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# Congenital limb anomalies: frequency and aetiological factors

## Data from the Edinburgh Register of the Newborn (1964–68)

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**Summary.** This paper reports a detailed follow up of 156 patients with structural upper and lower limb anomalies, obtained from the Edinburgh Register of the Newborn (a registration of 52,029 consecutive births between 1964 and 1968). At the time of this survey the patients were between 4 and 9 years of age.

The Register had noted probably 96% of all children born with limb defects in Edinburgh between 1964 and 1968. It was found that the diagnosis was completely accurate in only 26% of cases, and partially so in a further 42%.

The frequency of each anomaly has been noted, subdivided into isolated anomalies; those that occurred with other limb anomalies, and those that formed part of a syndrome. Syndactyly of toes, post-axial polydactyly of the fingers, polysyndactyly, and brachydactyly were found to have a genetic basis. All 'absence' defects, pre-axial polydactyly, and multiple limb deformities appeared to be sporadic. Amongst the sporadic group, the main aetiological factors noted were an excess of maternal toxaemia of pregnancy and of illegitimate children, when compared with the Register Control Data.

Little is known about the frequency of the individual structural deformities of the limbs. Some surveys mention 'skeletal anomalies' without further definition, and in others delineation of the individual anomalies is difficult because of variation in terminology and the general, purely descriptive terms so often used (Carter, 1963; Stevenson *et al*, 1966; Butler and Alberman, 1969). A further source of error is that most surveys have included only hospital (not domiciliary) births and thus many of the less severe anomalies will have been omitted. McIntosh *et al* (1954), Marden, Smith, and McDonald (1964), and Stewart, Keay, and Smith (1968/69) all used more detail in recording limb anomalies but their population samples (4412, 5964, and 2500, respectively) were too small to give a reliable population frequency.

Birch-Jensen (1949), by searching through all the Danish hospital records, found 625 patients with 'absence' deformities of the upper extremities who were living in Denmark and had been born before 1 January 1947. He defined 'absence' deformities as 'those due to absence or atrophy of larger or smaller portions of the skeleton of the extremity'. After classification, he related them to the population of Denmark published in the Danish Year Book of Statistics (1946) thus establishing the frequency of the separate deformities. However, this cannot have given the true incidence at birth since it excluded both perinatal and later deaths. His study did not include any other congenital deformities of the limbs. None of these surveys had follow-up studies to establish whether other defects became evident with growth.

Genetic factors have been described for several of the structural limb anomalies, particularly syndactyly, polydactyly, and brachydactyly (Temtamy and McKusick, 1969; Woolf and Woolf, 1970; David, 1972), and there have been innumerable reports of individual families with limb anomalies. However, most congenital limb defects seen in clinical practice are sporadic, whether occurring in

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isolation, together with another limb defect, or as part of a malformation syndrome.

The aim of this current survey was to establish the frequency at birth of the structural limb anomalies in the City of Edinburgh, using the Edinburgh Register of the Newborn from 1964 to 1968. Also, an attempt was made during 1972–73 to trace each individual with a limb anomaly on the Register, thus giving a 4 to 9 year follow-up, allowing alterations and additions to the Register to be made. A family survey of these individuals was carried out to determine the frequency of the same deformity amongst their first-, second-, and third-degree relatives. Data relating to possible environmental factors in the aetiology was noted and compared with that from the Register Controls. (Data from Edinburgh births over the same period of time as the index patients with congenital anomalies.)

## Material

**Edinburgh Register of the Newborn (1964–68).** The Edinburgh Register of the Newborn consists of a registration of 52,029 consecutive births in the City of Edinburgh in the 4½ years between 1 March 1964 and 31 October 1968. This register was under the direction of the University of Edinburgh Departments of Social Medicine and of Child Life and Health, supported by a grant to the University from the Distillers Company Ltd, after Thalidomide was removed from the market. Its aim was to establish the frequency of all congenital anomalies and to monitor it regularly in order to give an early warning of new toxic agents (Dean, 1973). It is held at the Department of Social Medicine.

The data was derived from clinical examination of all babies born within the city limits after the 28th week of pregnancy, including both live and stillbirths. Over the whole period 1712 infants with congenital anomalies were recorded (3% of the total births) of whom 10% were stillborn. Those born in hospital (88%) were examined by paediatric staff and domiciliary births (12%) were examined by medically qualified personnel employed specifically for this purpose. Only 3% of the total births over this period were not examined because of refusal by the attending general practitioner or the family. When the clinical examination revealed a congenital abnormality, a questionnaire was completed relating to the medical and social history of parents, sibs and second- and third-degree relatives, and the maternal obstetric history was recorded in considerable detail from medical records.

In order to establish control values, the same questionnaire was completed in a random sample of 707 births within the City, which was initially every 100th and later every 50th birth over the period 1964 to 1968. Six hundred and eighty-five of these were normal children, and 22 had some congenital defect.

**Congenital Limb Anomalies Survey, 1973.** This current report is based on the examination and follow up of the 157 index patients listed in the Register of the Newborn with congenital structural limb anomalies, excluding clubfoot and congenital dislocation of the hip. A further three patients omitted from the original Register were added (see below) making 160. During the survey, four patients on the Register were found to be normal, thus the final figure investigated was 156.

## Methods

An initial home visit was made to the families of all index patients who could be traced, whether the patient was alive or dead. The pedigree was drawn and the family medical history, maternal obstetric history, and progress of the index patients' growth and development noted.

Since the follow-up period of this survey was a minimum of 4 years and a maximum of 9 years, special attention was given to the appearance of developmental anomalies which had become evident with growth and were not recorded in the initial Register. A superficial examination of patients and first-degree relatives was made, with radiography carried out at hospital when indicated. Home visits were also made to other relatives with a history of limb anomalies and all available hospital records were reviewed, relating not only to index patients but to the maternal obstetrical history and to all relatives with limb or other developmental disorders. A systematic search was made of the Edinburgh city paediatric, plastic and orthopaedic surgery case records for patients with limb anomalies, born between 1964 and 1968 who had possibly been omitted from the Register.

