THE AETIOLOGY OF PERTHES’ DISEASE

GENETIC, EPIDEMIOLOGICAL AND GROWTH FACTORS
IN 310 EDINBURGH AND GLASGOW PATIENTS

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The aims of this survey were to establish the familial incidence of Perthes’ disease, to note any associated developmental anomalies and to collect information on preceding trauma or synovitis, on the pregnancy and birth, and on various sociological factors. Height and weight measurements were obtained for 217 patients, and comparisons made with those of their parents, unaffected sibs and (local) controls.

Results showed an extremely low frequency of Perthes’ disease among relatives, with no obvious pattern of inheritance. As genetic factors were not apparent, environmental and sociological causes were sought. The disease occurred particularly in children who were third-born or later in the family, and had older than average parents. Many came from low-income families and one in ten had been a breech birth, shown other malposition or had had a version late in pregnancy.

Many children were already undersized at the time of developing Perthes’ disease and remained shorter than average throughout life. Neither their parents nor sibs were shorter than normal, indicating that the patient’s short stature was not familial.

The child who is going to develop Perthes’ disease is already constitutionally and socially at a disadvantage, and during the perinatal period and the first few years of life is perhaps more susceptible to trauma than is a normal child.

The aetiology of Perthes’ disease is complex and there have been many suggestions of different contributory factors. The significance of preceding trauma or of a transient synovitis of the hip is difficult to evaluate as retrospective history is unreliable and most small children in this age group are subject to frequent minor accidents. Perthes’ disease can follow a transient synovitis, but not all cases are so affected. Jacobs (1960) reported it in up to 12 per cent of children who had had transient synovitis of the hip.

Experimental work in dogs by Zahir and Freeman (1972), and Sanchis, Zahir and Freeman (1973), suggested that Perthes’ disease in man could be vascular in origin, but due to more than one episode of infarction. McKibbon and Réal (1974) found pathological changes in a case of Perthes’ disease at necropsy after accidental death from drowning which supported this suggestion of multiple infarctions. Suramo et al. (1974), using intravenous venography, showed a disturbed pattern of venous drainage of the femoral neck. Kemp (1973) produced changes in the femoral heads of puppies, similar to those in the naturally occurring disease of certain breeds, by artificially raising the intracapsular pressure for various lengths of time and obliterating the vessels supplying the femoral head area.

Katz (1955) investigated the protein-bound iodine in Perthes’ disease, in view of the known defect of the epiphyses in hypothyroidism, but found no correlation.

Catterall, Lloyd-Roberts and Wynne-Davies (1971) reported an increased frequency of congenital abnormalities of the genito-urinary tract, both in patients with Perthes’ disease and in their near relatives, and noted that the chondrogenic cells associated with the mesonephros eventually contributed to the formation of limb girdle cartilage. Thus, in some instances of the disease there could be a primary deficiency either in these cells or in their blood supply.

The frequency of Perthes’ disease was studied by Harper, Brotherton and Cochlin (1976) who found an incidence of 1 in 4750 live births in South Wales between 1939 and 1964 (1 in 3000 boys, 1 in 11 800 girls). Molloy and MacMahon (1966) in Massachusetts estimated affected children as 1 in 1200 but their figure was arrived at indirectly on the assumption that the annual age-specific rates observed in one year (1964) were the same as would have been observed if a longitudinal study had been carried out.

There have been occasional reports of identical twins where both had Perthes’ disease (Giannestras 1954; Dunn 1960; Inglis 1960) but these were selected

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for reporting because of their concordance. The only unselected twins in the literature are the two pairs noted by Fisher (1972), and of these only one of each pair was affected.

A family incidence of Perthes' disease higher than that of the general population has been reported many times, but it is not always possible to know whether "bilateral Perthes' disease" with a strong family history is merely one of the many skeletal dysplasias involving the hip joints (for example, multiple epiphysial dysplasia, the spondylo-epiphysial dysplasias, or a tricho-rhino-phalangeal syndrome). Surveys that have eliminated these generalised bone dysplasias have always noted a very low incidence of Perthes' disease amongst first-degree relatives (parents, sibs and children of adult patients). Wansborough et al. (1959) reported that of sibs born after the index patient 1 in 35 were affected (approximately 3 per cent). Gray, Lowry and Renwick (1972) noted 0.8 per cent of parents, 3.8 per cent of sibs and 0.3 per cent of second and third-degree relatives, suggesting polygenic inheritance. Fisher (1972) studied 203 patients and noted amongst first-degree relatives only one affected father, two brothers and two sisters. He concluded there was no definite genetic predisposition to the disorder.

