothians & Fife only)

Index patients		Social Class 1&2	3	4&5	Total	Significance
Spina bifida group	Observed	4	11	17	32	Highly significant
	Expected	6.10	16.99	8.91	32	0.01>p>0.001
Multiple vertebral anomalies	Observed	2	6	12	20	Highly significant
	Expected	3.81	10.62	5.57	20	0.01>p>0.001
Localised vertebral anomalies	Observed	2	5	13	20	Highly significant
	Expected	3.81	10.62	5.57	20	0.01>p>0.001

The figures for the 72 patients from Edinburgh City, the Lothians and Fife are shown here, since these are likely to be the most accurate. These are the patients who would normally be treated in Edinburgh and results are not diluted by (probably upper social class) patients travelling long distances to come to a specialist clinic.

The 'expected' figure for social classes 4 and 5 in this area is 28 per cent, whereas the survey showed 58 per cent of index patients were in this low socio-economic grade.

REGIONAL DISTRIBUTION OF PATIENTS, PARENTS AND GRANDPARENTS

In view of the known differences in incidence of the neural tube defects in Britain, enquiry was made as to where the parents and grandparents of index patients came from. Data was available for 232 patients.

60 per cent of all index patients came from London, the south-east and east of England. 27 per cent came from Edinburgh, the east of Scotland and north-east England. Only 13 per cent came from areas of high incidence for the neural tube defects (Ireland, Wales and western regions).

There was only one point of interest relating to the regions from which parents and grandparents came. Among the 13 per cent of patients who lived in 'high incidence' areas, 89 per cent of parents of the spina bifida and multiple anomalies groups also came from these regions, whereas only 63 per cent of parents of children with localised vertebral anomalies came from Ireland and the west. This was just significant at the 5 per cent level.

DISCUSSION AND CONCLUSIONS

It became apparent from this survey that congenital scoliosis can be divided into three groups:

(1) Associated with spina bifida ± meningocele.

(2) " " multiple vertebral anomalies, without spina bifida.

(3) " " localised vertebral anomalies, including kyphoscoliosis and hemivertebrae.

It also became clear that the first two groups are aetiologically related. Therefore, since it is known from previous surveys that anencephaly is aetiologically related to spina bifida/meningocele, it follows that all three deformities must be classed together as neural tube defects.

Localised vertebral anomalies including the anterior defects of kyphoscoliosis and isolated hemivertebrae, appear to be a separate entity.

The evidence lies in the proportions of their sibs affected with anencephaly, spina bifida cystica and other vertebral anomalies. The proportions affected were very similar in the spina bifida and multiple vertebral anomalies groups, whereas in the localised anomaly group, sibs were almost unaffected. Localised vertebral defects appear to be isolated, sporadic events carrying no risk to subsequent members of the family.

Further evidence is obtained from the epidemiological side of the survey, results being very similar to published work relating to spina bifida cystica and anencephaly. The following was noted for the spina bifida/multiple vertebral anomalies groups of congenital scoliosis:

1) A sex ratio of approximately 3 females : 1 male
2) A raised maternal age (also paternal).
3) An excess of first born children.
4) An excess of low social class children.
5) Low birth weight of index patients.

Amongst the patients with localised vertebral anomalies it was noted that the parental ages were higher than normal and the children were of low social class, but the other features were not apparent.

It was found that toxaemia of pregnancy was more common amongst mothers of the spina bifida and multiple vertebral anomalies groups than expected for a random survey. It was also noted that in a few families there were an unusual number of abortions and stillbirths in addition to definite cases of anencephaly and spina bifida cystica.

Associated structural anomalies, of no definite pattern, were common in all groups of congenital scoliosis.

It is concluded that the aetiology of congenital scoliosis (apart from cases of localised vertebral defects) is the same as that of anencephaly and spina bifida/meningocele, carrying a 5-10 per cent risk to subsequent sibs for one or another of the defects. Inheritance is likely to be multifactorial, but environmental factors must play a major part in the aetiology.

Localised vertebral defects are a separate entity, sporadic and carrying no risk to other members of the family.

SUMMARY

1) A family survey of 339 index patients with congenital scoliosis has been carried out from scoliosis clinics in Edinburgh and the Royal National Orthopaedic Hospital, London.

2) Three clinical types of congenital scoliosis have been delineated and compared:

   (1) 118 patients with vertebral anomalies which include a definite neural arch defect (other than spina bifida occulta of the lumbo-sacral segments).

   (2) 118 patients with multiple vertebral anomalies without a neural arch defect.

   (3) 101 patients with localised or minor vertebral anomalies including kyphoscoliosis and isolated vertebrae.

3) Index patients with congenital scoliosis of types (1) and (2) both had a significantly high proportion of sibs with

   (a) anencephaly.

   (b) spina bifida with meningocele ± hydrocephalus.

   (c) multiple vertebral anomalies without spina bifida.

4) Other family survey data in types (1) and (2) were similar to that reported in many published surveys relating to anencephaly and spina bifida cystica:

   (a) a raised maternal age.

   (b) an excess of first born children.

   (c) " " " low social class children.

   (d) low birthweight of index patients when compared with their sibs.

In addition, a significant number of mothers had a history of toxaemia of pregnancy when compared with a normal population.

5) It is concluded that congenital scoliosis associated with neural arch defects and with multiple vertebral anomalies are aetiologically related to each other, to anencephaly and to spina bifida/meningocele/hydrocephalus occurring alone without vertebral defects. Together they form the neural tube defects.

6) The aetiology is likely to be multifactorial with a major environmental component, and carrying a 5-10 per cent risk to subsequent sibs for any one of these anomalies.

7) Localised vertebral anomalies do not appear to belong to the same group. There was no excess of any developmental anomaly within their families, and most other family survey data was dissimilar.

The group was only alike in having:

(a) a raised maternal age.

(b) an excess of low social class children.

8) It is concluded that localised vertebral defects are sporadic (non-familial) in nature, carrying no risk to subsequent sibs or children.

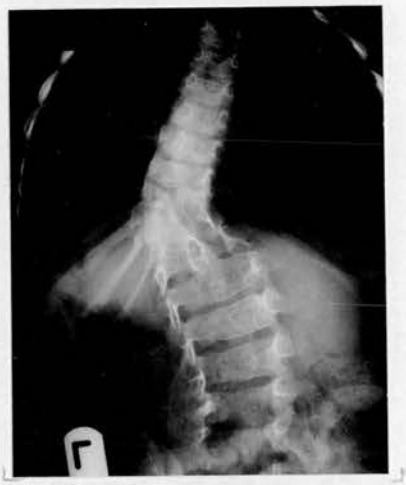


Plate 1: Wide spina bifida, lateral vertebral anomalies and diastematomyelia.

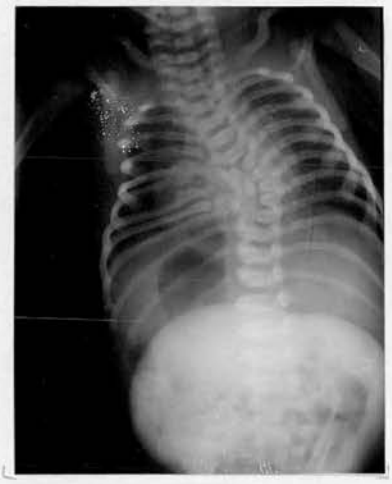


Plate 2: Segmental vertebral anomalies.

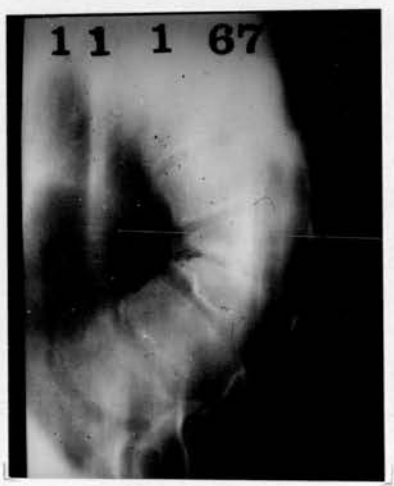


Plate 3: Kyphoscoliosis (lateral view).