The proportions of affected relatives with the same deformity as the index patients were noted and an attempt made to determine the mode of inheritance. Data relating to possible environmental factors in the aetiology was collected and compared with that in the Register Control Data. The factors investigated were: (1) parental ages and the parity of the index patient; (2) maternal history of past abortions and stillbirths; (3) birth and pregnancy history relating to the index patient, including maternal illness, medications, gestation length, presentation, and birth weight; (4) illegitimacy; (5) social class of father; (6) season of birth.

## Classification

There have been innumerable classifications of the congenital structural limb anomalies, particularly of those relating to the hand. For the purpose of this survey, the simplest possible one has been used relating to aetiology so far as it is known at present (Table I). The classification is similar to that described by Temtamy and McKusick (1969) for hand anomalies. (Only the defects which occurred in this survey are noted.)

In each case the anomalies were then subdivided into those: (1) present as a solitary, or isolated, defect; (2) present with other limb anomalies; (3) forming part of a malformation syndrome, chromosomal or other ('malformation syndrome' being defined as 'structural defects

TABLE I

CLASSIFICATION OF CONGENITAL LIMB ANOMALIES
Edinburgh Survey 1973

Limb hypertrophy/hypoplasia

'Absence' defects
- Transverse
- Radial/tibial side of limb (pre-axial)
- Ulnar/fibular side of limb (post-axial)
- Split hand/foot

Congenital ring constrictions

Syndactyly/Polydactyly
- Syndactyly
- Polydactyly
  - Radial/tibial side of limb (pre-axial)
  - Ulnar/fibular side of limb (post-axial)
- Polysyndactyly

Brachydactyly

Symphalangism

Contracture

Forearm defects (excluding 'absence')
- Radial head dislocation
- Radio-ulnar synostosis

affecting more than one part of the body or more than one system').

## Results

**Tracing of patients.** The search of the Edinburgh City paediatric, plastic, and orthopaedic surgery case records revealed only three patients (all domiciliary births), who should have been included on the Register, one with syndactyly of toes, one with syndactyly of fingers and toes, and one with pre-axial polydactyly. One hundred and fourteen index families were visited, and 98 index patients examined, the other 16 being dead. Forty families were not visited because of failure to trace their current address or because they had moved a long distance from Edinburgh. Six families (3·7%) refused to cooperate. In only 14 of all 160 cases (9%) were there no hospital records, index patients, or families available to complement the Register information. That is, it was possible in 91% of all cases to supplement the Register data from subsequent medical records.

**Age at follow up.** This was considered to be the age at which the patient was examined by us, or the age noted on the last available hospital record. Twenty-eight per cent of index patients were assessed at birth only, 9% between the age of 2 weeks and 4 years, and 61% over the age of 4 years.

The total number of deaths at the time of the current survey was 26, comprising seven stillbirths, 13 perinatal deaths, and six after the first month of life.

**Accuracy of the Register of the Newborn.** In only 26% of cases was the Register diagnosis unchanged on subsequent examination. Four patients had been overdiagnosed in that on the subsequent visit to the family no abnormality was found. In 42% of cases the deformity was correctly named but the exact site and extent omitted—for example, terms such as 'polydactyly' and 'syndactyly' were used without further qualification. In 4% of cases a major limb deformity was omitted or wrongly named and in 8%, a minor limb deformity omitted. (Major deformities were defined as those of significance to the function or cosmesis of the limb, for example, radio-ulnar synostosis or a dislocated radial head. Minor deformities did not have this significance, for example, syndactyly of the toes.)

The name of a syndrome was established in 4% of cases by this current survey, insufficient evidence having been apparent at the time of birth to make a complete diagnosis then.

There may be further inaccuracies relating to the following: 14 cases could not be traced for follow up, some patients with a major or minor deformity may have been omitted from the Register and subsequently attended a hospital outside Edinburgh, or minor limb defects may have been omitted from the Register and were not found on the subsequent search of city records because no attendance had ever been made at a hospiial.

## Population frequency

There was a total of 156 index patients with structural limb anomalies, those with a bilateral distribution of a single deformity being regarded as single units (Table II). Fifty-eight per cent were male and 42% female. Details of the frequency of individual defects, whether isolated, with other limb anomalies, or as part of a syndrome are shown in the population frequency Tables III to VIII.

The following clinical details were noted.

**Syndactyly** (Table III). (When the syndactyly was less than one-third the length of the second toe it was not considered a congenital defect.) There was a total of 74 patients. In isolated syndactyly of the toes the webbing was always between the second and third toes, 82% were bilateral, and skin was the

TABLE II

CLASSIFICATION OF 156 PATIENTS IN THE CONGENITAL LIMB ANOMALIES SURVEY Edinburgh 1973

| Divisions | Patients | % of 156 |
|---|---|---|
| Isolated anomalies | | |
| Syndactyly | 52 | 33·3 |
| Post-axial polydactyly | 21 | 13·5 |
| Pre-axial polydactyly | 18 | 11·6 |
| 'Absence' defects | 7 | 4·5 |
| Brachydactyly | 3 | 1·9 |
| Finger contracture | 1 | 0·6 |
| More than one limb anomaly | 24 | 15·4 |
| Syndromes | | |
| Chromosome disorders | 8+11* | 12·2 |
| Named syndromes | 8 | 5·1 |
| Unclassifiable | 3 | 1·9 |

* 8 proven, 11 probable.

TABLE III

FREQUENCY OF SYNDACTYLY

| Site | Isolated | With Other Limb Anomalies | Part of Syndrome | Population Incidence | |
|---|---|---|---|---|---|
| | | | | Per 52,029 | Per 10,000 |
| Fingers | 0 | 5 | 3 | 8 | 1·5 |
| Toes | 51 (74%) | 9 (13%) | 9 (13%) | 69 | 13·0 |
| Both | 1 | 0 | 2 | 3 | 0·6 |

only tissue common to both toes. When syndactyly of toes occurred with other deformities, 46% were between toes other than the second and third.

