Introduction

The epidemiological study of disease aims to increase our understanding of the aetiology, patterns of occurrence and natural history of clinical conditions by reference to populations and defined sub-populations. One of the potential gains from such an approach is the possibility of drawing inferences regarding the contributions of genetic and specific environmental factors in causation. On a more immediately practical level, the determination of prevalence of disease in defined populations is important for the planning of specialist facilities and the prediction of direct and indirect costs of treatment.

Tumours of endocrine glands, although rare in the context of the overall burden of oncological disease, have provided important insights into the mechanisms of sporadic and familial tumour formation, important examples being the primary role of constitutively activated cell membrane G protein-linked mechanisms in determining proliferation in pituitary somatotroph adenomas (Spada et al. 1990), and the recent elucidation of the molecular basis of the multiple endocrine neoplasia (MEN) syndromes (Ponder 1994, Chandrasekharappa et al. 1997). However, it is often difficult to obtain an epidemiological perspective for endocrine tumours, either because of asymptomatic disease which results in incomplete case ascertainment or the rarity of individual tumour types (Table 1). The reported incidence of parathyroid adenoma is a classical example of the dependence of incidence data on diagnostic facilities and local policies for routine serum calcium measurements. These problems are magnified by the fact that clinical care of endocrine tumours may occur in a variety of settings (including endocrinology, oncology, surgery and neurosurgery) with variable levels of communication and case registration. In addition, the frequently indolent nature of endocrine tumours and their response to therapy means that, in contrast to the situation with most solid tumours, mortality rates cannot provide a surrogate measure of tumour incidence. Nonetheless, reliable data for the incidence of thyroid carcinoma are available, and approximate estimates for incidence of adrenomedullary, adrenocortical and gastropancreatic neuroendocrine tumours have been obtained in geographically defined populations. Similarly, data for functioning and non-functioning pituitary tumours have been reported with reasonable concordance between series. This review aims to provide an overview of illustrative aspects of the epidemiological features of these tumours.

Endocrine tumours in relation to the overall burden of malignant disease

Endocrine tumours are rare in comparison with the spectrum of malignant disease. Thus, in the UK, whereas lung carcinoma has an incidence of approximately 72 and 19 per 100 000 per year in males and females respectively, and breast carcinoma has an incidence of 54 per 100 000 per year, the incidence of thyroid carcinoma, with the exception of gonadal tumours the most common endocrine malignancy, is rare, with an overt incidence of 0.6–1.5 per 100 000 per year (Muir et al. 1987). Other malignant endocrine tumours, including adrenocortical carcinoma, carcinoid and other neuroendocrine tumours are extremely rare, with incidence figures of <0.5 per 100 000 per year. Parathyroid tumours giving rise to hyperparathyroidism are more common, with a minimum incidence of 28 per 100 000 per year but the tumours are rarely malignant (Melton 1991).

Thyroid carcinoma

Carcinoma of the thyroid may arise from follicular cells or from parafollicular c cells. The former are more common (90% of total incidence) and consist of two differentiated histological subtypes, papillary (40–70%) and follicular (10–40%) carcinoma and undifferentiated or anaplastic carcinoma (5–15%). Both papillary and follicular carcinoma are more
common in female subjects and anaplastic carcinoma tends to occur in older subjects. Tumours of c cells (medullary thyroid carcinoma) may be sporadic or familial, the latter in the context of MEN types 2A and 2B and familial medullary carcinoma of the thyroid. The familial forms of medullary carcinoma of the thyroid are preceded by premalignant c cell hyperplasia and, as a consequence, are frequently multifocal in contrast to sporadic medullary lesions. Medullary thyroid tumours constitute between 5 and 10% of all thyroid carcinoma and are familial in approximately 25% of cases.