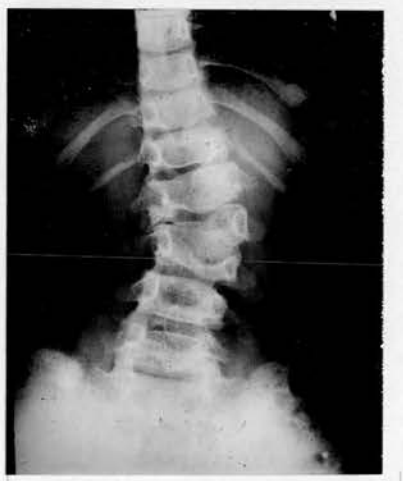


Plate 4: Solitary hemivertebra.

NOTE OF FAMILIES WITH BOTH IDIOPATHIC AND CONGENITAL SCOLIOSIS

Amongst the 200 index patients with idiopathic scoliosis, there was one instance only of an affected mother with congenital scoliosis - a right thoracic curve due to multiple vertebral anomalies. The index patient was female, with juvenile idiopathic scoliosis. No other member of the family was affected. This gives an incidence of 1 of 681 first degree relatives with a congenital type curve - near the estimated population incidence of 1 per 1,000 for vertebral anomalies, and presumably the two are coincidental.

Amongst the 337 index patients with congenital scoliosis, two index patients had affected relatives with idiopathic scoliosis.

(1) An index patient with spina bifida and meningocele, as well as other vertebral anomalies, had two sisters with idiopathic curves, both with onset in adolescence. Both parents were normal.

(2) An index patient with an isolated hemivertebra had a monozygous twin with idiopathic scoliosis. The mother also had an idiopathic curve, and the father had bilateral congenital type inguinal herniae.

This is an interesting family, but the association of the two types of scoliosis is again likely to be coincidental. The family incidence is 4 of 1,401 total first degree relatives (or 4 of 665 female first degree relatives), which is near the population frequency of 2 per 1,000 all cases or 3.9 per 1,000 adolescent girls).

APPENDIX

IDIOPATHIC SCOLIOSIS - KINDREDS WITH AFFECTED 1st DEGREE RELATIVES

No.	Sex	Type of* idiopathic scoliosis	DATES OF BIRTH									
			Index patient	Father	Mother	SIBS 1	2	3	4	5	Abortions	Stillbirths
202	F	A	4/51	8/22	11/26 (R)Th-L 15° **	M.7/47	M.5/56 (L) L. under 10°	F.8/61			'54	
203	F	A	5/52	7/20	12/21	F.6/48 (R) Th. 20°						
206	M	J	2/57	4/28 (R)Th-L under 10°	10/28	F.7/54	M.5/62					
208	M	IR	5/61	7/30	7/38 (L)Th. 10°	F.5/61	F.5/63					
217	F	J	1/61	1/37	2/34 (L)Th. 15°						'59 '60	
218	M	J	3/60	3/34	2/34 (L)Th-L under 10°	F.4/63						
222	M	J	8/55	2/33	10/30 (R) L. under 10°	F.7/56						
228	F	J	9/57	12/22	4/25 (L)Th. 47°	F.6/50 (L)Th. 15°	F.5/54				'52 '56 '61	
235	F	J	11/43	12/01	4/12 (L)Th-L 10°	M.2/35	M.5/36	M.10/39			'41	
249	F	A	2/54	8/25	8/29	F.10/52 (R)Th-L 13°	M.12/57	F.12/64				

* A = adolescent; IR = infantile resolving; IP = infantile progressive; J = juvenile

** (R) and (L) = Right and left; Th = Thoracic; Th-L = Thoraco-lumbar; L = lumbar

No.	Sex	Type of idiopathic scoliosis	DATES OF BIRTH										
			Index patient	Father	Mother	SIBS					Abortions	Stillbirths
						1	2	3	4	5		
251	M	IR	10/67	2/43 (R) L. 20°	11/47	M.8/66	F.10/67	M.11/68	M.3/70		'71	
254	M	A	2/55	7/21 (R)Th. 24°	7/24	F.10/51						
259	M	A	11/52	7/20	11/26 (L) L. 12°							
263	F	A	2/53	2/21	10/25 (L)Th. 10° (R) L. 7°	F.8/44	F.2/52					
271	M	IR	10/67	7/37	8/37 (R)Th. 9° (L) L. 14°	F.9/62					'61 '69	
283	M	IP	6/62	1/44	2/45 (R)Th. 10°							
284	M	IR	8/60	5/26	9/27 (L) Th. under 10°	F.7/53	M.5/55	M.10/56	F.2/64		'58	
288	F	J	1/45	3/08 (R) L. 16°	1/29 (R)Th.69° (L)L. 91°	M.11/43	F.4/52					
293	M	A	9/50	12/17	10/22 (L) Th. under 10°	M.4/57 (L) L. under 10°	M.11/62				'61	

No.	Sex	Type of idiopathic scoliosis	DATES OF BIRTH									
			Index patient	Father	Mother	SIBS					Abortions	Stillbirths
						1	2	3	4	5		
294	M	IP	5/56	8/15	9/19	F.1/39 (L)L.10°	M.9/40	F.8/41	M.3/48	F.9/62		
297	F	A	3/53	12/26	12/26 (R)Th.10°	F.7/57						
300	F	A	7/42	8/13 (R)Th. under 10°	4/18 (R)Th. under 10°	M.6/47 (R)Th. under 10°						
308	F	A	2/52	10/23 (R)Th.10°	6/26	M.2/50	F.3/59					8/48
341	F	IR	1/56	6/32	12/32 (L)L. 23°	F.12/54 (L) L. under 10°	M.10/57	F.7/60	M.4/62	F.11/63	8/59	12/52 6/69
358	F	A	10/53	9/18	10/20 (L) Th. under 10°	F.10/44	M.8/48	M.12/58 (R) Th. 16°				
363	M	IP	1/72	5/12 (R) L. under 10°	6/13	M. 6/36	M.7/38	M.3/43	F.8/47			
365	F	A	1/35	11/08 (R)L. 11°	11/05							'47
378	F	A	2/46	4/02	1/14 (L)Th.12°	F.9/43	F.4/47 (R)Th. 16°					
381	F	J	3/56	3/17	2/20 (R) L. under 10°	F.1/47	M.7/49	M.9/60				
393	F	A	2/51	3/26	10/26	F.10/52 (R) Th. under 10°	F.1/55	M.8/60				
395	F	IP	10/54	10/08 (L) L.25°	4/21	M.3/48					'63	

No.	Sex	Type of idiopathic scoliosis	DATES OF BIRTH									
			Index patient	Father	Mother	SIBS					Abortions	Stillbirths
						1	2	3	4	5		
401	F	A	4/46	2/09	8/15 (R)Th.20°							
412	F	A	9/48	2/14	1/22	F.5/47 (L)L.10°	M.3/51					

APPENDIX

VERTEBRAL ANOMALIES - CONGENITAL SCOLIOSIS

KINDREDS WITH AFFECTED 1st DEGREE RELATIVES

No.	Sex	Type of congenital scoliosis*	DATES OF BIRTH								
			Index patient	Father	Mother	SIBS				Abortions	Stillbirths
						1	2	3	4		
2	F	S	4/60	8/36	9/37					2/61 10/61 11/62 '67 (Anencephaly)	2/64 (Anencephaly)
4	M	S	4/50	5/20	9/29	M.8/54	M.5/65 (Sp. bifida/ hydrocephalus)			'51 '60 '60 '67	
20	M	S	12/59	12/25	10/28	M.6/51 (Sp. bifida/ hydrocephalus)	F.5/53			'52 '57	
29	F	S	6/55	12/13	10/17	M.5/57	M.12/60 (MV)				'51
30	M	MV	12/60	"	"	F.6/55 (Meningocele and MV)	M.5/57				'51
36	F	MV	3/53	1/28	12/33	M.6/54	F.7/57	M.11/58			'61 (Sp. bifida/ meningocele)
42	F	S	6/47	5/20	2/19	M.4/46 M.9/57	F.11/49 M.3/59 (Sp.bifida)	M.4/52	F.9/53		
46	F	MV	11/53	5/21	2/26	M.6/52	F.5/55	F.11/56			10/47 (Anencephaly)
69	F	S	4/57	6/13	12/15	F.6/39 F.4/50	F.1/42 F.8/53	M.2/47 M.9/55	F.7/48		'41 (Anencephaly)
75	F	S	8/50	6/14	2/16	M.5/38	M.4/40				'42 (Anencephaly) '44 (Anencephaly)

