Pathology of tumours in children¹

The pattern of neoplasia in children

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SYNOPSIS An analysis of the types of tumour in children in the Manchester hospital region indicates that approximately two-thirds arose in the reticuloendothelial or nervous systems. The high mortality is largely due to the nature or site of the tumours, the majority of which cannot be eradicated by purely local measures. The most likely means of causing any significant improvement would be by greater centralization in the treatment of these children.

Before the introduction of antibiotics so many children died from bacterial infections that, by comparison, neoplastic diseases did not appear to be important in paediatric practice. However, during the past two decades the pattern of children's diseases has altered and in 1961 (Table I) tumours were the third commonest cause of death between the ages of 1 and 15 years in England and Wales (Registrar General, 1933-1963).

TABLE I

MAIN CAUSES OF DEATH IN CHILDREN
AGED 1 TO 15 YEARS IN ENGLAND AND WALES
IN 1961 (REGISTRAR GENERAL)

Accidents	1,454
Respiratory diseases	850
Tumours	809
Congenital malformations	621

Although it is easy to show that neoplasms have increased in importance relative to other diseases in children it is more difficult to be certain whether their absolute incidence has changed. In Fig. 1 the incidence of fatal tumours in children during the past 30 years in England and Wales is shown (Registrar General, 1933-63). The incidence of both leukaemic and non-leukaemic tumours appears to have increased, but the increase is almost entirely confined to the period between 1946 and 1953. Since then there has been, if anything, a slight decrease. These figures are based on the Registrar General's annual reports and they depend entirely on the accuracy of the diagnoses on death certificates. The

fact that the apparent increase in incidence occurred during the period when the pathological and paediatric services in this country were being greatly improved could easily be explained on the basis of improved diagnosis. It seems, therefore, that the Registrar General's figures do not provide convincing evidence that neoplasms in childhood have altered in frequency in England and Wales during the past 30 years.

Children with tumours are treated in many different centres and the value of series reported from individual hospitals is limited by selective factors. In an attempt to get a clearer picture of the problems

FIG. 1. Incidence of fatal tumours in children in England and Wales 1932-61 (Registrar General).

¹Papers read at the meeting of the Association of Clinical Pathologists in September 1963.

involved the Manchester Children's Tumour Registry was set up in 1953. Patients were included in the Register only if they were under 15 years old and lived in the Manchester hospital region which contains approximately one million children. Children with any tumour, benign or malignant, were included but those with frank hamartomas were not.

During the nine years from September 1953 to September 1962, 890 children were included in the Register, nearly two each week. It would be difficult to estimate what proportion this represents of the cases actually occurring in the region but a comparison of cases in the Register with the number of children certified as having died of tumours would indicate that over 90% of the fatal cases were included. The types of tumours from which these 890 children suffered is shown in Table II.

TABLE II
CASES INCLUDED IN THE MANCHESTER
CHILDREN'S TUMOUR REGISTER BETWEEN SEPTEMBER
1953 AND SEPTEMBER 1962

Type of Tumour	No. of Cases
<i>Reticuloendothelial</i>	324
Leukaemia	250
Hodgkin's disease	23
Histiocytosis X	23
Lymphosarcoma	22
Rare tumours	6
<i>Nervous system</i>	245
Gliomas	150
Sympathetic	68
Retinoblastomas	27
<i>Connective tissue</i>	107
<i>Nephrogenital ridge</i>	57
Wilms's	46
Others	11
<i>Teratomas</i>	43
<i>Epithelial</i>	33
<i>Ewing's</i>	21
<i>Miscellaneous</i>	32
<i>Malignant unclassified</i>	28
Total	890

It will be seen that the great majority of tumours were either reticuloendothelial or arose from some part of the nervous system or originated in connective tissue. Reticuloendothelial tumours accounted for over one-third of the cases, almost all being of leukaemia, lymphosarcoma, Hodgkin's disease, or belonging to the histiocytosis X group, that is, eosinophilic granuloma, Hand-Schuller-Christian and Letterer-Siwe disease. If a child appeared to have a reticuloendothelial tumour which could not be fitted into one of these categories it was dangerous to make the diagnosis of 'reticulosis' unless the pos-

sibility of a widely metastasizing neuroblastoma had been excluded. Tumours of some part of the nervous system—glial, sympathetic, or retinal—were only slightly less frequent than reticuloendothelial neoplasms. Connective tissue tumours comprised about one-eighth of all cases.

Other types of neoplasm were much less common. Wilms' tumours were less frequent than might be supposed from their prominence in textbooks, making up 5% of the total, only slightly more than teratomas and epithelial tumours. Most of the teratomas were of the benign ovarian variety, those in the presacral region being more likely to be malignant. Epithelial tumours were much less common than in adults; they included a number of cranio-pharyngiomas, salivary adenomas, carcinomas of the colon, one bronchial carcinoma, and one carcinoma of the floor of the mouth. No case of oesophageal or gastric carcinoma was seen. Twenty-one children were considered to have Ewing's tumours. Among the miscellaneous group there was one case of malignant melanoma.

PROGNOSIS

In July 1963 an assessment was made of the condition of the 890 patients included up to September 1962. Six hundred and five children had died or would inevitably succumb due to the nature or state of their disease. Thus there was a mortality of at least 68%.

FIG. 2. Prognosis of the types of tumours in the 890 children included in the Register up to September 1962.