There were no patients with isolated finger syndactyly, but when this occurred with other deformities the middle and ring fingers were involved in half the cases.

**Post-axial polydactyly (ulnar/fibular side)** (Table IV). There was a total of 35 patients. In 73% of cases the deformity was bilateral. Eighty-five per cent had bone in the extra digit and the remainder presented with a small skin nubbin.

**Pre-axial polydactyly (radial/tibial side)** (Table V). There was a total of 21 index patients.

TABLE IV

FREQUENCY OF POST-AXIAL POLYDACTYLY

| Site | Isolated | With Other Limb Anomalies | Part of Syndrome | Population Incidence | |
|---|---|---|---|---|---|
| | | | | Per 52,029 | Per 10,000 |
| Fingers | 15 | 5 | 8 | 28 | 5 |
| Toes | 5 | 4 | 6 | 15 | 3 |
| Both | 1 | 2 | 5 | 8 | 1·5 |

TABLE V

FREQUENCY OF PRE-AXIAL POLYDACTYLY

| Site | Isolated | With Other Limb Anomalies | Part of Syndrome | Population Incidence | |
|---|---|---|---|---|---|
| | | | | Per 52,029 | Per 10,000 |
| Thumb | 17 | 0 | 1 | 18 | 3 |
| Hallux | 1 | 1 | 1 | 3 | 0·6 |

Of the 17 with isolated thumb reduplication, 16 were unilateral. Five had only a bifid terminal phalanx and 12 a more extensive reduplication. The sex ratio was approximately equal.

**Polysyndactyly.** There were only eight patients with both syndactyly and polydactyly (seven post-axial, one pre-axial, see Table IX). This gives a population frequency of 1·54 per 10,000.

**'Absence' defects of the upper limb** (Table VI). Transverse congenital amputations were always isolated deformities, whereas patients with 'longitudinal' defects such as an absent radius or ulna always had other defects in addition. There was one definite and two probable cases of congenital ring constrictions associated with the 'absence' defects. In all seven patients with an isolated deformity the lesion was unilateral. The sex ratio was approximately equal in this group.

**Forearm and hand anomalies excluding 'absence' defects** (Table VII). One of the three patients with radial head dislocation also had bilateral radio-ulnar synostosis. The single patient with symphalangism had fusion of the proximal and middle phalanges of the little finger, together with a

TABLE VI

FREQUENCY OF 'ABSENCE' DEFECTS OF THE UPPER LIMB

| Site | Isolated | With Other Limb Anomalies | Part of Syndrome | Population Incidence | |
|---|---|---|---|---|---|
| | | | | Per 52,029 | Per 10,000 |
| Amelia | 0 | 1 | 0 | 1 | 0·2 |
| Transverse (below elbow) | 2 | 0 | 0 | 2 | 0·4 |
| Radius | 0 | 2 | 2 | 4 | 0·8 |
| Ulna | 0 | 0 | 1 | 1 | 0·2 |
| Transcarpal Hand | 2 | 0 | 1 | 3 | 0·6 |
| Pre-axial | 0 | 5 | 3 | 8 | 1·6 |
| Mid-hand | 2 | 9 | 2 | 13 | 2·5 |
| Post-axial | 1 | 6 | 2 | 9 | 1·7 |
| Split hand | 0 | 2 | 0 | 2 | 0·4 |

TABLE VII

FREQUENCY OF FOREARM AND HAND ANOMALIES EXCLUDING 'ABSENCE' DEFECTS

| Type of Anomaly | Isolated | With Other Limb Anomalies | Part of Syndrome | Population Incidence | |
|---|---|---|---|---|---|
| | | | | Per 52,029 | Per 10,000 |
| Radial head dislocation | 0 | 3 | 0 | 3 | 0·6 |
| Radio-ulnar synostosis | 0 | 1 | 0 | 1 | 0·2 |
| Brachydactyly thumb | 0 | 3 | 3 | 6 | 1·2 |
| Brachydactyly fingers | 2 | 0 | 0 | 2 | 0·4 |
| Clinodactyly | 1 | 2 | 5 | 8 | 1·5 |
| Symphalangism | 0 | 1 | 0 | 1 | 0·2 |
| Hand ring constriction | 0 | 2 | 1 | 3 | 0·6 |
| Finger contracture | 0 | 2 | 3 | 5 | 1·0 |
| Forearm and hand hypertrophy | 0 | 1 | 0 | 1 | 0·2 |
| Forearm and hand hypoplasia | 0 | 2 | 0 | 2 | 0·4 |

TABLE VIII

FREQUENCY OF LOWER LIMB ANOMALIES

| Type of Anomaly | Isolated | With Other Limb Anomalies | Part of Syndrome | Population Incidence | |
|---|---|---|---|---|---|
| | | | | Per 52,029 | Per 10,000 |
| Proximal femoral defect | 0 | 1 | 0 | 1 | 0·2 |
| Knee dislocation | 0 | 0 | 1 | 1 | 0·2 |
| Short tibia | 0 | 1 | 0 | 1 | 0·2 |
| 'Absence': foot | | | | | |
| Pre-axial | 0 | 2 | 7 | 9 | 1·7 |
| Mid foot | 0 | 2 | 0 | 2 | 0·4 |
| Post-axial | 0 | 4 | 0 | 4 | 0·8 |
| All toes | 1 | 0 | 0 | 1 | 0·2 |
| Lower limb hypertrophy | 0 | 1 | 0 | 1 | 0·2 |

split hand. There were only three patients with an isolated anomaly—the two with brachydactyly of fingers were bilaterally affected and the one with clinodactyly was unilaterally affected.