**Ethnic and geographical considerations**

The incidence of overt, or clinically evident, thyroid carcinoma is influenced by geographical, ethnic and gender considerations (Franceschi *et al.* 1993), and reported series document a variation in incidence between 0.6 and 18.2 per 100 000 per year. Because differentiated thyroid carcinoma is frequently a treatable condition, mortality rates do not provide a sensitive indicator of these factors. Importantly, the variation in incidence between groups of different ethnic origin living in the same locality provides a means of distinguishing between hereditary and environmental factors in pathogenesis. Particularly high incidence rates for thyroid carcinoma have been reported from Iceland and Hawaii and within the latter region there is marked ethnic variation, so that male Chinese and female Filipinos exhibit the highest rates (Muir *et al.* 1987). However, these high rates are specific to Hawaii rather than reflecting an effect of ethnicity *per se* in that rates of thyroid carcinoma amongst Chinese males are not increased in other geographical areas (Lee *et al.* 1988). Rates are also high in Israel but in this circumstance the effect is not related to geography; non-Jews do not demonstrate an increased incidence and Jews have a higher incidence regardless of their country of origin. Clearly, the quality of registration of cancers, which is proportional to the quality of medical services, will influence these comparisons to a large extent.

**Influence of iodine deficiency**

A number of epidemiological studies have demonstrated an increased prevalence of thyroid carcinoma in areas with a high prevalence of endemic goitre due to iodine deficiency (Muir *et al.* 1987). Animal data support an association between iodine-deficient goitrogenesis and tumour formation, therefore suggesting that the epidemiological observations in human populations are not simply due to increased ascertainment occurring by virtue of surgery for benign disease (Yamashita *et al.* 1990). In support of a causal connection is the observation of reduction in thyroid cancer mortality rates in Switzerland over the early part of this century in parallel with the introduction of salt iodisation (Levi *et al.* 1988). However, this phenomenon was not observed with the introduction of iodisation in Italy, possibly because of the persistence of iodine deficiency in some areas (Decarli & La Vecchia 1984), or in the United States (Ron 1982).

**Influence of irradiation and benign thyroid pathologies on thyroid carcinoma incidence**

There is a striking increase in the incidence of thyroid carcinoma (particularly papillary) in individuals exposed to ionising radiation, especially in the form of X-rays, either given therapeutically for other conditions (Hempelmann 1968) or by inadvertent exposure (Hamilton *et al.* 1987). The risk is most evident in children and may have a prolonged lag phase of decades. There is, however, no evidence of an increased risk of thyroid neoplasia as a result of $^{131}$ I exposure (Dobyns *et al.* 1974).

Whereas the presence of benign thyroid nodules has been associated with an increased incidence of thyroid neoplasia, there is no reported association between the presence of either hyperthyroid Graves’ disease or autoimmune hypothyroidism and thyroid neoplasia (McTiernan *et al.* 1984, Preston-Martin *et al.* 1987).

**Changes in reported incidence rates over time**

There are striking gender differences in the changes in incidence rates of thyroid carcinoma reported over time. Thus, in males, an upward trend in incidence was observed in a number of countries including the United States in the 1960s and 1970s with stabilisation thereafter (Devesa *et al.* 1987). In males, this increase in incidence was evident particularly in individuals aged >60 years. In contrast, females demonstrated an increase in incidence which was maximum between 20 and 39 years of age (Weiss 1979, Devesa *et al.* 1987). In both sexes, mortality rates from thyroid cancer remained constant with time and demonstrated a predictable age-related increase which contrasts with the increase in incidence rates in younger women. This apparent paradox may be explained by two linked phenomena. First, benign thyroid disease is much more common in females (Ron 1982), and this is likely to lead to a higher rate of investigation and diagnosis of incidental papillary thyroid carcinoma. Secondly, the data point towards differences in malignant severity between some of these intrathyroidal papillary carcinomas and thyroid malignancies presenting overtly.

**Occult papillary thyroid carcinoma**

The reported prevalence rate of occult intrathyroidal papillary carcinoma discovered at post mortem is very much higher (6–36%) than would be predicted on the basis of the known incidence rates of the disease (Bondeson & Ljungberg 1981, Harach *et al.* 1985, Franssila & Harach 1986, Ottino
In contrast to the gender difference observed in prevalence and incidence of clinical thyroid carcinoma, there is no such difference in occult papillary carcinoma. Furthermore, occult tumours, although uncommon in the prepubertal age group, have a stable prevalence thereafter, consistent with origin in early adulthood and a quiescent natural history (Franssila & Harach 1986). These findings have obvious implications for the management of incidentally identified intrathyroidal papillary carcinoma.