Many surveys of Perthes' disease report a higher proportion of patients than noted here with a "family history" of the condition, but without stating the degree of relationship. However, since Perthes' disease is quite common in the general population, distant relatives may well be affected by chance; the most significant figures to consider are those of the first-degree relatives.

About 80 per cent of patients with Perthes' disease are male, only about 10 per cent have bilateral disease and the typical age of onset is between four and seven years (Cameron and Izatt 1960; Molloy and MacMahon 1967). Fisher (1972) noted no significant findings for parental age or the position of the child in the family and only a suggestion of low birthweight among young female patients. Molloy and MacMahon (1967) also noted no significant findings for parental age but did find a highly significant excess of children of low birthweight.

The growth of these children as evidenced by their height, weight and skeletal maturation has been found abnormal by a number of investigators, though Cameron and Izatt (1960) found no significant growth retardation. Ralston (1955) noted a lag of development and of bone age in seventy-two patients. Weiner and O'Dell (1970) noted a retardation of linear stature in conjunction with average or above average weight. Fisher (1972) reported that the mean height of patients was just below the population mean, that the weight was not significantly different from normal but that patients showed a consistent retardation of skeletal maturation. Harrison, Turner and Jacobs (1976) studied skeletal maturation in 182 patients and ninety-three unaffected sibs and noted retardation, and in some instances a "skeletal standstill" for as long as three years. Burwell et al. (1976) reported a continuing anthropometric study in which various body measurements of patients with Perthes' disease were smaller than those of controls.

The aims of this current survey of Edinburgh and Glasgow patients were to establish the familial incidence of the disease in patients from the orthopaedic clinics, to note any associated developmental anomalies in them and their families, and to collect information on the pregnancy and birth, on preceding trauma or synovitis, and on epidemiological features such as parental age, the position in family and the social class. Details of growth were less complete than for other aspects of the survey: comparisons of some birthweights and later weights and of heights have been made between patients, their parents, unaffected sibs and (local) controls.

MATERIAL AND METHOD
A total of 390 case records were examined from the orthopaedic clinics of the Princess Margaret Rose Orthopaedic Hospital, Edinburgh, and the Royal Hospital for Sick Children, Glasgow. In all of them the diagnosis of Perthes' disease was considered definite and not secondary to another disorder such as congenital dislocation of the hip or a generalised skeletal dysplasia. The records extended from 1942 in Edinburgh and 1955 in Glasgow and an attempt was made to follow-up all patients. In seventy instances the family could not be traced or had gone abroad, one patient had died from a cause unrelated to Perthes' disease and nine refused to take part in the survey. Thus the final survey was of 310 index patients and their families (132 from Edinburgh and 178 from Glasgow).

The index patients were all seen at home, together with their parents, sibs and (of adult patients) children. A history was taken in relation to Perthes' disease or other hip problems, particularly in the immediate family but also among the more distant second and third-degree relatives. A positive history of the disease or of associated anomalies in the patient and relatives was noted and confirmed by personal visiting or by examination of medical records. In most instances the family history and epidemiological information were obtained from the mother of the patient.

At the start of the survey the heights and weights of the first forty-three index patients and their parents and sibs were measured, but as these findings were thought to be unremarkable when compared with each other and with national standards this examination was discontinued. However, by 1974 a number of papers had commented on the growth retardation in Perthes' disease, so a second attempt was made to collect this information from the patients and families most readily available. Comparison was made, this time, with more closely matched controls. Only 217 patients were studied for this aspect of the survey, because thirty-six patients could no longer be traced, fifty-five had moved some distance from Edinburgh and were not easily available for visiting, and two families refused to co-operate further.

RESULTS
Clinical features and associated anomalies
Of the 310 patients 246 were male, giving a sex ratio of males to females of 3.8:1, and thirty-five had bilateral disease (11.3 per cent). These figures were similar to those of all other reports. There was a history of trauma or immediately preceding synovitis of the hip in only 17 per cent of children, equally often in boys and girls. Such
a history was absent among the children who developed Perthes' disease under three years of age; it may have occurred but was not admitted.