**Lower limb anomalies** (Table VIII). The patient with a proximal femoral defect had coxa vara, a short bowed femur, short tibia, and absence of the fifth ray of the foot, all on the left side. The patient with congenital dislocation of the knee had Potter's syndrome (agenesis of the kidneys and oligohydramnios with compression of the fetus). There was only one patient with an isolated anomaly —'absence' of all toes, the lesion being bilateral.

**More than one limb anomaly.** Each defect has been noted separately in the population frequency Tables; Table IX shows details of the 24 individual patients who had more than one limb anomaly, including the eight patients with polysyndactyly; five were bilaterally affected and three were unilaterally affected.

### Associated anomalies

Amongst the patients with isolated limb defects, other developmental anomalies noted were as follows.

**Syndactyly.** One patient had mental retardation, one had cerebral palsy and mental retardation, and one patient died of leukaemia at the age of six years.

**Post-axial polydactyly.** One patient developed a branchial cyst.

**Pre-axial polydactyly.** Two patients were suspected of having a ventricular septal defect. In the absence of confirmation they have not been included amongst the 'syndromes'.

**Brachydactyly.** One patient developed a midbrain glioma at the age of three years.

Amongst the patients with more than one limb defect, the associated anomalies noted were: one patient with a malformed kidney, one with a speech defect, one with mental retardation, and one with neonatal bowel obstruction (type unknown).

### Malformation syndromes

The frequency of limb anomalies in those patients with malformation syndromes has been noted in the population frequency Tables III to VIII.

## TABLE IX

PATIENTS WITH MORE THAN ONE LIMB ANOMALY (n = 24)*

| Record Number | 51 | 90 | 93 | 101 | 184 | 185 | 189 | 207 | 210 | 211 | 213 | 220 | 229 | 241 | 264 | 273 | 275 | 278 | 284 | 287 | 296 | 297 | 289 | 315 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Sex | M | F | M | M | F | F | M | F | M | M | M | F | M | M | F | M | F | M | M | M | M | M | F | F |
| *Anomalies* Vertebral anomalies | ✓ | | | | | | | | ✓ | | | | | | | | | | | | | | | |
| Amelia | L | | | | | | | | | | | | | | | | | | | | | | | |
| Radial head dislocation | | L | | | | | | | | L | | L | | | | | | | | | | | | |
| Radio-ulnar synostosis | | | | | | | | | | B | | | | | | | | | | | | | | |
| *Absence defects* Radius | R | R | | | | | | | | | | | | | | | | | | | | | | |
| Hand Pre-axial | R | | | L | | | | | | L | | L | | | | | | | R | | | | | |
| Mid hand | R | | L | L | | | L | | | | | | L | | B | | | | R | | B | | | L |
| Post-axial | | | | L | | | L | | | | | | | | B | | | | R | | | | | L |
| Split hand deformity | | | L | | | | | | | | | | L | | | | | | | | | | | |
| Brachydactyly | | | L | | B | B | L | | | | | | | | | R | | | | | B | | | |
| *Hand* Post-axial polydactyly | | | | | B | B | | | | | R | | | | | R | | | | | | | B | |
| Syndactyly | R | | | | | | | | | | B | | | | B | R | | | R | | | | | |
| Symphalangism | | | L | | | | | | | | | | | | | | | | | | | | | |
| Contracture | | | | | | | | L | | | | | | | | | | | | | | | | |
| Ring constriction | | | | L | | | | | | | | | | | B | | | | | | | | | |
| Forearm + hand hypertrophy | | | | | | | | L | | | | | | | | | | | | | | | | |
| Forearm + hand hypolasia | | | | L | | | | | | | | L | | | | | | | | | | | | |
| Proximal femoral defect | | | | | | | | | L | | | | | | | | | | | | | | | |
| Short tibia | | | | | | | | | L | | | | | | | | | | | | | | | |
| *Absence defects* Foot Pre-axial | | | | | | | | | | | | | | | | | B | | | | | L | | |
| Mid foot | | | | | | | | | | | | | | | | | B | | | | | L | | |
| Post-axial | | | | | | | | | L | | | | L | | | | B | | | | | L | | |
| *Foot* Pre-axial polydactyly | | | | | | | | | | | | | | | | | | B | | | | | | |
| Post-axial polydactyly | | | | | B | B | | | | | | | | L | | | | | | L | | | | |
| Syndactyly | | | | | B | B | | | | | | | | L | | | | B | | L | | L | B | |
| Lower limb hypertrophy | | | | | | | | L | | | | | | | | | | | | | | | | |

* R = right; L = left; B = bilateral.

**Chromosomal disorders.** There were eight proven cases of chromosomal anomalies—four with trisomy 21, one with 69,XXX, one with 47,XXX, and two with trisomy 13. A further 11 cases (five with trisomy 13 and six with trisomy 18) were suspected on clinical grounds but no chromosome count had been done and in each case the child was dead. Details of the limb anomalies are shown in Table X. The suspected cases of trisomy 13 all had some form of post-axial polydactyly. Amongst the six cases with probable trisomy 18, five had a short hallux and the remaining case had hand contractures with brachydactyly of the thumb.

TABLE X

CHROMOSOME ANOMALIES AND CONGENITAL LIMB DEFECTS

| Chromosome Anomaly | Limb Defect |
|---|---|
| Trisomy 21 (4 patients) | Four with bilateral clinodactyly; Three with syndactyly of toes |
| 69,XXX (1 stillbirth) | Syndactyly of middle and ring fingers (unilateral); Short hallux and long fifth fingers |
| 47,XXX (1 patient) | Bilateral clinodactyly |
| Trisomy 13 (2 patients) | Post-axial polydactyly |

**Known syndromes.** There were eight patients with limb deformities which formed part of a known syndrome.

*Spinal muscular atrophy* (male). The initial diagnosis in this patient was arthrogryposis but this was changed at the age of 2 years when slowly progressive proximal muscular weakness developed in the lower limbs. Muscle biopsy was compatible with spinal muscular atrophy.