**Parathyroid adenoma**

Parathyroid neoplasms are responsible for approximately 85% of all cases of primary hyperparathyroidism and the vast majority are benign (>95%). Hyperparathyroidism is the most common cause of hypercalcaemia in non-hospitalised populations, but determining incidence is difficult by virtue of the fact that most cases are asymptomatic and the rate of diagnosis is directly related to the availability and use of routine multichannel clinical chemistry. The incidence has been estimated at 28 per 100 000 per year with a prevalence of 1:1000 in hospitalised populations (Melton 1991). The overall impact of asymptomatic hyperparathyroidism on health remains a subject for debate.

**Pituitary adenoma**

Pituitary macroadenomas constitute approximately 10% of all intracranial tumours overall but account for a higher percentage in African Americans (Table 2). The majority are clinically non-functioning and present as a result of either space-occupying effects or clinical hypopituitarism. Functioning tumours producing growth hormone, adrenocorticotropic hormone or prolactin result in the classical endocrine conditions of acromegaly, Cushing’s disease and galactorrhoea/oligo/amenorrhoea (impotence in the male) respectively. Non-functioning pituitary mass lesions may also produce modest hyperprolactinaemia as a result of disinhibition of the effects of hypothalamic dopamine on lactotroph cells.

Pituitary adenomas have an overt incidence of between 0.4 and 8.2 per 100 000 per year with the highest recorded incidence occurring in females aged 45–64 years in a UK series (Table 3). Most studies indicate an approximately equal sex incidence but there was a female predominance in both the Mayo Clinic and UK series in the 1970s, a finding which has been attributed to the availability of prolactin assays and the more frequent presentation of symptoms of hyperprolactinaemia in females than males. An alternative explanation has been sought in the context of oral contraceptive use and the possible effects of oestrogen on pituitary tumorigenesis but has not been confirmed in relatively small-scale case control studies.

Although overt pituitary tumours are rare, autopsy studies indicate a very high prevalence of occult small pituitary adenomas of between 22 and 27% (Costello 1936, Burrow et al. 1981). The majority of studies demonstrate an increasing incidence with age, up to 50 to 60 years, for both overt (Table 3) and occult pituitary adenomas (Costello 1936).

**Acromegaly**

Acromegaly has a reported incidence of between 2.8 and 4 per 100 000 per year (Alexander et al. 1980, Bengtsson et al. 1988, Ritchie et al. 1990, Etxabe et al. 1993). Although there is a relative paucity of epidemiological studies the data from these studies are concordant in terms of incidence, and prevalence data are also broadly similar at 53 and 60 per million in the Newcastle, UK and Vizcaya, Spain studies respectively (Alexander et al. 1980, Etxabe et al. 1993). The Newcastle study documented the highest prevalence in the population living closest to the referral centre, consistent with either ascertainment bias or an overall higher rate of diagnosis, and also demonstrated a predictable peak in the numbers of patients diagnosed subsequent to the availability of radioimmunoassay for growth hormone. In contrast to the Newcastle study, the Vizcaya study documented an increased prevalence in women (1.8:1). In addition, the Vizcaya study documented an inverse relationship between age at diagnosis and growth hormone (Fig. 1), a finding consistent with an inherently greater severity of disease in younger patients. Both studies documented an increase in cardiovascular and malignant mortality in males; cerebrovascular mortality was increased in females in the Newcastle study.

Increased mortality in acromegaly has been a feature of most studies (Wright et al. 1970, Alexander et al. 1980, Bengtsson et al. 1988, Etxabe et al. 1993, Orme et al. 1998), although a significant increment was not observed in one large series (Nabarro 1987). Taken overall, the data indicate an increased incidence in vascular disease in both sexes. However, there are significant differences between series in relation to possible gender differences in incidence of incidence.