* S = spina bifida group; MV = multiple vertebral anomalies; LV = localised vertebral anomalies

No.	Sex	Type of congenital scoliosis	DATES OF BIRTH							Abortions	Stillbirths
			Index patient	Father	Mother	SIBS 1	SIBS 2	SIBS 3	SIBS 4		
81	F	S	9/50	N/K	11/29						'48 (MV)
96	F	S	6/50	7/24	9/20	(MV) F.7/45	M.7/47	F.8/48	M.9/57		
97	F	S	7/45	"	"	M.7/47	F.8/48	F.6/50 (MV)	M.9/57		
98	M	MV	3/56	'40	12/34	F.10/57	F.12/58 (MV)	F.11/61	M.5/64		
99	F	MV	12/58	"	"	M.3/56 (MV)	F.10/57	"	"		
105	M	S	3/61	8/27	6/30	F.10/55 (Sp. bifida/ meningocele)	F.3/59	M.2/63		'51 '52 '53 '56 '64	
123	M	MV	1/54	5/08	7/14	M.7/48	M.9/51 (Sp.bifida/ hydrocephalus)				
129	F	S	11/67	3/37	6/38	M.2/61	F.9/63				1/60 (Anencephaly)
518	F	S	8/51	'19	'28	F.'49	M. '52	F. '57		'56	'56 (Anencephaly) '60 (Sp.bifida/ hydrocephalus)
541	F	S	2/46	2/13	1/14	F.6/42 (Sp. bifida/ meningocele)	F.8/44	M.1/47	M.6/51		
574	F	LV	3/52	7/11	5/13	F.'33 (Sp. bifida/ meningocele)	F.2/35	F.9/47			
617	F	MV	8/54	7/30	8/28 (MV)						

No.	Sex	Type of congenital scoliosis	DATES OF BIRTH										
			Index patient	Father	Mother	SIBS					Abortions	Stillbirths
						1	2	3	4	5		
624	M	MV	8/34	1/93	2/96	M.3/22 M.10/30	M.11/23 M.3/33	M.3/25 M.1/36	M.3/26 M.8/37	F.10/27 F.1/39 (MV)		
631	F	MV	6/49	3/11	1/23	M.11/46	M.6/50	M.8/51 (MV)				
632	M	MV	8/51	"	"	"	F.6/49 (MV)	M.6/50				
645	M	MV	3/48	5/26	11/24	F.12/50 (Sp.bifida/ meningocele)	M.'56 (Sp.bifida/ hydrocephalus)					
660	F	MV	2/51	3/17	12/16	M.10/49						8/47 (Sp. bifida)
665	F	MV	8/34	8/09 (MV)	3/07	M.1/38						
670	F	MV	7/64	12/31	12/32	F.2/61 (Sp.bifida)						
696	M	S	7/50	1/16	3/17	F.11/49						'53 (Anencephaly)
697	M	MV	10/59	7/27	11/26	F.2/56 (MV with sp. bifida)						
698	F	S	2/56	"	"	M.10/59 (MV)						

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A GENETIC SURVEY OF IDIOPATHIC SCOLIOSIS IN BOSTON, MASSACHUSETTS

BY

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EDINBURGH, SCOTLAND

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A Genetic Survey of Idiopathic Scoliosis in Boston, Massachusetts

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ABSTRACT: Families of 207 index patients, including first, second, and third degree relatives were surveyed for scoliosis, and the incidence was compared with that from a similar study in Edinburgh. The data suggest a multifactorial mode of inheritance.

This paper presents the results of a genetic survey of idiopathic scoliosis in Boston, Massachusetts. Following an Edinburgh survey [12], it was decided to compare the findings there with those in a North American genetic survey, and to determine if there is any difference in the clinical types of idiopathic scoliosis on each side of the Atlantic. It had been known for many years that the incidence of infantile idiopathic scoliosis is very low in North America compared with that in Europe, but no precise figures were available.

The clinical and family investigations in this study were conducted from large scoliosis clinics at the Massachusetts General Hospital and Massachusetts Hospital School in Boston (E. J. R.), and the subsequent analysis was done in Edinburgh, Scotland (R. W.-D.). The aim, in addition to comparing the incidence of clinical types, was to determine the familial incidence of idiopathic scoliosis in first, second, and third degree relatives, to note any associated anomalies, and to assess the effect of parental age, if any.

Literature

The early literature on idiopathic scoliosis is confusing, particularly in relation to rickets and neurofibromatosis. There are references to what is probably hereditary idiopathic scoliosis in the European literature of the last century, but the first fairly definite reports [6,8] of inheritance in this condition in the English literature were in 1934. The first large family survey [4] was carried out in Germany of a condition which was called rachitic scoliosis. This was almost certainly adolescent idiopathic scoliosis and the conclusion was reached that rickets was not the true etiology in the cases studied. This was a remarkable survey in that Faber traced 660 index patients, examined most of them personally, and obtained roentgenograms of parents and siblings. He found that in 26.4 per cent of the families another individual was affected, a sibling in 7 per cent of the cases, and a parent in 13.5 per cent. He also found several pedigrees which illustrated full dominant inheritance. It is probable, though not certain, that Faber and we are discussing the same condition.

In the Edinburgh survey of 114 index patients, it was found that 27.2 per cent of the families had more than one individual affected, a parent in 3 per cent, a sibling in 5 per cent, and a child of an index patient in 5 per cent. The screening of relatives in this survey was done initially by clinical examination and subsequently the diagnosis was confirmed by roentgenography.

Reports of familial surveys for idiopathic scoliosis have appeared since the

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present study was started. One [3] was from New York City, using medical records and tracing patients and their relatives by means of a questionnaire. The conclusion was that there was no evidence to support a simple genetic basis for idiopathic scoliosis, although there was a familial concentration of cases. However, scoliosis is a difficult condition to diagnose accurately and since relatives were not personally examined by the authors, their data are not comparable with those from other surveys.

Cowell and associates reported on seventy-five cases from Wilmington, Delaware, and also noted a high familial concentration of affected individuals. In their study, the parents and siblings all had a roentgenographic examination and approximately one-third of them were found to have a curve of more than 10 degrees. It was suggested that there was an x-linked dominant inheritance, in view of the excess of females and absence of inheritance from father to son in their survey. A survey from the U.S.S.R. [1] also showed a strong familial concentration of cases with probable dominant inheritance. There were three cases of father-to-son inheritance in this series. In a study in Toronto [5], 201 families were analyzed in which there were members with idiopathic scoliosis, and 7.2 per cent of the siblings and 5.7 per cent of the parents were affected. The conclusion was that probably the mechanism of inheritance was multifactorial.

The current survey may be of value for several reasons. Unlike the previous studies cited, the clinical investigation was carried out entirely by one individual and included personal examination and roentgenography. Not only the first degree relatives, but also a large number of the second and third degree relatives were included. Every effort was made to secure as accurate a diagnosis as possible.

Materials and Method

The selected cases were all the new patients with idiopathic scoliosis attending either of the two clinics during 1967 to 1970, a total of 240 individuals. This sample came from the many ethnic groups which make up the population of greater Boston.

Three foster children were excluded. In addition, several of the clinic patients who were from the same family were also excluded. In view of the difficulty in determining whether subsequent cases within one family were diagnosed solely because the first patient had already been diagnosed, only index patients from families with one member attending the clinic were included. This gave a total of 208 index patients. They were divided according to the age of onset of the scoliosis into three groups: infantile, juvenile, and adolescent [7] (Table I).