*Rubenstein-Taybi syndrome* (female). This patient presented with bilateral short broad thumbs, and the first toes had a double complement of phalanges. There was post-axial polydactyly of one foot. It was subsequently noted that she had mental retardation, a beak nose, low set ears, high arched palate, cramped teeth, hirsuitism, pectus excavatum, cervical ribs, lumbar scoliosis, and dwarfism. The diagnosis was established by this survey.

*Cornelia de Lange syndrome* (female). This patient presented with absence of the left ulna, a one-digit left hand (probably the index finger), brachydactyly of the right fingers, syndactyly of toes and with the facies typical of this syndrome. She died at 5 weeks of age.

*Apert's syndrome (acro-cephalo-syndactyly;* female). This patient presented with the typical massive syndactyly of hands and feet, a flat face, tower skull, and severe mental retardation. She died at the age of 5 months after surgery to separate the cranial sutures.

*Mandibulo-facial dysostosis with limb anomalies* (female). This patient presented with the typical facies and bilateral radius and thumb absence. She also had a large cleft between the first and second toe. She died 4 hours after birth.

*Potter's syndrome* (female). This patient had bilateral small non-functioning kidneys and the typical compressed facies and external features due to the oligohydramnios, together with congenital dislocation of one knee. She died 3 hours after birth.

*Chondrodysplasia punctata (? Conradi's syndrome;* stillborn female). This tentative diagnosis is made because of the irregular epiphyseal calcification noted both on pre-natal radiographs and confirmed by a postmortem histological section. She was severely deformed with gross syndactyly of the right hand, syndactyly of the middle and ring fingers of the left hand, gross syndactyly of the feet, spina bifida with large lumbar meningomyelocele, low set ears, small malformed eyes, hypoplastic thumb. It is possible that she should be included in the group of 'unclassifiable' syndromes.

*Conjoined twins* (both male), who were joined anteriorly from sternum to symphisis pubis. The left twin had an absent radius and thumb on the right side. There was a common heart, two aortas and a common liver. They died 3 hours after birth.

**Unclassified syndromes.** Three patients whose chromosome counts were known to be normal presented with multiple systemic malformations which could not be related to any known syndrome.

The first patient, a male, had pre-axial polydactyly of one hand, multiple hemivertebrae, oesophageal atresia, tracheo-oesophageal fistula, and died 7 days after birth.

The second patient, a female, had post-axial polydactyly of both hands and feet, bilateral dislocated hips, hydrocephalus, and odd facies. She died at 10 months of age after developing multiple foci of osteomyelitis.

The third patient, a male, had syndactyly of the toes, hare lip, high arched palate, hydrocephalus, fused cerebral hemispheres, a large spleen, and a ventricular septal defect. He died 49 minutes after birth.

TABLE XI

SYNDACTYLY OF TOES: PROPORTIONS OF AFFECTED FIRST-, SECOND-, AND THIRD-DEGREE RELATIVES

| Index Patients | Fathers | Mothers | Brothers | Sisters | Second-degree | | Third-degree | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Males | Females | Males | Females |
| Males (n = 35) | 8/35 | 5/35 | 12/36 | 5/31 | 10/194 | 5/154 | 1/132 | 1/137 |
| Females (n = 17) | 3/17 | 7/17 | 2/10 | 1/10 | 3/62 | 10/73 | 2/42 | 2/43 |
| Total (n = 52) | 11/52 | 12/52 | 14/46 | 6/41 | 13/256 | 15/227 | 3/174 | 3/180 |

TABLE XII

POST-AXIAL POLYDACTYLY: PROPORTIONS OF AFFECTED FIRST-, SECOND-, AND THIRD-DEGREE RELATIVES

| Index Patients | Fathers | Mothers | Brothers | Sisters | Second-degree | | Third-degree | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Males | Females | Males | Females |
| Males (n = 11) | 2/11 | 0/11 | 0/9 | 3/13 | 0/56 | 0/56 | 0/29 | 1/26 |
| Females (n = 10) | 1/10 | 1/10 | 2/10 | 0/8 | 1/52 | 2/51 | 0/30 | 1/33 |
| Total (n = 21) | 3/21 | 1/21 | 2/19 | 3/21 | 1/108 | 2/107 | 0/59 | 2/59 |

## Genetic factors

The only disorders in which there were affected relatives were amongst these groups of isolated limb defects: (1) syndactyly of the toes; (2) post-axial polydactyly of the hands; (3) polysyndactyly; (4) brachydactyly (one index patient only).

In the group of 18 patients with pre-axial polydactyly of the hands, there was one affected cousin of a total of 287 first-, second-, and third-degree relatives and this is thought to be coincidental.

No affected relatives were noted in any other group neither the 'absence' defects, nor other localized limb anomaly, chromosome anomalies, nor the known or unclassified syndromes.

**Syndactyly of toes** (Table XI). Approximately 22% of parents and of sibs, 5% of second-degree relatives, and 2% of third-degree relatives were affected with the same disorder.

It is likely that the ascertainment of this very minor deformity is incomplete amongst the second- and third-degree relatives, and the true proportions will be higher than noted here.

When syndactyly of the toes occurred as an isolated anomaly the sex ratio was approximately 2:1 (35 males, 16 females). This was unlike the sex ratio of syndactyly associated with other deformities in which there were an equal number of males and females. One patient had syndactyly of the toes together with a Sprengel's shoulder, and these two deformities occurring together are probably coincidental. This index patient's mother had syndactyly of the toes but no shoulder abnormality. There were no twins. There was one case of consanguineous parents, first cousins who were both normal, but an uncle was affected.

**Post-axial polydactyly** (Table XII). Approximately 10% of parents, 13% of sibs, 1·4% of second-degree relatives, and 0·9% of third-degree relatives were affected. The ascertainment of this deformity in relatives is probably nearly complete.