**Table 2** Pituitary tumours as percentage of intracranial tumours (adapted from Gold 1981)

<table>
<thead>
<tr>
<th>Study (reference)</th>
<th>Total</th>
<th>White male</th>
<th>White female</th>
<th>Black male</th>
<th>Black female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Washington DC, USA (Heshmat et al. 1976)</td>
<td>—</td>
<td>4.8</td>
<td>6.1</td>
<td>23.4</td>
<td>20.7</td>
</tr>
<tr>
<td>Mayo Clinic, Minnesota, USA (Percy et al. 1972)</td>
<td>12</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>AFIP, Bethesda, Maryland, USA (Fan et al. 1997)</td>
<td>—</td>
<td>8.0</td>
<td>7.2</td>
<td>20.4</td>
<td>10.7</td>
</tr>
</tbody>
</table>

AFIP, Armed Forces Institute of Pathology.
### Table 3: Reported annual incidence of pituitary adenoma (per 100 000 population) in USA (selected centres), UK and Israel (adapted from Gold 1981)

<table>
<thead>
<tr>
<th>Country (years)</th>
<th>Source</th>
<th>Age (years) or ethnic group</th>
<th>Incidence rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>US: Olmstead County Minnesota (Annegers et al. 1978) 1935–1969</td>
<td>Mayo Clinic Records</td>
<td>15–44</td>
<td>0.5 Male, 0.7 Female</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;45</td>
<td>4.6 Male, 0.7 Female</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15–44</td>
<td>0.5 Male, 7.1 Female</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;45</td>
<td>4.1 Male, 1.1 Female</td>
</tr>
<tr>
<td>US: Rochester, Minnesota (Percy et al. 1972) 1935–1968</td>
<td>Mayo Clinic Records</td>
<td></td>
<td>2.8 Male, 1.1 Female</td>
</tr>
<tr>
<td>US: Washington DC (Heshmat et al. 1976) 1960–1969</td>
<td>Registries of 26 hospitals</td>
<td>Black</td>
<td>1.1 Male, 0.76 Female</td>
</tr>
<tr>
<td></td>
<td></td>
<td>White</td>
<td>0.22 Male, 0.23 Female</td>
</tr>
<tr>
<td>US: Connecticut (Schoenberg et al. 1976) 1935–1964</td>
<td>Connecticut Tumour Registry</td>
<td></td>
<td>0.43 Male, 0.46 Female</td>
</tr>
<tr>
<td>England and Wales (Robinson et al. 1979) 1957</td>
<td>Hospital in-patient enquiry</td>
<td>15–44</td>
<td>2.5 Male, 4.7 Female</td>
</tr>
<tr>
<td></td>
<td></td>
<td>45–64</td>
<td>5.3 Male, 8.2 Female</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15–44</td>
<td>3.1 Male, 3.4 Female</td>
</tr>
<tr>
<td></td>
<td></td>
<td>45–64</td>
<td>5.4 Male, 6.6 Female</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15–44</td>
<td>3.8 Male, 7.3 Female</td>
</tr>
<tr>
<td></td>
<td></td>
<td>45–64</td>
<td>5.6 Male, 8.2 Female</td>
</tr>
<tr>
<td>Israel (Liebowitz et al. 1971a,b) 1961–1965</td>
<td>National Tumour Registry</td>
<td>Males and females</td>
<td>0.6 Asian born</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.4 African born</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.6 European</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.8 Israeli born</td>
</tr>
</tbody>
</table>

Malignant disease, with some indicating an increased risk in males (Alexander et al. 1980, Etxabe et al. 1993) and one showing an increase in females (Bengtsson et al. 1988). Various series indicate an increased risk of premalignant polyps and colon cancer in acromegaly (Klein et al. 1982, Ituarte et al. 1984, Pines et al. 1985, Brunner et al. 1990, Ezzat et al. 1991, Jenkins et al. 1997). The absence of an increased incidence and mortality rate from colonic neoplasia in earlier series may simply reflect the attrition rate of cardiovascular disease in an era before effective treatment of growth hormone excess was available for the majority of patients.