There was only one patient with infantile idiopathic scoliosis. Since it was apparent from the Edinburgh survey that the mode of inheritance of this condition was likely to be different, this boy (who also had club feet) was excluded, leaving 207 patients and their families for analysis.

All index patients and first degree relatives (parents and siblings) included in the survey were seen personally and roentgenograms were obtained. Second degree relatives (grandparents, uncles, and aunts) and third degree relatives (first cousins only) whenever possible were seen and examined. In the case of those living at a distance, diagnosis was made on the basis of the roentgenographic examination only. The total number of second degree relatives was 1,720. No information was obtained on 543 of them (350 were dead at the time of the survey and 193 could not be traced). Roentgenograms were obtained for the remaining 1,177 (that is, 86 per cent of those still living).

The total number of third degree relatives (first cousins) known to the index patients' families was 1,231, and of these 933 (76 per cent) were traced and roentgenograms obtained.

It is probable, therefore, that the figures for relatives of the second and third

TABLE I

IDIOPATHIC SCOLIOSIS INDEX PATIENTS

Type of scoliosis	Male	Female	Total
Infantile (birth to 3 years)	1	0	1
Juvenile (4–9 years)	3	19	22
Adolescent (10 years and over)	35	150	185
Total	39	169	208

TABLE II

TOTAL INDIVIDUALS IN FAMILY SURVEY

		1st Degree Relatives (Parents, Siblings)	2nd Degree Relatives (Grandparents, Uncles, Aunts)	3rd Degree Relatives (1st Cousins Only)	Total
Male index patients	38*	81	233	164	516
Female index patients	169	471	944	769	2353
Total	207	552	1177	933	2869

* Excluding the only patient with infantile idiopathic scoliosis.

degree are less accurate than for those of the first degree. It is, however, unlikely that the diagnosis would be missed on roentgenography, and likely that curves not due to scoliosis would be wrongly included. Thus the proportions of second and third degree relatives found to have a curve are likely to be too high. Analysis of the family survey is based on 207 index patients and 2662 relatives. The relationships of individuals from whom data was collected are shown in Table II.

Population Incidence

It was not possible to carry out a population survey in the Boston area and therefore figures were used from other surveys, one from Delaware [9] and the other from Edinburgh [12]. The American survey was based on a large number of minifilms of the chest made during a survey for tuberculosis in the State of Delaware. In the first 15,000 individuals surveyed (all over fourteen years of age) 230 with curvatures (1.5 per cent) were found. Of these 150 were regarded to have curves, diagnosed as probably trivial postural changes, while twenty curves were associated with some obvious pathological process. Therefore there were sixty cases of probably idiopathic scoliosis (four per 1,000). It is interesting that of these sixty, 81 per cent were right sided. However, the authors were careful to point out the hazards of making a diagnosis by the films at their disposal, and a certain number of lumbar curves must not have been visible on the roentgenograms of the chest.

The Edinburgh survey was carried out on 7,894 normal school children over seven years of age. Those in whom vertebral rotation was clinically apparent had a roentgenographic examination to confirm the diagnosis. Incidences of 3.9 per 1,000 girls and 0.3 per 1,000 boys were found, giving an over-all total of 1.8 per 1,000. These figures do not differ greatly from Shands and Eisberg's figure [9] of four per 1,000. It is probable that roentgenographic examination alone would have produced a higher figure than would be arrived at by a clinical and subsequent roentgenographic examination, as a number of minor and non-idiopathic curves would be missed. We thought it reasonable for the current survey to take an over-all population incidence of two per 1,000, assuming the figure for females to be about four per 1,000 and for males to be under one per 1,000.

Clinical Features and Associated Anomalies

In the curves of juvenile type, the sex ratio was 0.16 (approximately one boy to six girls) and all curves were right sided. In the curves of adolescent type the ratio was 0.23 and 97 per cent of the curves were right sided. In both groups combined there were only four lumbar curves, all of which were of adolescent type; all the rest were thoracic or thoracolumbar.

There were no associated anomalies among the twenty-two patients in the juvenile group, while in the adolescent group, the following were noted: cleft palate in seven girls, bilateral inguinal hernia in two boys, club foot in two girls, patent ductus arteriosus in one girl, talipes calcaneovalgus in one boy, and epilepsy in one girl.

Associated anomalies in relatives, apart from idiopathic scoliosis, were unremarkable.

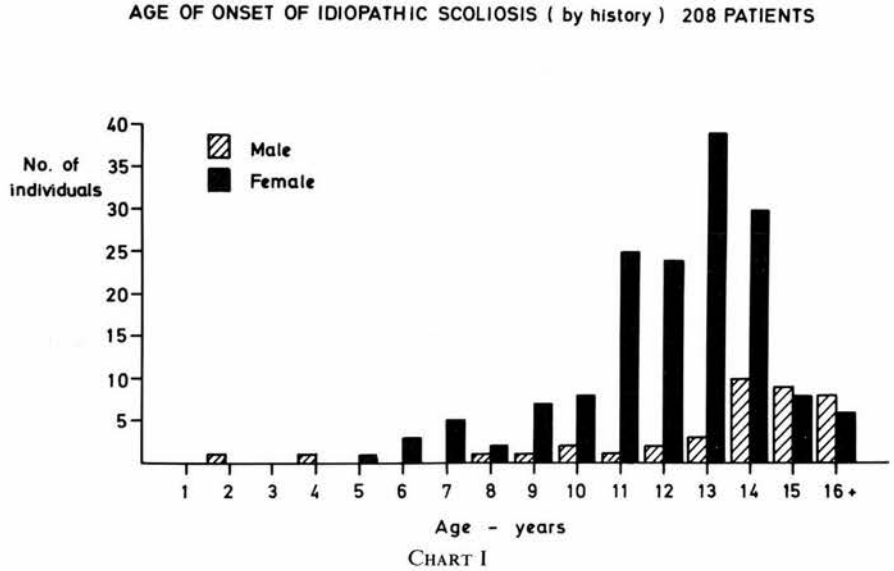

CHART I

Age of Onset of Scoliosis and Age of Correction for Siblings

The age distribution for the onset of the curve in the 208 index patients is shown in Chart I. The most common age at onset was thirteen years for girls and about fourteen years for boys.

A graph was constructed from the 240 patients attending the clinic, showing the percentage of males and females affected at each year age (Chart II). Using this graph corrections were computed for the ages of the siblings. It is apparent (Table I) that the curvature can develop at any age up to fifteen or sixteen years. Thus, when considering the number of siblings affected with idiopathic scoliosis, younger siblings cannot be given full weight in the calculation. For example, a young sister, ten years old, only counted as 0.15 of a person, because at this age only 15 per cent of girls who will develop scoliosis have done so. Thus, the total number of siblings, when corrected for age, was less than the actual number of individuals seen.

Numbers of Siblings Fourteen to Fifteen Years Old

The proportions of affected siblings, excluding all under the age of fourteen years, are: brothers, 10 degree curves, 6 per cent; 20 degree curves, 3.9 per cent; and sisters, 10 degree curves, 26.4 per cent; 20 degree curves, 15.5 per cent. These

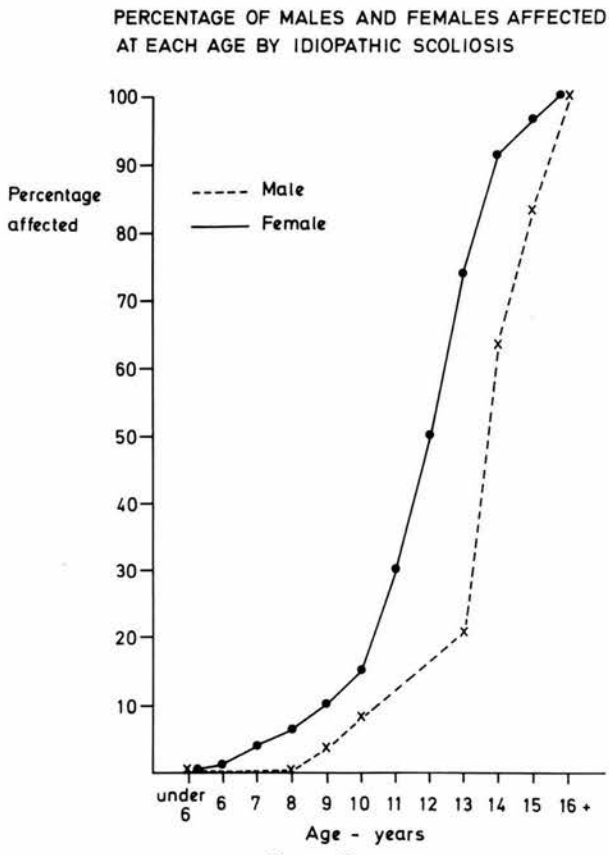

CHART II

proportions agree well with the estimated figures using all siblings and correcting for age (brothers, 7.8 per cent and 3.9 per cent; and sisters, 28 per cent and 17.4 per cent); 59 per cent of all siblings were fourteen years old or older when examined.