Associated developmental anomalies were as follows: four males had had pyloric stenosis, two patients had coeliac disease and there was one instance each of radio-ulnar synostosis, branchial fistula, talipes equinovarus, talipes calcaneovalgus and mental retardation. Specific enquiry was made regarding osteochondritis dissecans but only one patient had this as well as Perthes' disease, both knees being affected. Other members of his family were normal.

Table I. Proportions of relatives affected with Perthes' disease

<table>
<thead>
<tr>
<th>Index patients</th>
<th>First degree</th>
<th>Second degree (nephews, nieces, half-sibs only)</th>
<th>Third degree (first cousins only)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Parents</td>
<td>Sibs</td>
<td>Total</td>
</tr>
<tr>
<td>Male n = 246</td>
<td>0/492</td>
<td>13/738</td>
<td>0/38</td>
</tr>
<tr>
<td>Female n = 64</td>
<td>0/128</td>
<td>2/202</td>
<td>1/11</td>
</tr>
<tr>
<td>Total n = 310</td>
<td>0/620</td>
<td>15/940 (1.6 per cent)</td>
<td>1/49 (2.0 per cent)</td>
</tr>
</tbody>
</table>

Ten male patients had inguinal herniae, there were three instances of congenital defects of kidney or ureter (duplication, accompanied by staghorn calculi), and one case of severe hypospadias. The association with genito-urinary tract anomalies was more marked among the first-degree relatives, in whom there were three proven instances of double kidneys or ureters (one mother, one sister and one daughter), two brothers had congenital hydronephrosis due to ureteric stenosis, and one brother had severe hypospadias. There were four instances of nephrectomy for renal calculi at an early age (one father, two mothers and one sister), indicating a probable congenital renal tract defect. This genito-urinary pattern was maintained by the more distant relatives: among the second-degree relatives there were individuals with bilateral polycystic kidneys, ureteric stenosis and hydronephrosis, stenosis of the renal artery with secondary hypertension, renal aplasia and two cases of early nephrectomy for renal calculi. Among the third-degree relatives (about whom less is usually known by the index patient's family) there were instances of a teratoma of the testis, a stillborn child with renal agensis and one individual who had had a heminephrectomy for a congenital cystic lesion. The incidence of these deformities in the general population is not known, but in the last three genetic surveys completed by this unit the frequency of genito-urinary anomalies (excluding herniae) among adult first-degree relatives (parents) was only 1 in 1704 (0.06 per cent). This is ten times lower than the frequency among parents in the current survey (0.6 per cent).

There were thirteen families (4 per cent) with a history of congenital dislocation of the hip which is probably significantly higher than expected for the general population (1 to 4 per 1000). Other developmental anomalies were unremarkable in type or in numbers, being only what might be expected from a random survey.

Genetics

There were five dizygous and one monozygous twin pairs among the patients; all were discordant, Perthes' disease being present in only one of each pair. There were two instances of consanguinous parents, both patients being female and the parents being first cousins in one case and second cousins in the other, but there were no relatives affected with Perthes' disease in these two families.

The proportions of first, second and third-degree relatives affected with Perthes' disease are shown in Table I. The only second- and third-degree relatives included in the table are those about whom the patient's family was likely to be well informed (nephews, nieces, half-sibs and first cousins), and medical information thus more likely to be up to date and accurate. The overall proportions of affected relatives was very low: no parent appeared to be involved, only 1.6 per cent of sibs and 2 per cent of children, this last figure being only one affected child of a total of forty-nine children of the original (now adult) index patients. The numbers of second- and third-degree relatives with Perthes' disease dropped immediately to the population frequency. The proportions of affected relatives of male and female index patients were similar, as were those with bilateral disease compared with unilateral.

Epidemiology

Previous stillbirths and abortions. There were thirty-five stillborn sibs of patients and 112 abortions, or 3 per cent and 10 per cent respectively of all conceptions. This is not significantly different from the expected national figures of 1 per cent and 8 per cent.