The sex ratio was approximately equal (11 males and 10 females). There was one pair of twins, dizygous females, of whom only one was affected. There was one case of consanguinity of parents; first cousins, both normal.

Not included amongst these index patients with isolated post-axial polydactyly was one pair of monozygous twin sisters. They each had identical deformities of bilateral post-axial polydactyly of the hands and feet and brachydactyly of the thumb.

**Polysyndactyly.** There were only eight patients in this group (five males, three females). There were no twins and one case of consanguinity of parents, who were first cousins once removed; the father had bilateral polydactyly of the great toes. Twenty-two per cent of 27 first-degree, 1·2% of 86 second-degree, and none of 91 third-degree relatives were affected.

**Brachydactyly.** There were three patients noted as having brachydactyly, but they differed from each other and only one had the type which has previously been reported as of dominant inheritance. This patient was female and the index and

middle fingers were shortened. There was a history of her father being similarly affected, and he also had absence of the distal interphalangeal joint of the index and middle fingers. The family had emigrated to Australia and no further information was available.

The second patient with brachydactyly had radially deviated terminal phalanges of the little fingers, a form of brachydactyly of the middle phalanx. This is known sometimes to be of dominant inheritance but she had no affected relatives.

The third patient had a radially deviated left index finger resulting from a deformed proximal phalanx and does not come within the usual definition of 'brachydactyly'. There were no affected relatives.

### Epidemiology and environmental factors

Data relating to possible environmental factors in the aetiology of all groups is noted and compared with Register of the Newborn Control Data in Tables XIII and XIV. Table XV notes similar data for the eight patients with known syndromes. Only the 685 normal 'control' children are included, but when the remaining 22 'controls' with congenital defects were added, no difference was noted in any levels of significance.

Table XIII gives the parental age and previous live and stillbirths, as well as abortions, relating to the 122 index patients with localized limb anomalies. (That is, omitting 30 patients with syndromes, two with atypical brachydactyly, and the only two with finger contractures.) The only significant findings are: (1) the unusually young age of the parents of children with transverse 'absence' defects ($0{\cdot}05 > p > 0{\cdot}01$). (2) An excess of abortions before the birth of the index patients with pre-axial polydactyly ($0{\cdot}02 > p > 0{\cdot}01$).

Table XIV records some details of the birth history in the same 122 index patients. The following points were noted: (1) A significant number of cases with a gestation length of less than 38 weeks occurred amongst index patients with syndactyly ($p = 0{\cdot}03$), pre-axial polydactyly ($p = 0{\cdot}02$) and this feature almost reached a significant level amongst index patients with 'absence' defects.

(2) Hydramnios was present in two cases (Record nos. 90 and 229, Table IX), and oligamnios in one (Record no. 51, Table IX). All three had 'absence' defects of the longitudinal type.

(3) A significant number of cases of threatened abortion occurred amongst index patients with post-axial polydactyly ($p = 0{\cdot}04$).

TABLE XIII

PARENTAL AGE AND PARITY
Edinburgh Register of the Newborn 1964–68

| Group | Mean Paternal Age (yr) | Mean Maternal Age (yr) | Mean Parental Age Differential (yr) | Maternal Age (30 yr and over) | Parity, Abortions, Stillbirths | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Previous Live Births | | | Previous Abortions | | Previous Stillbirths | |
| | | | | | 0 | 1 | 2+ | No. | % of All Conceptions | No. | % of All Conceptions |
| Controls (n = 685) | 28·82 ± 6·54 | 26·03 ± 5·79 | 2·79 ± 3·81 | 168 (24·5%) | 290 (42%) | 177 (26%) | 218 (32%) | 140 | 8·4 | 19 | 1·1 |
| *Genetic* Syndactyly of toes (n = 52) | 29·67 ± 7·18 | 26·76 ± 6·61 | 2·91 ± 3·59 | 12 (23·1%) | 19 (36%) | 17 (33%) | 16 (31%) | 12 | 9·2 | 2 | 1·5 |
| Post-axial polydactyly (n = 21) | 29·78 ± 7·28 | 26·91 ± 6·48 | 2·87 ± 3·77 | 5 (23·8%) | 6 (29%) | 8 (38%) | 7 (33%) | 8 | 11·1 | 2 | 3·7 |
| Polysyndactyly (n = 8) | 28·25 ± 4·88 | 27·91 ± 4·41 | 0·34 ± 4·32 | 2 (25%) | 6 | — | 2 | 2 | 12·5 | 0 | — |
| Brachydactyly (n = 1) | 29 | 29 | 0 | 0 | — | — | 1 | 0 | — | 0 | — |
| *Sporadic* 'Absence' defects Transverse (n = 7) | 24·42 ± 4·03 | 22·83 ± 2·42 | 1·59 ± 3·28 | 0 | 4 | 2 | 1 | 1 | 8·3 | 0 | — |
| Longitudinal (n = 15) | 30·25 ± 9·82 | 26·33 ± 5·24 | 3·92 ± 6·45 | 3 (20%) | 4 | 7 | 4 | 6 | 16·2 | 0 | — |
| Pre-axial polydactyly (n = 18) | 27·79 ± 6·13 | 24·80 ± 5·98 | 2·99 ± 3·40 | 4 (22·2%) | 9 | 4 | 5 | 9 | 20·0 | 0 | — |

Data from 685 controls and 122 index patients with localized congenital limb anomalies.