Family Survey Results

Among the index patients there was an unexpectedly low proportion of twins, one pair of girls who were dizygotic twins, both with right thoracic curves presenting at the age of nine years.

The findings in first degree relatives (Table III) showed no significant difference between the proportions of affected relatives of male and female index patients. (The ratios of affected to unaffected first degree relatives in the families of the male and female index patients were essentially the same, that is, 17.3 per cent and 15.5 per cent.)

The ratio of males affected to unaffected first degree relatives (fathers and brothers) was very much less than that of females (mothers and sisters), mirroring the sex ratio observed in the index patients. Over-all, female relatives were affected five times more often than male.

The figures shown relate to curves of 10 degrees or more, although including curves of this minor degree inevitably raises problems of diagnosis and uncertainty as to whether a curve is present or not. If the smallest curve allowed was 20 degrees, the percentages were: for fathers, 2.6; mothers, 18.5; brothers, 3.9; and sisters, 17.4, while for all first degree relatives the percentage was 11.1. These figures are probably a more reliable indication of the incidence. It is interesting to note that the per-

TABLE III

PROPORTIONS OF FIRST DEGREE RELATIVES WITH IDIOPATHIC SCOLIOSIS
(10 Degree Curves and Over)

Index Patients		Fathers	Mothers	Brothers	Sisters	Total
Male	(38)	1/26	4/28	3/11	6/16	14/81 (17.3%)
Female	(169)	3/129	34/134	5/92	31/116	73/471(15.5%)
Total	(207)	4/155	38/162	8/103	37/132	87/552
		(2.6%)	(23.5%)	(7.8%)	(28.0%)	(15.8%)

TABLE IV

PROPORTIONS OF SECOND DEGREE RELATIVES WITH IDIOPATHIC SCOLIOSIS
(20 Degree Curves and Over)

Index Patients		Paternal Side		Maternal Side		Total
		Male	Female	Male	Female	
Male	(38)	1/48	2/71	0/44	2/70	5/233 (2.1%)
Female	(169)	1/203	2/250	4/234	16/257	23/944 (2.4%)
Total	(207)	2/251	4/321	4/278	18/327	28/1177
		(0.8%)	(1.2%)	(1.4%)	(5.5%)	(2.4%)

TABLE V

PROPORTIONS OF THIRD DEGREE RELATIVES WITH IDIOPATHIC SCOLIOSIS
(20 Degree Curves and Over)

Index Patients		Paternal Side		Maternal Side		Total
		Male	Female	Male	Female	
Male	(38)	0/36	0/43	0/46	2/39	2/164 (1.2%)
Female	(169)	0/201	2/184	1/222	8/162	11/769 (1.4%)
Total	(207)	0/237	2/227	1/268	10/201	13/933
			(0.9%)	(0.4%)	(5.0%)	(1.4%)

centages for fathers plus brothers and for mothers plus sisters were almost identical. There was one instance of father-to-son inheritance, and both individuals had right thoracic curves of over 20 degrees.

The ratios of affected to unaffected second and third degree relatives are shown in Tables IV and V. Again there was no significant difference between the proportions of individuals affected among the relatives of the male and female index patients, but there was an excess of affected individuals on the maternal side of the family, among both the second and third degree relatives. This increased incidence has not previously been described.

The over-all percentages of those affected were 2.4 for the second degree and 1.4 for the third degree relatives. These percentages were in marked contrast to the high percentage of first degree relatives with curves over 20 degrees (11.1 per cent). All of these figures were much in excess of the normal population incidence of about two per 1,000 (0.2 per cent).

There was no difference between the juvenile and adolescent groups in the ratios of affected to unaffected individuals among the first, second or third degree relatives. The great majority of the 126 relatives with scoliosis had right-sided thoracic or thoracolumbar curves. There was only one individual with a left-sided curve and only four with lumbar curves.

Parental Age and Parity

The average age of the mothers at the time of birth of the index patient in the

juvenile group was 30.25 years and of the fathers, 33.46 years (the fathers being 3.21 years older). In the adolescent group the average age of mothers was 27.7 years and of fathers, 30.0 years (the fathers being 2.3 years older). The relationship of the age of the mother to the parity of the index patients is shown in Table VI.

These figures differ significantly, being higher than the expected figures for the general population in which the greater number of children (167.4 per 1,000 mothers) are first born to mothers in the twenty to twenty-four year old age group [10].

It would appear that for the juvenile group the average maternal age (which was over thirty years) was very much higher than the expected normal, but there were too few patients in that group to be certain.

TABLE VI

IDIOPATHIC SCOLIOSIS
MATERNAL AGE AND PARITY—ALL CASES

Age of Mother (yrs.)	Parity				
	1st born	2nd	3rd	4th +	Total
15–19	2	2	0	0	4
20–24	33	10	2	0	45
25–29	35	30	23	1	89
30–34	16	13	15	6	50
35–39	0	4	3	7	14
40 +	1	1	0	0	2
Total	87	60	43	14	204*

* Insufficient information in 3 cases.

In view of reports of an effect of paternal age in some disorders of dominant inheritance where a new mutation has occurred, the average age of the fathers was determined in the apparently sporadic index cases (that is, the cases in which no other individual in the family was affected). In the sporadic cases of the juvenile group the fathers' ages averaged 28.75 years (eighteen months older than the mother) and in the sporadic cases of the adolescent group, the fathers' ages averaged thirty years (2.5 years older than the mother).

Genetic Counseling

Patients and parents are likely to ask questions relating to the probability of idiopathic scoliosis recurring in the family. Risk figures were compiled from this survey. However, no estimate can be made of the severity of the curve; many of the curves predicted by these figures would be only minor ones of under 20 degrees. The figures are dissimilar for males and females, and there is a sharp increase in risk if either the father or the mother also has a curve. The percentages are obtained from the proportions of the siblings with scoliosis (shown in Table III), divided into two groups; those in whom the parents were normal (165 index cases) and those in whom one parent had scoliosis (forty-two index cases). There was no instance in which both parents had scoliosis.

If both parents of an index patient are normal, the risk to a subsequent brother is 2 per cent and the risk to a subsequent sister is 7 per cent.

If one parent has idiopathic scoliosis, the risk to a subsequent brother is 7 per cent and the risk to a subsequent sister is 42 per cent.

There are no figures yet available for a patient-child risk, as these family surveys must be based on the index patients—those who have drawn attention to the family and in whom the diagnosis is as certain as it can be. Using them as the base line, one looks at their parents, their siblings, and (when possible) their children.

Discussion

The clinical features found in Boston showed several differences from those in Edinburgh. The most obvious difference was the fact that only one patient of 208 consecutive cases (0.5 per cent) had infantile idiopathic scoliosis. In the Edinburgh survey 50 per cent of patients with idiopathic scoliosis presented in infancy, although many of these curves, in due course, resolved.

In the Boston survey 11 per cent of the 208 patients presented with juvenile scoliosis (aged four to nine years). The figure for Edinburgh was 12 per cent overall, but in that series if only juvenile and adolescent cases are included then the proportion of juveniles was 17 per cent. This figure indicates that in Edinburgh idiopathic scoliosis was being recognized rather earlier than in Boston. There was also a difference in the sex ratio in the two juvenile groups. The Boston survey showed six girls to one boy while there were three girls to two boys in the Edinburgh study. A further point of difference between the two juvenile groups was the side of the curve. In Boston all curves were right-sided whereas there was an approximately equal number of left-sided and right-sided curves not only in the Edinburgh study but also in a previous London survey [7].

