metabolism. Though the patients with rheumatoid arthritis in this study received larger quantities of salicylates and prednisone and for longer periods of time than patients with other disorders, the role of increased utilization of folic acid remains speculative for the present time.

The relationship between reduced serum-folate levels and the anaemia of rheumatoid arthritis is also problematical. In the present study there was no correlation between reduced levels of serum folic-acid activity and either anaemia or macrocytosis. It is therefore unlikely that folic-acid deficiency is important in the mechanism of anaemia in this condition, though a controlled clinical trial of folic-acid therapy is probably indicated. There is certainly no experimental or clinical evidence to suggest that the disturbance in folic-acid metabolism has a more fundamental significance in the pathogenesis of the rheumatoid process itself.

Summary

An investigation of the haematological effects of phenylbutazone in patients with various forms of arthritis has

demonstrated no inhibitory effect of this drug on folic-acid metabolism. Thirty-two per cent. of patients with rheumatoid arthritis had low serum-folate levels, and normal levels were found in other joint and rheumatic conditions.

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Need for a "Team Approach" to Clinical and Research Problems of Children's Tumours*

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The Manchester Children's Tumour Registry was started in 1953 and in the first 10 years 998 cases were included. All the patients were under 15 years old and lived in the Manchester Hospital Region; and there is reason to believe that over 90% coverage was obtained. This means that 100 out of a population of a million children develop tumours each year. The frequency of the various neoplasms is most easily expressed as their annual incidence in the region. This is shown in Table I.

TABLE I.—Average Annual Incidence of Children's Tumours in the Manchester Hospital Region (Population under 15 Years, One Million)

Leukaemias	27
Non-leukaemic reticuloendothelial tumours ..	9
Gliomas	17
Sympathetic tumours	8
Retinoblastomas	3
Connective-tissue tumours	12
Wilms's tumours	5
Teratomas	5
Epithelial tumours	4
Ewing's tumours	2
Miscellaneous	5
Malignant unclassified	3
	100

In December 1964 the condition of the 894 children included in the Registry up to September 1962 was assessed. Altogether 616 of these 894 cases have already proved fatal, giving a mortality rate of 69%. The outcome of the various types of tumours is shown in Table II.

Is the high mortality inevitable? In this paper it is emphasized that children with tumours are being cared for in a hospital system which was not designed for their special needs and which in fact does not allow the optimal use of thera-

peutic methods that are available now or may become available in the future.

TABLE II.—Prognosis of Various Types of Tumours in the 894 Children Included in the Registry up to September 1962. Assessment made in December 1964

	Alive	Fatal	Total
Leukaemias	0	250	250
Non-leukaemic reticuloendothelial tumours ..	31	41	72
Gliomas	50	102	152
Sympathetic tumours	17	51	68
Retinoblastomas	24	4	28
Connective-tissue tumours	57	50	107
Wilms's tumours	13	33	46
Epithelial tumours	23	13	36
Teratomas	32	12	44
Ewing's tumours	3	18	21
Miscellaneous	25	17	42
Malignant unclassified	3	25	28
	278 (31%)	616 (69%)	894

Diagnosis

Are these patients diagnosed as early as possible? Considering that the symptoms are often vague and that a general practitioner sees on an average only one child with a tumour every 20 years, it is perhaps surprising that these children are admitted to hospital more quickly than adults with such common tumours as carcinomas of the breast or cervix (Aitken-Swan and Paterson, 1959; Campbell *et al.*, 1961). An analysis of the pre-admission histories of children included in the Registry over a period of five years rarely revealed unreasonable delay either by the parents or by the general practitioner. Once they are in hospital 80% are diagnosed within one week and 90% within one month. It is unrealistic to expect anything better than this, and little benefit would accrue from any policy of making doctors or the lay public more aware of

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the possibility of tumours arising in children. It is necessary to accept the therapeutic problem as it presents to-day and to concentrate on the management of the child after diagnosis.

Therapeutic Problems

Many factors are involved in this problem, and Table III brings out four difficulties that have to be faced.