**Cushing’s disease**

Epidemiological information on the prevalence of pituitary corticotroph adenomas is scarce. Ambrosi & Faglia (1991) reported an incidence rate of 0.7 per million per year in Lombardy, Italy and a subsequent study from Vizcaya, Spain documented a rate of 2.4 per million per year (Etxabe & Vazquez 1994). Importantly, the latter study documented a striking and progressive increase in prevalence over the 18-year period of study (1974–1992). This might be explained by a combination of increased awareness and precision of diagnosis, or may be a true increase in incidence. The disease is more common in women (Howlett et al. 1986) and is associated with a striking increase in mortality particularly due to vascular disease (Standardised Mortality Ratio) (Sandler et al. 1987). Persistence of glucose intolerance or hypertension after treatment of Cushing’s disease conveys a poorer prognosis (Etxabe & Vazquez 1994).

**Adrenocortical tumours**

Benign adenomas of the adrenal cortex are a frequent incidental finding and their precise incidence is unknown. Identification of these lesions is increasing as a consequence of...
the widespread availability of computerised tomographic and magnetic resonance imaging for intra-abdominal disease. More rarely, adrenal adenomas may present with hypersecretion of aldosterone (Conn’s syndrome), Cushing’s syndrome or androgen excess. The incidence of Conn’s syndrome has been reported as 0.8 per million population per year (Andersen et al. 1988) but this is likely to be a very conservative estimate since it is probable that many cases go undiagnosed.

Adrenocortical carcinoma is a rare, highly malignant tumour carrying a poor prognosis. In a detailed retrospective study of 99 patients reported to the Norwegian Cancer Registry between 1970 and 1984, Soreide et al. (1992) documented an age-adjusted incidence of 1.5 per million population per year with a peak incidence between the ages of 50 and 70 years (range 2–80 years). This study, carried out in a clearly defined population, provides the clearest epidemiological information for this condition. In 18 cases the diagnosis was made at autopsy. A slight male predominance was evident and the overall prognosis was predictably determined by the size of the lesion at diagnosis with tumours of <5 cm diameter without obvious metastases having the most favourable outcome. Only 35% of tumours were confined to the adrenal and approximately 40% were associated with excess secretion of cortisol and/or androgens. The overall outcome was bleak, with only nine patients surviving over at least 6 years of follow-up. Importantly, the diagnosis was usually made when the tumour was manifest by mass effects, local invasion or metastases and therefore at a stage when complete surgical removal was frequently not possible. The presence of hormonal secretion resulted in diagnosis at an earlier stage in 12 out of 26 patients with functioning tumours (Table 4).

Phaeochromocytoma

Information on the epidemiology of phaeochromocytoma has been obtained from two studies carried out in defined populations with good ascertainment (Hartley & Perry-Keene 1985, Andersen et al. 1988). In a statewide survey in Queensland, Australia, Hartley & Perry-Keene (1985) surveyed the characteristics of 46 cases of phaeochromocytoma presenting between 1970 and 1983. The incidence was 1.55 per million per year. Of the total, 15% were diagnosed at post mortem and this was particularly evident in patients aged >80 years, 11% were extra-adrenal, 11% were multiple, 7% were malignant and 9% occurred in the context of MEN. A similar incidence rate of 1.9 per million per year was obtained by Andersen et al. (1988) in a survey of 47 cases of phaeochromocytoma reported to the Danish National Register of Hospital Patients between 1977 and 1981.

Gastrointestinal endocrine tumours

Clinically manifest neuroendocrine tumours of the gastrointestinal tract are rare. In a detailed study of annual incidence in Northern Ireland, based on a central diagnostic laboratory and register, Watson and colleagues (1989) reported incidence rates per million population per year of 13 for carcinoid, 1.2 for insulinoma, 0.7 for islet cell tumour of
Monson: The epidemiology of endocrine tumours