## TABLE XIV

BIRTH HISTORY
Edinburgh Register of the Newborn 1964–68

| Group | Gestation Less than 38 Weeks | Mean Birthweight (g) | Complications | | | | | | | | Illegitimacy (unmarried mothers and no. with infants born within 3 months of marriage) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Hydramnios | Oligamnios | Threatened Abortion | | Toxaemia | | | Breech Presentation | |
| | | | | | 1st Trimester | Later | Mild | Moderate | Severe | | |
| Controls (n = 685) | 43 (6·3%) | 3376 ± 541 | 17 (2·5%) | 2 (0·3%) | 33 (4·8%) | 13 (1·9%) | 34 (5·2%)* | 19 (2·9%)* | 11 (1·7%)* | 18 (2·6%) | 58 (8·5%) |
| *Genetic* Syndactyly of toes (n = 52) | 7 (13·5%) | 3497 ± 500 | 0 | 0 | 2 | 1 | 3 | 1 | 0 | 1 | 5 (9·6%) |
| Post-axial polydactyly (n = 21) | 0 | 3459 ± 339 | 0 | 0 | 3 | 1 | 4 | 0 | 0 | 1 | 2 |
| Polysyndactyly (n = 8) | 2 | 3189 ± 911 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 |
| Brachydactyly (n = 1) | – | 3515 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| *Sporadic* 'Absence' defects Transverse (n = 7) | 2 | 3386 ± 729 | 0 | 0 | 1 | 0 | 3 | 0 | 0 | 0 | 1 |
| Longitudinal (n = 15) | 3 | 3225 ± 555 | 2 | 1 | 1 | 1 | 3 | 1 | 0 | 0 | 3 (22·5%) |
| Pre-axial polydactyly (n = 18) | 4 | 3207 ± 623 | 0 | 0 | 1 | 0 | 2 | 0 | 0 | 0 | 5 |

Data from 685 controls and 122 index patients with localized congenital limb anomalies.
* Not recorded in 35 cases, therefore expressed as percentage of 650 controls.

## TABLE XV

KNOWN SYNDROMES: EPIDEMIOLOGICAL DATA

| Syndrome (1 patient each) | Paternal Age (yr) | Maternal Age (yr) | Previous Live Births | Previous Abortions | Previous Stillbirths | Gestation Length (wk) | Presentation | Complications | Birthweight (g) | Month of Birth | Social Class |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Spinal muscular atrophy | 24 | 21·5 | 0 | – | – | 40 | Breech | Oligohydramnios | 2693 | January | 5 |
| Rubinstein-Taybi syndrome | 21 | 21 | 1 | – | – | 35 | Vertex | Hydramnios (Rhesus baby) | 1984 | November | 5 |
| Cornelia de Lange syndrome | 23 | 20 | 1 | – | – | 34 | Vertex | – | 1984 | May | 3 |
| Apert's syndrome | 36 | 32 | 0 | – | – | 40 | Vertex | – | 3657 | October | 3 |
| Mandibulo-facial dysostosis with limb anomalies | 37 | 35 | 2 | – | – | 35 | Vertex | Hydramnios | 2183 | August | 1 |
| Renal agenesis | 31 | 30·5 | 4 | 1 | – | 40 | Breech | – | 1956 | November | 3 |
| Chondro dysplasia punctata | 28 | 29 | 0 | – | – | 34 | Breech | Hydramnios | 1474 | July | 2 |
| Conjoined twins (1 pair) | 19 | 19 | 0 | – | – | 31 | Breech | – | 2239 (combined) | December | 3 |

(4) A significant number of cases of maternal toxaemia of pregnancy was found amongst index patients with 'absence' defects ($p = 0.004$). The diagnosis of toxaemia is a clinical one, but the evidence was recorded in some detail both for the Register Controls and the index patients, and it is felt the findings are valid, relying as they do on medical evidence rather than retrospective history taking from the mother.

(5) There was a highly significant excess of illegitimate children amongst the index patients with sporadic defects, that is, the 'absence' defects and pre-axial polydactyly ($p = 0.006$). The date of marriage for the great majority of Register Controls and index patients was obtained from Register House, Edinburgh, not from the parents. The only exceptions to this were the few couples who had not been married in Scotland.

No significant findings were noted amongst any group in relation to the social class of the father, the season of birth, nor to any other illness of, or medication taken by, the mother.

## Discussion

**Population frequency.** This is the first survey where the aim has been to establish as accurately as possible the frequency of structural limb anomalies, following up the patients from the records made at birth to between 4 and 9 years later. In Table XVI the figures are compared with findings from other surveys, where necessary with their data regrouped to conform with the classification and terminology used here.

The rarity of phocomelia and above-elbow amputation explains their absence from this current Edinburgh survey of some 52,000 births. If only live patients with radial absence defects are considered, as has been done by Birch-Jensen (1949), the frequency of this deformity is found to be similar in Edinburgh and Denmark (0·4 and 0·3 per 10,000). There was a significant difference in the frequency of 'absence' deformities of the hand, being 3·6 per 10,000 in Edinburgh and only 0·4 in Denmark. However, Birch-Jensen would not have noted minor

TABLE XVI

COMPARISON OF FREQUENCY OF CONGENITAL LIMB ANOMALIES IN DIFFERENT SURVEYS

| Anomaly | Edinburgh* | | Denmark† | | Wisconsin USA‡ | | World Health Organization** | |
|---|---|---|---|---|---|---|---|---|
| | Per 52,029 | Per 10,000 | Per 4,024,000 | Per 10,000 | Per 4,412 | Per 10,000 | Per 421,781 | Per 10,000 |
| Phocomelia | | | 5 | 0·012 | | | | |
| Above elbow amputation | | | 10 | 0·02 | | | | |
| Below elbow amputation | 2 | 0·4 | 176 | 0·42 | | | | |
| Radial 'absence' defect | 4 | 0·8 | 117 | 0·3 | 2 | 5 | | |
| Ulnar 'absence' defect | 1 | 0·2 | 19 | 0·04 | | | | |
| Transcarpal amputation | 2 | 0·4 | 58 | 0·14 | | | | |
| Split hand | 4 | 0·8 | 56 | 0·14 | | | | |
| Hand 'absence' defects | 19 | 3·6 | 189 | 0·4 | 7 | | | |
| Ring constriction, upper limb | 3 | 0·6 | 83 | 0·2 | | | | |
| Hand | | | | | | | | |
| Pre-axial polydactyly | 18 | 3·0 | | | 2 | 5 | 66 | 1·6 |
| Post-axial polydactyly | 29 | 6·5 | | | | | 430 | 10·2 |
| Syndactyly | 8 | 1·5 | | | 2 | 5 | 73 | 1·7 |
| Contracture | 5 | 1·0 | | | 4 | 9 | | |
| Other digital anomalies | | | | | | | 66 | 1·6 |
| Fibula absence | | | | | 1 | 2 | | |
| Foot syndactyly | 68 | 13·0 | | | 3 | 7 | | |
| Reduction deformities | | | | | | | 103 | 2·4 |
| Other limb anomalies | | | | | | | 108 | 2·6 |

* Present study.
† Birch-Jensen (1949).
‡ McIntosh *et al* (1954).
** Stevenson *et al* (1966).

