Symposium—Malignancy in childhood¹

Morphology and incidence of childhood tumours

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Cancer in childhood shows considerable differences from the disease in adults, particularly as regards the low incidence of carcinoma. Epithelial tumours of the alimentary tract are uncommon but may occur in the mouth, pharynx, salivary glands, and colon with only occasional examples at other sites.

The incidence of childhood tumours varies with age, geographical, ethnic, and genetic factors. Much of the material in the present paper has been taken from the Manchester University Children's Tumour Registry (CTR) which is a population-based registry started at the end of 1953 (Marsden and Steward, 1968) and includes about 1 million children under 15 years of age living in the area shown in figure 1.

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Fig 1 Manchester region from which the CTR cases were taken.

Age

Retinoblastoma and histiocytosis X are seen mainly in the first three years of life, and 83% of the patients with neuroblastoma in the CTR were aged 5 years or less.

Astrocytoma is distributed throughout childhood with the exception of pontine tumours which occur in older children, no example of which was noted in the first year of life. Ependymoma was seen in younger children and 78% occurred in the first five years.

Apart from incidence, the behaviour of individual tumours varies with age. Skin involvement is more common in infants than in older children with leukaemia, reticuloses, and neuroblastoma. The better prognosis in cases of neuroblastoma under 1 year of age does not appear to be related to a more benign histological appearance of the tumour, and the ganglioneuroma is more common in older children. Bone involvement in neuroblastoma is more frequent in older children while hepatic spread, and particularly the Pepper syndrome with massive deposits, is encountered in infancy.

Geographical and ethnic factors

There is variation in the incidence of children's tumours in different parts of the world, the best known example being Burkitt's lymphoma. This tumour occurs in the age range 2-25 years with a peak incidence at 6 years and accounts for 50% of the childhood neoplasms in some parts of tropical Africa (Williams, 1975). In the 22 years of the CTR no case of Burkitt's lymphoma has been included. Ten lymphosarcomas showing a prominent 'starry sky' of macrophages have been seen but the clinical picture as regards site and leukaemic transformation was different from that seen in African Burkitt's lymphoma.

LEUKAEMIA

In coloured children, leukaemia is relatively rare, and this applies to the coloured population in the United States as well as to native African children (Young and Miller, 1975). The figure of 4.5% of total tumours is given for leukaemia in Ibadan by Williams (1975) compared with 30% in the CTR. In addition to the variation in incidence there are differences in the types of leukaemia encountered.

Fig 2 *Primary nasopharyngeal carcinoma. Pale epithelioid cells and lymphocytes showing plasmacytoid transformation. (H and E $\times$ 540)*

Fig 3 *Ewing's tumour. Imprint. (PAS $\times$ 520)*

The myeloid and monocytic forms account for 42% of the cases of childhood leukaemia in Japan (Hanawa, 1969-73) whereas the figure of 18% applies to the CTR. Only occasional examples of chloroma and chloroleukaemia have been seen in the CTR although these are relatively common in Turkey (Çavdar *et al*, 1971).

NASOPHARYNGEAL CARCINOMA

This tumour shows variation in different parts of the world and may be mistaken for a lymphoma due to its small primary tumour and clinical presentation as cervical lymphadenopathy. The descriptive term 'lympho-epithelioma' has been applied but the tumours are carcinomas and the lymphocytic cells show considerable plasmacytoid transformation suggesting reaction to the tumour (fig 2).

EWING'S TUMOUR

The rarity of Ewing's tumour in the Negro is confirmed by Jensen and Drake (1970) in material from the Armed Forces Institute of Pathology, Washington, DC, with the following figures:

	<i>Ewing's tumour</i>	<i>Osteosarcoma</i>
White	237	595
Negro	2	82

Imprint preparations are particularly helpful in the diagnosis of Ewing's as in many other childhood tumours. The percentage of Ewing's tumours which are PAS positive is uncertain but positive results with imprints stained with PAS may be seen when the findings are negative with formalin-fixed, paraffin-embedded material (fig 3).

GLIOMA

As striking as the high incidence of lymphomas in African children is the relative rarity of glioma. Williams (1975) gives a figure of 1.3% of tumours compared with 18% in the CTR, gliomas being the largest group of solid tumours in the Manchester experience (Steward, 1974). The same order of frequency, namely astrocytoma, medulloblastoma, and ependymoma, which together account for the great majority of gliomas, is seen in the Manchester and Ibadan series and there does not appear to be a deficiency of any one particular tumour type in the latter.

The astrocytomas which account for the largest group are not, however, homogeneous, and separation of the juvenile type with Rosenthal fibres and spongioblastic cells from the adult type is a valid distinction. In the CTR, the juvenile tumours (81 cases) were commonly seen in the cerebellum and hypothalamic region and, after initial deterioration following diagnosis, the survival curve remained flat

for three years even for tumours in the brain-stem. The adult type astrocytoma (39 cases) showed no survivors at the end of this period.

RENAL TUMOURS

One tumour, the nephroblastoma (Wilms' tumour), has a relatively uniform incidence in different parts of the world (Innis, 1972), varying between 4.9% and 10% of childhood tumours with a mean of 6.9%. Renal carcinoma occurs in childhood and the mesoblastic nephroma may cause difficulties in differential diagnosis. However, an analysis of the renal tumours in the CTR gave the following results:

Wilms' tumour	82
Mesoblastic nephroma	2
Carcinoma	2
Angiosarcoma	1
	—
	87
	—

Renal tumours accounted for 5.5% of the total tumours in the CTR and Wilms' tumours for 5.2%.