Table 4 Stage of disease at diagnosis of adrenocortical carcinoma in relation to hormonal hypersecretion (Soreide et al. 1992)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Functioning (n = 26)</th>
<th>Non-functioning (n = 34)</th>
<th>Symptoms not reported (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No metastases</td>
<td>12</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Regional lymph nodes involved</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Local invasion</td>
<td>1</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Distant metastases</td>
<td>12</td>
<td>17</td>
<td>9</td>
</tr>
</tbody>
</table>

indeterminate type, 0.5 for gastrinoma, 0.5 for MEN, 0.12 for vasoactive intestinal polypeptideoma and 0.12 for glucagonoma. Interestingly, the classical carcinoid syndrome was not observed in any patients in the series, the majority of carcinoid tumours presenting either as radiological findings or with gastrointestinal symptoms. In a study based on the Trent Regional Cancer Registry, Woods et al. (1990) reported an overall annual incidence rate for abdominal and thoracic carcinoid tumours combined of 5.7 to 7.1 per million population between the years 1979 and 1986; 36% were in the small bowel, 22% in the lung and 13% in the appendix. Symptoms of carcinoid syndrome were present in >50% of patients with small bowel carcinoids.

In contrast to incidence rates for clinically presenting gastrointestinal tumours, the incidence of carcinoid tumours diagnosed post mortem is relatively high. In one post mortem study conducted in a defined population in southern Sweden, in which the average routine necropsy rate was 63%, carcinoid tumours were identified in 1.22% of patients (Berge & Linell 1976). Only 0.1% were thoracic, the remainder being gastrointestinal and 90% were an incidental post mortem finding. The relative incidence of carcinoid tumour identified incidentally post mortem was sevenfold higher than the clinical presentation rate, reflecting the indolent nature of these lesions, and the classical carcinoid syndrome was reported once only over the 12-year period of study.

**MEN type 1 (MEN1)**

MEN1 is inherited as an autosomal dominant trait and consists of the variable presence of combined tumours of parathyroid, pancreatic islet cells and pituitary. The largest published survey of the condition has been carried out by Trump et al. (1996) who described the clinical features of 184 MEN1 patients from 62 MEN1 families and 36 apparently sporadic MEN1 patients. Parathyroid tumours were found in 95% of patients, pancreatic islet tumours in 41% and pituitary tumours in 30%. Rarer reported manifestations included adrenocortical tumours in 5%, carcinoid tumours in 3.6%, lipoma in 0.9%, phaeochromocytoma in 0.5%, malignant melanoma in 0.5% and testicular teratoma in 0.5%. In 87% of patients, parathyroid disease was the first manifestation of the condition and was evident when sought in the majority of patients presenting with other features of

![Figure 2: Age-related onset of MEN1 in patients diagnosed by screening investigations and patients presenting with symptoms. Reproduced with permission from Trump et al. (1996).](image-url)
the condition. Of the pancreatic lesions, insulinoma was more common in patients presenting below the age of 40 years and gastrinoma occurred more commonly in patients presenting above 40 years. Pituitary lactotroph adenomas were the most common pituitary tumours (63%) but somatotroph tumours were more common in patients presenting at >40 years. Screening individuals at risk resulted in substantially earlier diagnosis (Fig. 2) and demonstrated a penetrance of 43%, 85% and 94% by the ages of 20, 35 and 50 years respectively. The high penetrance of the condition and high prevalence of hyperparathyroidism mean that screening by means of serum calcium measurement and serum prolactin is feasible and worthwhile.

Conclusions
It is evident from this review of a variety of endocrine tumours that epidemiological studies may yield important information for the practising clinician. Thus it may be possible to define the natural history of a tumour and this will be particularly important when there is a variation in malignant severity. In addition, epidemiological studies help to distinguish between changes in rate of diagnosis as opposed to changes in incidence of a particular tumour type. It may also be possible, as in the case of thyroid carcinoma, to confirm or refute the postulated environmental contributions to tumour changes in incidence of a particular tumour type. It may also distinguish between changes in rate of diagnosis as opposed to severity. In addition, epidemiological studies help to distinguish between changes in rate of diagnosis as opposed to changes in incidence of a particular tumour type. It may also be possible, as in the case of thyroid carcinoma, to confirm or refute the postulated environmental contributions to tumour development. Finally, epidemiological study may have an important role to play in predicting regional requirements for specialist treatment of rare tumours. This is particularly relevant in the context of specialist surgical management and the provision of high-quality laboratory and imaging facilities.

References
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childhood show a dose response over a wide dose range. Science 160 159–163.