In Fig. 2 the prognosis of the various types of tumours is shown. Although eight of the 250 children with leukaemia were still alive, all of these patients would, of course, succumb. Less than half of the children with solid reticuloendothelial tumours remained well, but as a number of these suffered from Hodgkin's disease the real prognosis in this group is uncertain. About a third of those treated for gliomas may be cured. Also, a quarter of the patients with sympathetic tumours were alive, but a number of these had benign ganglioneuromas and only 17% of the children with neuroblastomas remained well. Twenty-three of the 27 with retinoblastomas remained alive and well and this reflects the very good prognosis of this neoplasm. About half of the children with connective tissue tumours and 30% of those with Wilms' tumours remained well, while the prognosis of epithelial tumours and teratomas, which are generally histologically benign, is much better. The outlook of patients with Ewing's tumour is much worse: only three out of the 21 patients have a chance of being cured.

FACTORS INFLUENCING THE PROGNOSIS It might be supposed that neoplasms arising in young subjects would tend to be highly malignant but this is probably not a significant factor in causing the high mortality. Leukaemia is nearly always acute in children but this does not affect the number who die from this disease. Hodgkin's disease appears to behave in children as it does in adults. The juvenile cerebellar astrocytoma is histologically a benign lesion and the Ewing's tumour grows extremely slowly. At least two neoplasms, the neuroblastoma and the thyroid carcinoma, have a better prognosis in young subjects.

One might expect that there would be some delay in referring these patients to hospital since the initial signs of disease are often vague and a general practitioner sees on an average one child with a tumour every 20 years. However, Campbell, Gaisford, Paterson, and Steward (1961) have shown that these children are admitted to hospital more rapidly than adults with the common cancers and it would be unreasonable to expect that the diagnoses could have been made more expeditiously in the vast proportion of cases.

Thus it is necessary to accept the therapeutic problem of children's tumours as it presents at the present time and to concentrate on improving the management of these patients after diagnosis. There are many aspects of this therapeutic problem but four factors in it are brought out by an analysis of the 605 fatal cases included in the Manchester Children's Tumour Register up to September 1962 (Table III).

TABLE III
FATAL CASES IN MANCHESTER CHILDREN'S
TUMOUR REGISTER BETWEEN SEPTEMBER 1953
AND SEPTEMBER 1962

Reticuloendothelial	291	} 488 = 80 %
Posterior abdominal wall	92	
Brain-stem, cord, or third ventricle	60	
Connective tissue	45	
Others		117 = 20 %

Only a small proportion of reticuloendothelial tumours can be cured by means at present available. Neoplasms arising on the posterior abdominal wall must attain a large size before they can be detected. The surgeon and radiotherapist are limited to what extent they can interfere with lesions involving the central axis of the nervous system. In the case of connective tissue tumours, the radiotherapist can give little help to the surgeon and the chances of cure depend largely on the feasibility of complete excision.

Thus it must be realized that due to the nature and site of tumours in children there is a very definite limit on what can be achieved by local means and it seems from an examination of cases in the Register that, in the Manchester Hospital Region at least, that limit has very nearly been reached.

What more can be done? Is it necessary to wait until the perfect anti-cancer drug is produced before a significant improvement can be achieved? It is reasonable to suppose that the best chance of destroying a tumour lies in attacking it at the earliest possible moment with every means at one's disposal.

In Fig. 3a and b the regression of an orbital sarcoma following a course of Vincristine sulphate is shown. The drug was given 17 months after the growth was first treated by surgery and x rays and by the time chemotherapy was started the tumour could not be controlled by radiotherapy. Although most of the neoplasm was destroyed by the Vincristine, part of it was resistant to the drug. In this case, chemotherapy was given late in the disease and one wonders whether it might have been possible to destroy the whole of the tumour if the child had been treated by surgery, irradiation, and chemotherapy at the beginning of the illness. If a drug can be shown to be even partially successful against a particular tumour, it seems logical to give it at an early stage in combination with more established forms of treatment provided this does not limit the amount of surgery and x-irradiation which the child will tolerate. But there is a danger here. A surgeon who sees one Wilms' tumour every five years or one Ewing's tumour every 20 years is unlikely to be able to evaluate any modification in treatment. The present system whereby children with tumours are operated upon in many different centres has the great disadvantage that these patients

FIG. 3a

FIG. 3b

FIG. 3a. February 1963.
FIG. 3b. July 1963. The effect of Vincristine sulphate on an orbital sarcoma. (Patient under the care of Professor Wilfrid Gaisford. Vincristine sulphate kindly supplied by Dr. Frederick Latham, Medical Director, Eli Lilly and Co. Ltd.)

are often treated by those who do not have the opportunity to gain much experience in this type of case. In an area the size of the Manchester hospital region, in which approximately 70 children develop non-leukaemic tumours each year, it would be an advantage if a small team were set up, consisting of neurosurgeons, paediatric surgeons, a radiotherapist, a chemotherapist, a paediatrician, and a pathologist, and children with tumours were treated by this team from the outset—if possible as soon as a clinical diagnosis had been made. Under such conditions it would be possible to benefit from previous clinical experience and also to assess new forms of treatment.

There is another reason why there should be a reorganization in the management of these patients. Even though malignant disease in children is one of the major causes of death and the problems which it presents differ in many ways from those of adult cancer, there can be no subject to which so few British research workers are devoting their time. This is due to the fact that children with tumours are scattered amongst so many hospitals. Research workers cannot be expected to be attracted to a

problem unless the material on which they can work is reasonably easily available. Thus, not only to improve care of the patient but also to encourage research, greater centralization in the treatment of children's tumours is absolutely necessary. Without this it is difficult to see how any significant progress can be made.

This work was made possible by the ready cooperation of the consultants of the Manchester hospital region. Thanks are also due to the panel of pathologists who have given their services to the Registry, and to Professors A. C. P. Campbell and Wilfrid Gaisford for their help and encouragement, and to Mrs. N. Rowe for secretarial assistance.

During a part of the investigation the author was in receipt of a grant from the British Empire Cancer Campaign.

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