Genetic surveys of idiopathic scoliosis are always bedeviled by uncertainty as to the diagnosis, since this condition can only be diagnosed by exclusion of all other known causes of spinal curvature. It has been mentioned previously that early writers had difficulty in distinguishing idiopathic scoliosis from that due to rickets or neurofibromatosis. Reports of more than about fifteen years ago are therefore of limited value.

Following the 1968 Edinburgh survey it became apparent that there were also difficulties relating to the diagnosis of minor, unsuspected curves in the relatives of index patients. Spinal curvature due to osteoporosis and osteomalacia in the elderly was one cause of difficulty [11]. Another was Scheuermann's disease (adolescent kyphosis) with mild scoliosis in younger relatives because this condition may wrongly be included as idiopathic scoliosis. There are also a variety of causes of postural scoliosis which must be excluded by clinical examination. We do not believe that an adequate family survey of idiopathic scoliosis can be conducted except by careful examination of each individual by someone experienced in this particular condition.

The maternal age effect noted in the Edinburgh survey (and also in de George and Fisher's survey) was also apparent in the Boston study; both the few juvenile and adolescent patients did appear to have older mothers than would be expected in the general population.

It is interesting that in Faber's 1936 survey the proportion of kindreds with another affected relative was exactly the same as in the present survey (26.4 per cent), and that the Edinburgh figure of 27.2 per cent was almost identical. The proportions of first degree relatives affected in the present survey were much in excess of those noted in Edinburgh (11.1 per cent compared with 5 per cent) but the more complete examination in the present study, including roentgenography of all individuals, would no doubt account for this. Both surveys showed relatively low proportions of affected males (fathers or brothers) when compared with the proportions of affected females (mothers and sisters). The fact that there was one instance of father-to-son inheritance makes x-linked dominant inheritance unlikely.

Unlike the Edinburgh survey, the present study showed a much more precipitous drop in proportions of affected first, second and third degree relatives (11.1, 2.4 and 1.4 per cent) compared with the Edinburgh survey (7.0, 3.7 and 1.6 per cent). The sharp drop in the Boston figures is noteworthy because the former is more characteristic of multifactorial inheritance. However, against this concept is the

fact that male patients with idiopathic scoliosis (the rarer sex to be affected) had no more affected relatives than did female patients.

If the inheritance of this condition is multifactorial, one would expect the families in which there were several affected members to have the more severe curves. This is difficult to determine because "severity" of a curve will depend on a number of factors such as the age when it first develops, the speed with which it develops, when the child is brought for treatment, and the efficacy of the treatment. It remains uncertain, therefore, whether idiopathic scoliosis is of dominant or multifactorial inheritance, though the latter is perhaps more likely judging from the figures obtained in this study.

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FAMILIAL (IDIOPATHIC) SCOLIOSIS

A Family Survey

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The diagnosis of idiopathic scoliosis is made after other known causes of the deformity have been excluded. This paper does not deal with scoliosis resulting from vertebral anomalies, nor with that associated with conditions of known genetic etiology, such as neurofibromatosis, Marfan's syndrome or muscular dystrophy. Also, the diagnosis of idiopathic scoliosis is only made when the curve is structural, that is, when vertebral rotation accompanies the lateral curve. This is a clinical feature, made evident as the individual bends forwards to touch his toes, when a " rib hump" appears (Fig. 1).

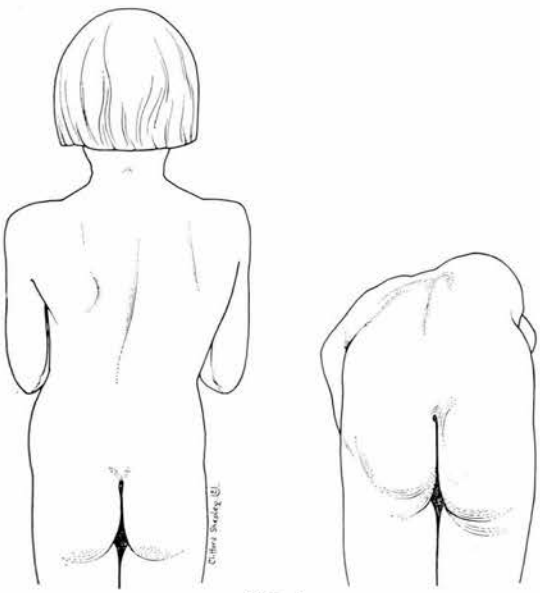

FIG. 1
Right thoracic curve with rib hump, indicating the vertebral rotation of structural scoliosis.

The aim of this study was to establish the family incidence of the deformity in 114 patients and to compare this with the incidence in the general population. This would indicate if there is a concentration of the deformity within families and would give some guide as to the nature of any genetic factor involved. In addition, the patients were subdivided by age of onset of the curve, whether the deformity resolved or progressed, and whether it was accompanied by any other developmental anomaly. By comparing the figures from the family survey in each of these groups it is possible to obtain some evidence as to whether these differing clinical patterns share the same basic etiology.

MATERIAL AND METHOD

A total of 180 case records from the Edinburgh Scoliosis Clinic were analysed. One hundred and sixty-one individuals with idiopathic scoliosis as the only deformity were noted, and nineteen with scoliosis together with some other (non-vertebral) defect. Eight further patients with scoliosis and some associated defect were added from the orthopaedic department of the Royal Hospital for Sick Children, Glasgow, by courtesy of Mr N. J. Blockey. One hundred and fourteen of these index cases were selected and the families of each of them (the first, second and third degree relatives) were personally examined for a " rib hump." This is not sufficient for a firm diagnosis of idiopathic scoliosis because it is present in all patients with structural scoliosis whatever the etiology; but it is a useful method of rapid screening. Individuals with this physical sign were then brought to their nearest hospital for a more detailed examination and radiography. This work entailed travelling all over the British Isles, seeing well over 2,000 individuals. The project was started in 1962 by Mr R. S. M. Ling who collected the first thirty-eight pedigrees.

Age distribution and side of curve—These were similar to those described by James, Lloyd-Roberts and Pilcher (1959). The typical curve in the infant patient was left thoracic (88 per cent), and in the adolescent right thoracic (90 per cent), with a change-over in the middle years of childhood.

There are two peaks of incidence, one in infancy and the other in adolescence (Fig. 2). The deformity is rarely apparent at birth, but develops during the first year of life. There are very few new cases in the middle, juvenile years, but there is a big increase during adolescence, almost exclusively in girls. Two main groups were therefore available for comparison: early onset scoliosis (under eight years) and late onset (eight years and over). The early onset type might be " resolving " or " progressive." Once growth ceases the deformity becomes static.

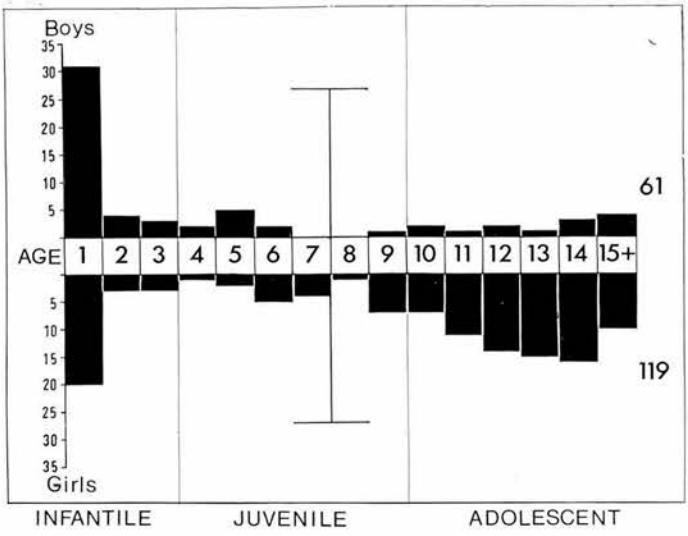

FIG. 2
Age of onset of idiopathic scoliosis in 180 patients.