Length of gestation. The number of premature infants was unremarkable, only twenty-five of the 310 patients (8.1 per cent) being less than thirty-eight weeks' gestation. This was close to the expected figure of about 6 per cent for the normal population. However, as a
group the premature children who subsequently developed Perthes' disease differed from the remaining patients: of these twenty-five premature babies only one developed bilateral disease. Eight of them (32 per cent) had a family history of genito-urinary malformations; seven (28 per cent) had been breech presentations, other malpositions or versions late in pregnancy. As expected, most (80 per cent) were of low birthweight, but notwithstanding this, only two of them were subsequently noted to be of short stature.

**Presentation.** An unexpected finding among the 299 patients for whom information was available was that thirty-two of them (10.7 per cent) had an abnormal presentation (sixteen breech, fourteen versions late in pregnancy and two with a transverse lie). This was a highly significant excess over the expected figure of 2 to 4 per cent for the normal population. Of these thirty-two patients with malposition, only one subsequently developed bilateral disease, just under half of them were of low birthweight, and one-third were premature births. Over half (58 per cent) were from low-income families. The age at which their Perthes' disease developed was in no way different from the remaining patients.

**Parental age and parity.** The age of both parents was significantly higher than that found in the general population: fathers 31.67±0.37 years (expected local figures 28.82 years), mothers 28.92±0.33 years (expected local figures 26.03 years). Even more significant was the age of the parents of patients with bilateral disease: fathers 33.27±1.11 years, mothers 30.15±1.02 years. The parental age difference was 2.75±0.22 years, not significantly different from the expected national figure of approximately 2.8 years. In addition, of children who subsequently developed Perthes' disease, a significant excess were born late in the family (Table II).

| Table II. Parity of index patients with Perthes' disease
<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Position in the family</td>
<td>Total</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6 or later</td>
</tr>
<tr>
<td>-----------------</td>
<td>-----------------</td>
<td>-----------------</td>
<td>-----------------</td>
<td>-----------------</td>
<td>-----------------</td>
<td>-----------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Observed</td>
<td>84</td>
<td>86</td>
<td>60</td>
<td>31</td>
<td>17</td>
<td>30</td>
<td>306**</td>
</tr>
<tr>
<td>Expected*</td>
<td>111.80</td>
<td>85.47</td>
<td>50.33</td>
<td>26.89</td>
<td>14.85</td>
<td>18.66</td>
<td>308</td>
</tr>
</tbody>
</table>

Difference significant: 0.01>P>0.005 ($\chi^2 = 16.6$)
*based on the 1954 Report of the Registrar-General for Scotland
**2 not known

When the group of 178 patients whose mothers were over thirty years of age and who were third-born or later were compared with the remaining patients it was found that a higher than expected proportion had developed bilateral disease (16 per cent compared with 5 per cent); a slightly higher proportion had a definite history of preceding trauma (20 per cent compared with 13 per cent) and, as expected from general sociology, more of them were of short stature and from low-income families.

**Social class.** This was estimated from the father's occupation (and hence, income) and the findings were compared with the figures from the Registrar-General for Scotland (1955), divided into the appropriate areas of Edinburgh and Glasgow cities and their surrounding regions. A highly significant excess of patients from low-income group families (social classes IV and V) was found. Table III shows the figures for the whole survey, but the findings were similar when individual areas were considered separately (Edinburgh and the Lothians, Glasgow City). The "expected" proportion of low-income families in this population was approximately 28 per cent, whereas the "observed" proportion among the Perthes' families was 43 per cent.

| Table III. Social class of Perthes' families
<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I and II (high income)</td>
<td>III</td>
<td>IV and V (low income)</td>
<td>Total</td>
</tr>
<tr>
<td>-----------------</td>
<td>-----------------</td>
<td>-----------------</td>
<td>-----------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Observed</td>
<td>27</td>
<td>148</td>
<td>132</td>
<td>307**</td>
</tr>
<tr>
<td>Expected*</td>
<td>39.39</td>
<td>180.34</td>
<td>87.26</td>
<td>307</td>
</tr>
</tbody>
</table>

Difference very highly significant: 0<P<0.001 ($\chi^2 = 32.66$)
* based on the 1954 Report of the Registrar-General for Scotland
**3 not known

When the 132 children from low-income families were compared with the twenty-seven from high-income families, various differences were apparent. The former had an excess of late-born children (52 per cent were third-born or later, compared with 33 per cent in the upper income group); 14 per cent had been breech births, versions or other malposition compared with 4 per cent (which is also the normal population incidence), and 32 per cent compared to 11 per cent had been of low birthweight. These again, were not unexpected sociological findings.