The variation in the naked-eye and microscopical appearances of Wilms' tumour may be great with solid and cystic types (figs 4 and 5), and a variety of tissues may be seen including muscle, fat, bone, cartilage, and squamous and columnar epithelium but rarely neural tissue. The histological findings affect the prognosis; cyst formation, tubular differentiation, and possibly glomerular formation are good prognostic features. Wilms' tumour may be associated with hemihypertrophy, there being seven examples in a series of 225 nephroblastomas whereas no such association was seen in a series of 500 cases of neuroblastoma (Fraumeni *et al*, 1967). Hemihypertrophy is associated with hyperplastic visceromegaly of the adrenal (fig 6), liver, and kidney in the Beckwith-Wiedemann syndrome, and a Wilms' tumour has been associated with an adrenocortical tumour in one patient (Riedel, 1952) and a liver tumour in another (Fraumeni *et al*, 1968).

The incidence of Wilms' tumours in Uganda is higher than that of neuroblastoma (Davies, 1973). The reverse is seen in the CTR, and the differences in the incidence of childhood tumours in Manchester and Uganda are shown in table I.

Genetic factors

Genetic factors are apparent, particularly in the retinoblastoma, and other tumours may show an increased familial incidence. Figure 7 shows naevoid basal-cell carcinomata on the scalp of a boy who was treated for medulloblastoma, his father having died from a similar glioma. The skin lesions were related

Fig 4 *Solid Wilms' tumour showing some regimentation of cells. (H and E $\times$ 205)*

Fig 5 *Cystic Wilms' tumour with flattened and tall epithelium. (H and E $\times$ 60)*

Fig 6 Cytomegaly of the fetal adrenal cortex in a case of Beckwith-Wiedemann syndrome. (H and E $\times 205$)

Diagnosis	Manchester (CTR) (1953-68) %	Uganda (Davies, 1973) %
(Total no. of cases)	(1580)	(766)
Leukaemia	29.4	7.5
Non-leukaemic reticuloendothelial	9.7	49.3
Burkitt's	—	36.2
Hodgkin's	2.9	6.3
Other lymphomas	6.8	6.8
Glioma	17.8	1.3
Sympathetic	7.3	2.2
Retinoblastoma	3.2	7.4
Nephroblastoma	5.2	7.3
Epithelial	3.9	2.7
Connective tissue	11.8	14.75

Table I

to the amount of radiation received, being most marked over the scalp and less prominent along the spine.

The majority of childhood tumours show a male preponderance, as shown in table II.

The exception is the presacral teratoma, while Wilms' tumour not only shows an absence of ethnic and geographical variation in incidence but is also distributed equally between the sexes, possibly due to a different mode of origin from other childhood tumours.

Fig 7 Naevoid basal-cell carcinomata on the scalp of a boy with medulloblastoma.

Diagnosis	CTR 1954-1968	
	Male	Female
Leukaemia	252	212
Lymphoma		
(Hodgkin's and non-Hodgkin's)	66	30
Medulloblastoma	56	21
Neuroblastoma	67	35
Connective tissue	108	79
Presacral teratoma	3	11

Table II

Childhood cancer forms a relatively small part of the total picture of human neoplasia but studies in this field may throw light on a number of problems in oncology.

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Teratomas and yolk-sac tumours

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A teratoma may be defined as a tumour composed of multiple tissues foreign to the part of the body in which the tumour arises. Over the years many theories have been put forward to explain the origin of these neoplasms. It was customary at one time to regard them as representing the frustrated development of a conjoined twin. Willis (1967), following Askenazy (1907), concluded that they arise from totipotent cells which become scattered throughout the various parts of the body during embryonic life, normally remaining dormant but capable of further growth and differentiation if suitably stimulated. The theory commended in this paper is that arising largely from the work of Pierce and Abell (1970) and Teilum (1971) and accepted as a working hypothesis by the British Testicular Tumour Panel (Pugh, 1976), namely, that teratomas arise from germ cells, these being the only truly totipotent cells in the body.

The germ cells first appear in the embryo in the wall of the yolk sac whence they migrate (fig 1) around the hinder end of the primitive gut to the genital ridge on the posterior abdominal wall. Here they congregate and are absorbed into the developing gonad which later descends to the pelvis or scrotum. It is suggested that during this migration some germ cells may get left behind on the journey or may stray too far and come to rest at various sites along the dorsal wall of the embryo near the mid-line (fig 2). If these cells do not degenerate but remain viable they may give rise to tumours in precisely these situations, that is, the retroperitoneum, sacral region, mediastinum, and pineal region.

If one accepts Teilum's contention (fig 3) that seminoma, dysgerminoma, teratoma, yolk-sac tumour, and choriocarcinoma are all tumours derived from germ cells then it follows that any of these tumours, alone or in combination, could arise not only in the gonads but also at any of the sites mentioned above where stray germ cells may come to rest. This accords well with observation and experience as the examples given in this paper will help to show.

Teratoma of the testis

The Testicular Tumour Panel classified teratomas of