It is of interest that the infantile form of scoliosis is very uncommon in North America, where attendances at scoliosis clinics consist almost entirely of adolescent cases. Figures are available from Iowa (Ponseti 1966) where the number presenting under eight years of age is only 8 per cent of the total compared with 50 per cent in Britain.

Sex ratio—In the early onset group there is a slight excess of boys over girls (1·21, or approximately five boys to four girls). Late onset scoliosis is rare in boys, the ratio being 0·15 (one boy to seven girls).

Correction for age—Because scoliosis could develop at any age up to fifteen years, it was apparent that younger relatives could not, as it were, count their full weight. A graph has, therefore, been constructed from the total number of cases attending the scoliosis clinic, showing the percentage of boys and girls affected at each age (Fig. 3). For example, a young sister aged three years counts as only 0·26 of a person because by this age only 26 per cent of the girls who will develop scoliosis have done so.

Population incidence—It was necessary to do a population survey, because from the beginning of the family survey it was apparent that many individuals had a mild degree of scoliosis without being aware of it, and the figures were thus unreliable until the general population incidence was established. This survey was done in Edinburgh schools, nursery schools and infant clinics and included children from two weeks to eighteen years of age. The same criteria were used for diagnosis, and children with a rib hump were brought to hospital for

further examination and radiography. The results (Table I) were in reasonable agreement with the proportions observed in the scoliosis clinic; only one child was found with resolving scoliosis.

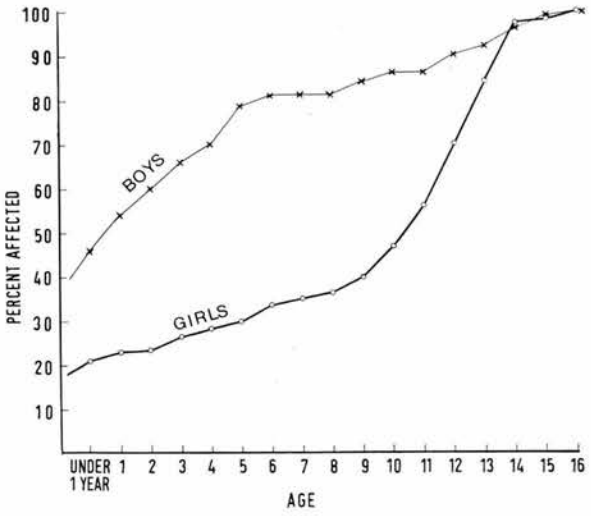

FIG. 3

Percentage of boys and girls affected at each age by idiopathic scoliosis.

RESULTS

Family survey—There were ninety-two index patients with scoliosis as the only deformity (including thirteen with resolving scoliosis), and twenty-two with some other anomaly in addition (including one resolving case). Sixty-one were of the early onset type and fifty-three late onset.

Of the 114 index patients investigated, thirty-one (about one-quarter) had one or more affected individuals in the family. The incidence of scoliosis amongst relatives in all groups of index patients was considerably in excess of the population rate.

TABLE I

IDIOPATHIC SCOLIOSIS SURVEY: 11,087 EDINBURGH CHILDREN

Number of children	Population incidence per 1,000		
	Male	Female	Total
Early onset (3,193)	1·2 (2 of 1,653)	1·3 (1 and 1 resolving of 1,540)	1·3
Late onset (7,894)	0·3 (1 of 3,789)	3·9 (16 of 4,105)	1·8

Scoliosis and osteoporosis—When the figures of the idiopathic survey were first analysed, it was found that there were more individuals with scoliosis amongst second degree relatives than amongst first degree, which genetically was not explicable. This group was reviewed again and it was then appreciated that many of them were elderly individuals with osteoporosis and a curve. This has formed a subsidiary research project which will be reported in due course.

The histograph (Fig. 4) illustrates the figures for first, second and third degree relatives added, and so overall percentages are low. The highest incidence is among the first degree relatives (parents, siblings and children) of the adolescent girls' group (Table II), and this number is approximately halved in the second and again in those of the third degree; but

even in these distant relatives the incidence is still four times that of the general population figure of 0·39 per cent.

The highest incidence of all was among the first degree female relatives of these adolescent girl patients, with 12 per cent affected.

The early onset group did not show such a high percentage of affected relatives, and the incidence from first to third degree dropped very little (2·6 per cent, 2·3 per cent, 1·4 per cent). However, compared with a population incidence of 0·1 per cent the family figures were clearly increased.

The male and female relatives of male and female index cases were analysed separately, because the sex incidence is unequal in both early and late onset groups. The results indicated only that the groups in which scoliosis is commoner (infant boys and adolescent girls) had more affected relatives than those in which it is less common (infant girls and adolescent boys).

There was an approximately equal incidence amongst parents, siblings and children (3 per cent, 5 per cent, 5 per cent).

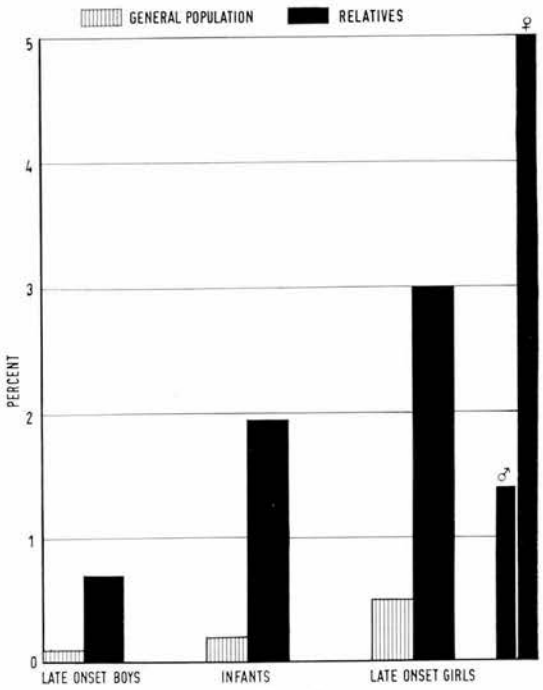

FIG. 4
Comparison of incidence of scoliosis in the general population and among the relatives of scoliotic patients.

One of the points that emerged from the survey was that a child who had developed a curve in infancy might have a relation with the adolescent type of curve, and vice versa. However, there were many cases in which there was no information as to age of onset of scoliosis, the individual being unaware of its presence. Indirect evidence was obtained from

TABLE II
IDIOPATHIC SCOLIOSIS—LATE ONSET GIRLS
(Forty-two index patients)

Affected relatives*		
First degree	**Second degree**	**Third degree**
10 of 144 (6·94 per cent)	8 of 217 (3·69 per cent)	3 of 194 (1·55 per cent)

* Figures corrected for age.

noting the sex of all the affected relatives, and the side of the curve. In the infantile group of patients the curve is typically in a boy and convex to the left, and in the adolescent group, in a girl and to the right. The pattern among the relatives of each group did not conform with this distribution. Male and female, left and right, approached equal numbers, indicating a probable mixture of infantile and adolescent cases amongst them.

Resolving scoliosis—In this series, of children seen under one year of age, the scoliosis resolved without treatment in half of them, and in half progressed to a more severe deformity. The onset was nearly always during the first six months of life, and the deformity disappeared over the next year or so. In all other respects it was like the progressive type, being nearly always left-sided and rather more common in boys than girls. The evidence for including

them with the children with a progressive type of curve is that scoliosis is found among their relatives in precisely the same proportions as in the main " early onset " group, and much in excess of the population incidence. This suggests that the resolving type of scoliosis is the mildest manifestation of what may be a very severe disorder.