Considering the twenty-seven children from high-income families, a higher than expected proportion (59 per cent) had mothers over the age of thirty years; only one child was subsequently noted to be of short stature; and there was no single instance of a child developing the disease before the age of three, whereas 9 per cent of the poorer children developed Perthes' disease under this age.

**Seasonal onset.** There was no significant finding in relation to the season of onset of Perthes' disease, though it was not always possible to be certain on retrospective history-taking exactly when the first signs did appear. Slightly more patients reported symptoms starting in the summer than in the winter (1.2:1).
Growth factors

Standards for height and weight. In a retrospective survey such as this it was a great problem to obtain accurate matching control data for the height and weight of patients. Initial comparison with national standards had shown little deviation from normal, and significant results were only obtained by compiling more exact standards for Edinburgh and Glasgow separately, as it was found that in both sexes and at all ages the mean normal values for Glasgow were considerably below those for Edinburgh, which itself was slightly different from London. The standard charts finally used were those of Tanner, Whitehouse and Takaishi (1966) with the scale shifted to mean values for Glasgow and Edinburgh. Details of how these standards were derived are noted in the Appendix.

Height. Three age groups were considered: first, the years during which an individual might be expected to suffer from Perthes' disease, and when a standing height, rather than a supine length, could be obtained (2 to 11.99 years); second, the growth spurt years (12 to 15.99); and, finally, adults (16 to 30 years). Numbers were only sufficient for statistical evaluation of males and the discussion is largely confined to them.

From the results for Glasgow (Fig. 1 and Table IV) it can be seen that, for children up to the age of twelve years, the distribution was significantly different from normal, with more patients than expected of short

### Table IV. Centile height distribution in 160 Glasgow and Edinburgh male patients with Perthes' disease

<table>
<thead>
<tr>
<th>Age group</th>
<th>Below 10</th>
<th>10–</th>
<th>25–</th>
<th>50–</th>
<th>75–</th>
<th>90+</th>
<th>Total</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glasgow (145 measurements)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Childhood: 2–11.99 years</td>
<td>13 (5.5)*</td>
<td>11 (8.25)</td>
<td>13 (13.75)</td>
<td>10 (13.75)</td>
<td>5 (8.25)</td>
<td>3 (5.5)</td>
<td>55</td>
<td>significant 0.025 &gt; P &gt; 0.01</td>
</tr>
<tr>
<td>Growth spurt: 12–15.99 years</td>
<td>5 (4.0)</td>
<td>10 (6.0)</td>
<td>10 (10.0)</td>
<td>6 (10.0)</td>
<td>5 (6.0)</td>
<td>4 (4.0)</td>
<td>40</td>
<td>not significant</td>
</tr>
<tr>
<td>Adult: 16–30 years</td>
<td>11 (5.0)</td>
<td>10 (7.5)</td>
<td>15 (12.5)</td>
<td>9 (12.5)</td>
<td>4 (7.5)</td>
<td>1 (5.0)</td>
<td>50</td>
<td>significant 0.025 &gt; P &gt; 0.01</td>
</tr>
<tr>
<td>Edinburgh (55 measurements)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Childhood: 2–11.99 years</td>
<td>1 (0.4)</td>
<td>— (0.6)</td>
<td>1 (1.0)</td>
<td>2 (1.0)</td>
<td>— (0.6)</td>
<td>— (0.4)</td>
<td>4</td>
<td>(too few to test)</td>
</tr>
<tr>
<td>Growth spurt: 12–15.99 years</td>
<td>1 (1.1)</td>
<td>1 (1.65)</td>
<td>2 (2.75)</td>
<td>4 (2.75)</td>
<td>1 (1.65)</td>
<td>2 (1.1)</td>
<td>11</td>
<td>(too few to test)</td>
</tr>
<tr>
<td>Adult: 16–30 years</td>
<td>10 (4.0)</td>
<td>2 (6.0)</td>
<td>5 (10.0)</td>
<td>10 (10.0)</td>
<td>8 (6.0)</td>
<td>5 (4.0)</td>
<td>40</td>
<td>significant P = 0.01</td>
</tr>
</tbody>
</table>

*'expected' figure in parenthesis (from modified standards, see Appendix)*
stature (below the 10th centile). However, from twelve to sixteen years of age, during the main growth spurt, there was no significant difference. From sixteen years on (i.e. in adult life) the difference again became significant, with more index patients who had previously had Perthes' disease below the 10th centile than expected. Thus it would seem that at the time of diagnosis of Perthes' disease many of these patients are already shorter than normal, that they catch up to some extent during the growth spurt years but fall back later, never quite to reach normal adult height. The Edinburgh patients (Fig. 2 and Table IV) showed the same significant difference in adult life, but in the two earlier groups the numbers were too small to test.