'absence' defects since he only recorded cases requiring medical attention.

Congenital radio-ulnar synostosis and radial head dislocation are rare deformities. In the Edinburgh survey neither appeared as isolated defects, only occurring with other limb deformities. Almquist, Gordon, and Blue (1969), added 18 cases of congenital radial head dislocation to the 54 reported in the world literature. Of their total of 72 cases, 40% were associated with a syndrome. Hansen and Andersen (1970) found only 37 cases of congenital radio-ulnar synostosis in a 10-year study of all orthopaedic patients in Denmark.

In the Edinburgh survey there were no severe femoral defects, isolated 'absence' defects of the tibia or fibula, or bowing or pseudarthrosis of the tibia, implying a frequency of less than 1 in 52,000 for each of these anomalies.

It is of interest that no patients presented with isolated syndactyly of the fingers in this survey. Marden *et al* (1964) also noted that all their patients with syndactyly of the fingers had some other major deformity. Kite (1957) reviewed 166 children with hand anomalies and found 77 cases of syndactylism of the fingers. Of these 77, 30% had either an affected parent or grandparent, 50% had other hand anomalies, and 62% had other major developmental anomalies.

In the Edinburgh survey, one third of the 156 cases had either multiple limb deformities or their limb deformity was part of a syndrome. Nine per cent of patients with isolated limb anomalies had some significant non-skeletal defect.

With regard to the accuracy of the Edinburgh Register of the Newborn, it was remarkable that apparently only three patients had been omitted from this 4½-year survey, and though there may be others, the deformities are likely to be minor. A note of caution is necessary to those who may wish to use computer analysis to draw conclusions from similar large surveys not designed to give detailed information—the Register diagnosis was completely accurate in only 26% of cases, and partially accurate in an additional 42%. However, its initial aim was to note, using only a very general classification, patients born with limb and other anomalies and, once noted, this group was then available for further study, as has been done here.

**Genetic factors.** It is probable that syndactyly of the second and third toes is a defect of autosomal dominant inheritance with 50% penetrance, and it appears to be partially sex limited to males. Firm conclusions cannot be drawn as it is unlikely that ascertainment is complete, particularly in second- and third-degree relatives.

Post-axial polydactyly probably has a more complete ascertainment of affected relatives and in view of the rapid fall of the proportions affected from first- to second- and then to third-degree relatives (13%, 2%, 1%); it is suggestive of multifactorial inheritance.

There were only eight index patients with polysyndactyly. Again, a rapid fall in the proportions of affected relatives was noted. It is not known if this is a homogeneous group or whether it should belong to one of the two preceding ones.

No paternal age effect was noted amongst the sporadic cases with these three types of deformity.

With regard to the remaining cases of isolated deformities, there were no affected relatives amongst 22 index patients with 'absence' defects, and amongst the 17 patients with pre-axial polydactyly there was only one affected (third-degree) relative. It is likely that both these conditions are non-genetic in nature. (There were no cases of tri-phalangeal pre-axial polydactyly, a condition known sometimes to be of dominant inheritance.) All other cases appeared to be sporadic, but numbers are too small for firm conclusions to be drawn. Larger family surveys for each individual deformity are needed.

**Environmental factors.** Several of the subdivisions of index patients are small, but the control data has been carefully matched and it is thought that the findings are of value. Retrospective history taking from the mother is notoriously unreliable and so particular note has been made of disorders in the pregnancy or birth history which could be confirmed by medical evidence.

Amongst the 'genetic' group the only points noted were in syndactyly, that an excess of children were born before the 38th week of pregnancy, and in post-axial polydactyly, that an excess of cases had threatened abortion. Both these reached significance at the 5% level.

Amongst the 'sporadic' group the significant findings were: (1) Transverse 'absence' defects: the parents of these children were significantly younger than average. However, there were only seven patients in this group. (2) Amongst the 22 patients with 'absence' defects there was an excess of maternal toxaemia of pregnancy. There were two cases of hydramnios and one of oligamnios. All three had some form of longitudinal 'absence' defect. (3) Pre-axial polydactyly; an excess of abortions before the birth of the index patient was noted. (4) There was a highly significant excess of illegitimate children amongst the whole 'sporadic' group of

40 children, taking 'illegitimate' to include those infants with unmarried mothers and those born within three months of marriage.

All these points were confirmed by medical evidence or obtained from sources other than the mother herself, and are likely to be as accurate as clinical evidence can be.

The significance of these factors is not clear, though one can speculate from the excess of young parents, previous abortions, and illegitimate children, that there may have been ineffectual attempts at abortion of a fetus which subsequently presents with a congenital limb anomaly. This survey confirms the well-known clinical observation that congenital transverse 'absence' defects are isolated deformities, and sporadic in nature. There has been, perhaps, a localized vascular accident in the fetus.

No relationship could be found with other factors such as social class or season of birth. The only other point of interest was that during two pregnancies which resulted in infants with trisomy 13, the mothers had taken hormonal preparations during the first month of pregnancy; one to induce menstruation and the other for treatment of infertility.

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