TABLE III

MATERNAL AGE DISTRIBUTION IN NINETY-FOUR CASES OF ADOLESCENT IDIOPATHIC SCOLIOSIS

Age of mother (*years*)	15–24	25–29	30–34	35 and over	Total
Adolescent scoliosis	22	17	29	26	94
Normal population	28·54	28·77	20·54	16·15	94·00
$x^2_{(2)}=15{\cdot}81 \quad 0{\cdot}001<p<0{\cdot}01$					

Twins—There was one pair of female twins (probably identical) in the survey, with the adolescent type of scoliosis; one had a left and the other a right lumbar curve. Further investigation was refused, but another sister also had scoliosis. The parents were both dead, but were thought to have been normal.

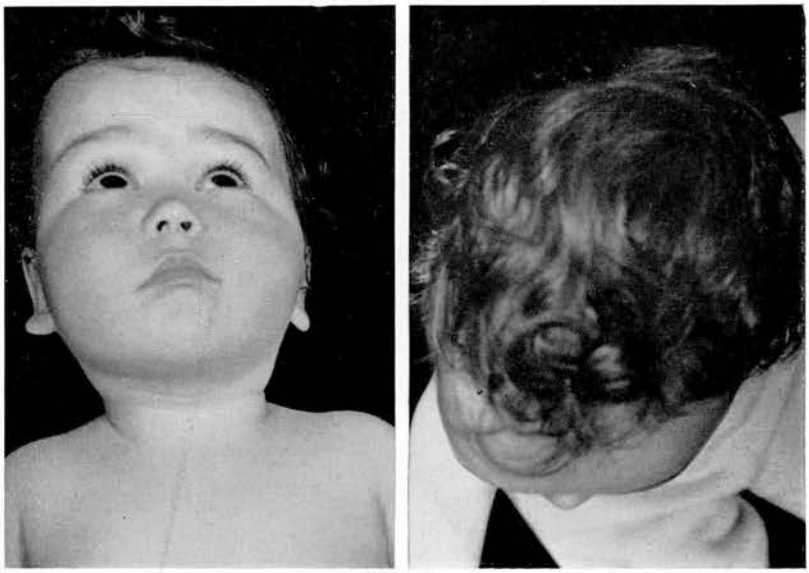

FIG. 5

Left-sided plagiocephaly, accompanied by left thoracic scoliosis.

There were three pairs of dizygotic twins, one only of each pair affected: a girl with adolescent scoliosis with a male twin; a boy with adolescent scoliosis with a male twin; and a boy with infantile resolving scoliosis with a female twin. Another girl with adolescent scoliosis had a male twin who died at birth.

Consanguinity—There was no instance of parental consanguinity.

Parental age and parity—There was a positive finding here in the group of children with adolescent scoliosis. The mother was significantly older than normal by comparison with a control series covering the same years obtained from the Registrar General's figures on parental age. The trend was apparent in the cases in which the detailed family survey was being carried out, and a questionnaire was then sent to a further group in order to increase the numbers (Table III).

Paternal age and parity showed no significant (independent) difference from normal, and neither was there any maternal age effect in the children with early onset scoliosis.

Associated anomalies. *Plagiocephaly*—Moulding of the head was present in all infants with scoliosis seen under the age of one year, and was present both in the resolving and progressive types (Fig. 5). The deformity was transient, and by the age of three years only half of them showed it, and by five years there was only the occasional child with a persistent deformity. In all cases the plagiocephaly agreed with the side of the curve (that is 88 per cent of infants had left-sided curves, and the left side of the head appeared pushed back).

A control group of infants under one year in the city clinics was examined, and seventy-nine of 625 (11 per cent) were found to have plagiocephaly, equally left- and right-sided. Between one and three years 3 per cent were found, but none above this age.

Other associated anomalies—The case records of twenty-seven children with apparent idiopathic scoliosis together with some other developmental defect have been analysed and the families of twenty-two of them visited (Fig. 6).

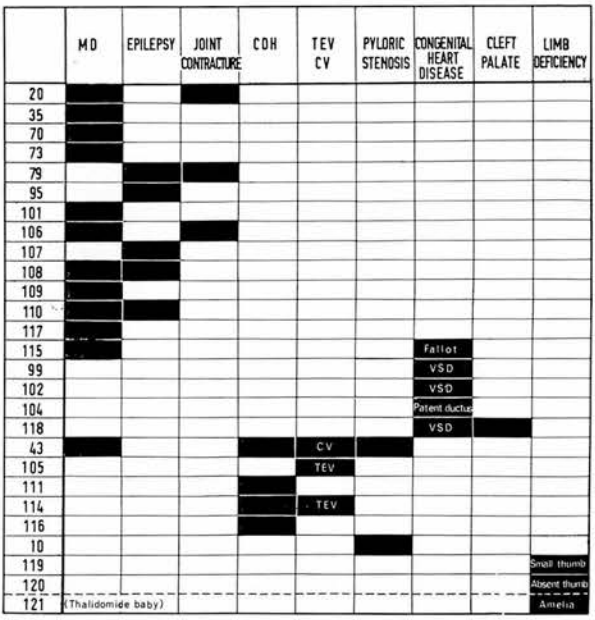

FIG. 6
Anomalies associated with idiopathic scoliosis (twenty-seven patients).

Mental defect and epilepsy, taken together, were the commonest of the associated features (fifteen children). Other cases presented with congenital dislocation of the hip, club foot, various congenital heart disorders, and upper limb defects. One thalidomide child has developed scoliosis.

In a review of the largest group (mental defectives and epileptics), and examination of their families, several relatives were found with uncomplicated idiopathic scoliosis. The proportions of affected relatives were the same as in the main group and much in excess of the population incidence.

The other groups were too small to consider separately, but there was one instance of idiopathic scoliosis in the family of a child with both scoliosis and congenital dislocation of the hip.

Associated anomalies in relatives—Apart from the high incidence of scoliosis already noted, developmental anomalies amongst the relatives showed no difference from that which would be expected from a random survey.

DISCUSSION

There is undoubtedly a concentration of idiopathic scoliosis within the families of index patients. It is probable that the infantile and adolescent types share the same basic etiology, since families contain instances of each, but there are distinct differences between the two groups. In the early onset type the curve is usually to the left, is common in boys, and the deformity resolves in half the cases presenting under one year of age. It occurs only rarely in North America. The number of relatives affected with scoliosis is less than in the following group, and the incidence remains similar in those of the first, second and third degree. The age of the parents is not significantly different from normal.

In the late onset type the curve is usually to the right and in a girl. Although the curve is often severe it may not be so, but it does not disappear spontaneously. There is a very much stronger family history of scoliosis in the girls, but not in the boys with adolescent scoliosis. The incidence in relatives is halved from first to second and then to third degree. The maternal age is significantly increased.

It is probable that there is a strong environmental factor acting in the early onset type. It has been suggested (Browne 1965, Lloyd-Roberts and Pilcher 1965) that intra-uterine compression contributes to the onset of scoliosis in infants, and this at least could account for the constant association of infantile scoliosis and plagiocephaly.

The genetic factor is stronger in the adolescent group and shows some of the characteristics of dominant inheritance. However, the numbers are too small to allow a definite conclusion between this and multiple gene inheritance. The maternal age effect is not understood, but there may be an association between this, the rise in incidence of scoliosis in adolescent girls and the physiological changes at puberty.

SUMMARY

1. Idiopathic scoliosis is a familial condition.
2. The findings suggest either dominant or multiple gene inheritance, but a larger series is needed before a firm conclusion can be drawn.
3. The infantile and adolescent types of scoliosis seem to share the same basic etiology, because their families contain instances of each.
4. Infants with resolving scoliosis have affected relatives in the same proportions as in the main group, suggesting this is a mild form of the same disorder.
5. In this series all infants seen with scoliosis under one year of age had plagiocephaly, which was usually transient.
6. Mental defect and epilepsy are the commonest findings associated with scoliosis.
7. In adolescent scoliosis the age of the mother is significantly raised by comparison with the expected figure for the normal population.

I am much indebted to Professor J. I. P. James for access to records and patients in his scoliosis clinic and for his great interest and help throughout the study. Acknowledgement and thanks are also due to Dr C. E. Blank and Mrs S. C. Bairstow of the Sheffield Human Genetics Centre for their interest in the maternal age effect in scoliosis and for a detailed analysis of the figures summarised in Table III.

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