The only female patients who could be evaluated in the same way were a small group of twenty-two from Glasgow, aged fourteen to thirty years. Here, although the height reduction was not so obvious as in the males, it did approach a significant difference from normal (0.1 > P > 0.05).

**Table V. Centile height difference between male patients with Perthes' disease and unaffected brothers**

<table>
<thead>
<tr>
<th>Age group</th>
<th>Number of pairs</th>
<th>Observed (± standard error)</th>
<th>Expected</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Glasgow</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(114 patient/brother pairs)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Childhood: 2–11.99 years</td>
<td>33</td>
<td>-14.7 ± 5.98</td>
<td>-1.65</td>
<td>probably significant 0.05 &gt; P &gt; 0.025</td>
</tr>
<tr>
<td>Growth spurt: 12–15.99 years</td>
<td>35</td>
<td>-8.91 ± 3.45</td>
<td>-1.52</td>
<td>probably significant 0.05 &gt; P &gt; 0.025</td>
</tr>
<tr>
<td>Adult: 16–30 years</td>
<td>46</td>
<td>-17.12 ± 4.66</td>
<td>+0.98</td>
<td>highly significant P &lt; 0.001</td>
</tr>
<tr>
<td><strong>Edinburgh</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(55 patient/brother pairs)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Childhood: 2–11.99 years</td>
<td>6</td>
<td>-5.0 ± 9.5</td>
<td>-1.25</td>
<td>not significant</td>
</tr>
<tr>
<td>Growth spurt: 12–15.99 years</td>
<td>17</td>
<td>-1.8 ± 8.44</td>
<td>-0.9</td>
<td>not significant</td>
</tr>
<tr>
<td>Adult: 16–30 years</td>
<td>32</td>
<td>+4.18 ± 6.51</td>
<td>-0.4</td>
<td>not significant</td>
</tr>
</tbody>
</table>

* negative sign occurs when patient is shorter than his brother

The tests for significance were carried out on the means of the differences found between the observed and expected value of centile height difference for each patient/brother pair within the three age groups.

**Comparison with parents.** In twenty-seven instances it was possible to obtain the height of index patients and of both parents at the time the child was in hospital with Perthes' disease. When these details were plotted on charts allowing for parental height (Tanner, Goldstein and Whitehouse 1970), the patients' distribution was still significantly different from normal, while that of their parents was not (using the mid-parent height).

The heights of an additional 121 fathers and 121 mothers were obtained, and compared with the local modified standards of full adult height at nineteen years. No significant difference was observed. The mean heights of the fathers and mothers of Edinburgh patients were 68.8 and 64.0 inches, compared with standard figures of 68.1 and 63.4 inches; fathers and mothers of Glasgow patients had means of 67.2 and 62.7 inches, compared with standard figures of 67.5 and 62.7 inches. This indicates that the tendency to short stature in patients with Perthes' disease is likely to be associated with the disease itself rather than being inherited from their parents.

**Comparison with sibs.** In addition to comparing with normal children, comparison was also made between the index patient and his sibs, in order to make some allowance for heredity and to obviate the possible effects of social class and other environmental factors. The heights of male index patients compared with their brothers are shown in Table V. All available information was used, whether the brothers were older or younger than the patient, and the necessary corrections made for age, family size and position in the family. The
occur between thirteen and seventeen years, which is later than the twelve to sixteen years described for the London children on whom Tanner and colleagues based their charts (see Appendix).

When considering only the children known to be of short stature (below the 10th centile) it was noted that a higher than expected proportion of them were male, that they had an increased tendency to bilateral disease and that over one-third of them developed the disease over the age of seven years. Sixty per cent of them were born third or later in the family and, not unexpectedly, a high proportion came from low-income families.

**Weight at birth and later.** The birthweight was recorded in all but seven of the 310 patients, being 7.30 pounds±0.09 for males and 6.98 pounds±0.15 for females. These figures were not significantly different from normal. However, in view of the low birthweight found by Molloy and MacMahon (1967) a smaller group of 128 children from Edinburgh were compared with more nearly matched controls from the Edinburgh Register of the Newborn. There was a significant difference here, not in the mean birthweight but in its distribution: there were more children of low birthweight and more of high birthweight than expected. However, it was not possible to obtain accurate figures for birthweight from obstetric records, and on the visit to some of these families we found that the mother recalled a completely different birthweight from the first visit; thus the significance of this finding is doubtful.

Few of the seventy-five children reported to be of low birthweight were subsequently noted to have markedly short stature. They came chiefly from low-income families, had older than average mothers, and 15 per cent of them developed Perthes' disease under the age of three years.

The weight of patients at the onset of Perthes' disease and subsequently, up to the age of twenty years, was not significantly different from normal.

**DISCUSSION**

**Anomalies associated with Perthes' disease.** Harper and colleagues did not find that Perthes' disease and congenital anomalies of the genito-urinary tract were associated, and there were few patients with such defects in this current survey. However, the proportions of relatives with these abnormalities was probably higher than would be expected from a random population survey—precise figures are difficult to obtain—and were certainly higher than found in any other genetic survey carried out by this department over the past thirteen years. The numbers of close relatives with congenital dislocation of the hip was higher than expected, these families and those with genito-urinary anomalies being mutually exclusive. There may be small groups of "Perthes' disease", not conforming to the general pattern and with differing aetiologies.

**Genetics.** It seems unlikely that there are any genetic factors in the great majority of cases. The frequency of Perthes' disease among near relatives was extremely low and it rarely involved both identical twins. The proportions of affected second and third-degree relatives dropped immediately to the probable population frequency (about 3 per 1000 males). Furthermore, no genetic pattern of inheritance could be demonstrated: there was no evidence for single-gene inheritance, and if Perthes' disease were of multifactorial inheritance it would be expected that the more rarely affected sex (girls) would have a higher proportion of affected relatives than boys, and this was not the case.

**Environmental factors.** In the absence of genetic factors one must look for environmental and sociological evidence pointing to the cause of this disease. It was possible to identify a number of adverse factors among affected children compared with both the normal population and their sibs. The disease occurred particularly in children who were born late in the family (at least third-born and quite often sixth-born or later), and with this was associated a greater than average age of the parents. A high proportion of these children came from low-income families, and approximately 1 in 10 of them had been a breech birth, shown other malposition or had had a version late in pregnancy. A definite history of trauma or preceding synovitis of the hip was present in less than one-fifth, though possibly breech presentation or version could have been the first in a series of minor traumatic episodes in some additional cases.

**Growth factors.** Some children were already undersized at the time of developing Perthes' disease, and remained shorter than average throughout life. However, this was not markedly so, needing very careful matching with local standards for the findings to become significant. The disparity between the patients and their sibs was least during the years of the growth spurt. Neither parents nor sibs were short when compared with local standards. Height did correlate, however, with the age of onset of the disease: only 14 per cent of children who developed it under the age of three years were later of short stature, whereas 33 per cent of those who developed it over the age of seven were subsequently undersized. Starting, and recovering from, the disease at an early age seemed to allow time for growth to "catch up" in most instances. It was not possible to show that low birthweight was a particular feature nor did a low birthweight correlate with subsequent short stature.

There are clearly a number of different environmental and social influences. A child from a poor home seems at a much higher risk of developing Perthes' disease than one from a high-income family. It is clear that he is already smaller than his brothers and sisters at
the time he develops the disease; is he more susceptible to minor trauma? Being at the end of the family, has he had rough handling from his numerous older brothers and sisters? Could this disease be one of the later consequences of being a battered baby? Prenatal factors can certainly be relevant: we should probably be looking for trauma to the hip joint, whether by accident or from malhandling, from birth to three years of age, preceding the clinical appearance of Perthes' disease at the usual age of four to seven years.

APPENDIX

Derivation of standard charts for height and weight of Edinburgh and Glasgow children

Information on the mean values came from Keddie (1956) and the Scottish Home and Health Department Research and Intelligence Unit (1972). Keddie gave mean heights and weights for children at 5, 9.5 and 13.5 years of age in local authority schools in Glasgow and Edinburgh at intervals from 1913-14 to 1953-54, and for children of 16.5 years from 1948-49 to 1953-54. These were matched to the Scottish Home and Health Department's more recent values of mean heights and weights of school entrants (5 years of age) and older children (13.5 years) at all local authority schools in Glasgow and Edinburgh. The bias to social classes IV and V (low-income families) was corrected using information provided by both sources and by the Registrar-General for Scotland.

The resulting mean values of height and weight (Tables VI and VII) were used to determine the shift in scale to be applied to the standard height and weight charts of Tanner, Whitehouse and Takashii (1966). The values for the two cities were noticeably different, those for Glasgow being consistently less in both sexes and at all ages than those for Edinburgh (up to one inch in height and almost three pounds in weight).

For Edinburgh males the charts compiled by Tanner and colleagues for height were used without alteration, and for Glasgow males the scale was shifted down. For weight, the figures were shifted up for Edinburgh and down for Glasgow. In all cases the shape of the curve was adhered to, although this meant that all mean values for 13.42 years lay below the 50th centile.

Standards for the differences in height and weight to be expected between index and sib were derived from Grant (1964), who compiled tables of mean height and weight by sex, birth rank and family size at ages 6, 10, 12, and 14 years for 1061 families. If the assumption is made that a normal child follows the same centile throughout development then Grant's figures can be used to calculate a mean centile value for each child in the family according to sex, position in the family and family size. Thus, differences in height and weight to be expected between members of a family can be expressed in centiles.

Table VI. Mean height of Edinburgh and Glasgow children (modified standards)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Boys Mean height (inches)</th>
<th>Girls Mean height (inches)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Edinburgh</td>
<td>Glasgow</td>
</tr>
<tr>
<td>5.33</td>
<td>43.2</td>
<td>42.4</td>
</tr>
<tr>
<td>9.42</td>
<td>52.3</td>
<td>51.7</td>
</tr>
<tr>
<td>13.42</td>
<td>60.4</td>
<td>59.5</td>
</tr>
<tr>
<td>16.58</td>
<td>68.6</td>
<td>67.6</td>
</tr>
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</table>

Table VII. Mean weight of Edinburgh and Glasgow children (modified standards)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Boys Mean weight (pounds)</th>
<th>Girls Mean weight (pounds)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Edinburgh</td>
<td>Glasgow</td>
</tr>
<tr>
<td>5.33</td>
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<td>16.58</td>
<td>135.8</td>
<td>132.9</td>
</tr>
</tbody>
</table>

Late onset of growth spurt in Edinburgh and Glasgow. At the age of 13.42 years the mean height of normal London boys (Tanner et al. 1966) is 61.5 inches whereas those in Edinburgh are 60.4 inches and in Glasgow 59.5 inches—approximately 1 and 2 inches shorter. This age group shows the widest disparity between London and the Scottish cities: at ages before and after this the differences are only of the order of 0.3 inches (Edinburgh) and 1 inch (Glasgow). Thus, it would seem that the normal Scottish child is starting his growth spurt at a later age than the Londoner.

This later start for the growth spurt was confirmed by the figures for the height difference between boys who had had Perthes' disease and their unaffected brothers. Between the ages of 12 and 15.99 years the Perthes' disease patients were significantly shorter than their brothers (centile height difference —8.91 ± 3.45, Table V), whereas when the years 13 to 16.99 are considered, the difference between them is less (—7.39 ± 3.99) and no longer significant. Thus, in Edinburgh and Glasgow the main growth spurt for both patients and sibs appears to occur between the years of 13 and 17. When Table IV was revised, using 13 to 16.99 as the growth spurt years instead of 12 to 15.99, it was found that the disparity in height between male patients and the normal population was but little altered.

We are grateful to all the orthopaedic surgeons at the Princess Margaret Rose Orthopaedic Hospital, Edinburgh and the Royal Hospital for Sick Children, Glasgow, for access to case records and permission to visit their patients. Thanks are due to the doctors carrying out the family visiting: Drs M. Anderson and M. Whitmore (Edinburgh) and Drs H. Cameron, M. Davies and H. Fulton (Glasgow).

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