TABLE III.—Fatal Cases in the Children's Tumour Register: September 1953 to September 1962

Reticuloendothelial	291	} 491 (80%)
Posterior abdominal wall	90	
Brain-stem, cord, or third ventricle	60	
Connective tissue	50	
Others	125 (20%)	
	616	

Of the 616 fatal cases 80% fell into four categories: (1) reticuloendothelial; (2) they arose on the posterior abdominal wall; (3) they involved the brain stem or cord; (4) they were connective tissue in origin. Only a small proportion of reticuloendothelial tumours can be cured by local measures; neoplasms of the posterior abdominal wall must attain a considerable size before they can be detected; surgical and radiological intervention with lesions in the brain stem, cord, or third ventricle is limited by the danger to vital structures; and with connective-tissue tumours the radiotherapist can often give little help and the patient's chances largely depend on whether the surgeon can make a complete excision. Thus

FIG. 1.—4 February 1963.

FIG. 2.—26 March 1963.

FIGS. 1 and 2.—Effect of vincristine sulphate on recurrence of a Ewing's tumour. (Patient under care of Professor Wilfrid Gaisford. Vincristine sulphate kindly supplied by Dr. Frederick Latham, Eli Lilly & Co. Ltd.)

there is reason to believe that in the vast majority of these children local treatment by itself cannot effect a cure, however skilfully the excision or irradiation is carried out.

What is to be done? Will there be no significant improvement until the perfect anti-cancer drug is produced?

Fig. 1 shows a recurrence of Ewing's tumour in a 6-year-old boy. The primary had presented at the upper end of his right femur four years previously and was first treated with adenopterin and x rays. Two years later a recurrence necessitated disarticulation at the hip, and another course of x rays was required; by the time this photograph was taken there was a huge fungating mass at the site of the disarticulation. The boy was given a course of vincristine, and six weeks later the mass had almost disappeared (Fig. 2). However, the tumour had not been completely destroyed, and the boy eventually died with generalized metastases.

The baffling question which a case like this raises is, "How does a drug destroy only a part of a tumour?" Is it because the neoplasm consists of a number of stem lines of different sensitivity? Or do some cells become resistant during treatment? Or is it due to varying environmental conditions, such as the vascular supply, in different parts of the tumour? The answers to these questions are not yet known, but from a practical point of view it seems that if vincristine can be partially successful in a late case of Ewing's tumour its real place in this disease is as an adjuvant to surgery and irradiation—all three forms of treatment being given as early as possible. This is not a new idea, but the surprising thing is that it is very difficult to find evidence which would satisfy the most lenient statistician that early chemotherapy combined with the well-established forms of local treatment alters the prognosis. Nevertheless, this lack of evidence should not raise doubts about the rightness of using combined treatment. Rather the question must be asked whether in present circumstances it is possible to evaluate properly any variation from traditional treatment methods.

It would be unwise to attempt to destroy a tumour by a combination of treatments unless there were not only the closest co-operation from the beginning between paediatrician, surgeon, radiotherapist, and chemotherapist, but also the opportunity to follow up enough patients to assess the value of new techniques. For the past 10 years there has been a complete coverage of the country with specialist services—every town has its paediatrician and surgeon. But for the optimal treatment of children's tumours more concentrated centres are essential. Consider the 21 children with Ewing's tumours in the Manchester Region during nine years. They were treated by 17 different surgeons. In these circumstances it is difficult to assess any new technique. It would be better in an area containing a million children to have a small central team consisting of surgeons, radiotherapists, paediatricians, and pathologists, all of whom have experience in tumour chemotherapy. Children with non-leukaemic tumours should, if possible, be referred to this team as soon as the clinical diagnosis is made.

A National Centre

It was suggested earlier that children with tumours are treated in a hospital service which was not designed primarily for their special needs, and this applies particularly to the present system of hospital regions. This can be illustrated by two examples. The first is the rather specialized case of bilateral retinoblastoma. Probably about 30 new cases of retinoblastoma occur each year in this country. Ten of these are bilateral and require radium treatment to save the sight of the less-affected eye. Surely the best results would be obtained if all these 10 children were treated in one national centre.

The second example is a more general one. The annual incidence in each hospital region can be calculated in two ways: (a) from the number of cases notified to the Registrar-General under the National Cancer Registration Scheme (Registrar-General, 1965); and (b) by assuming that the numbers occurring in different parts of the country depend only on population density and making an estimate from the Manchester Children's Tumour Registry figures for the other hospital regions according to their population. Table IV shows the incidence of non-leukaemic malignant extracranial tumours calculated by these two methods.

TABLE IV.—*Annual Incidence of Non-leukaemic Extracranial Malignant Tumours in Children and Wilms's Tumours in the Hospital Regions*

Region	Total Population 1961 (Thousands)	Non-leukaemic Extracranial Malignant Tumours in Children		Wilms's Tumours	
		Cancer Registrations 1961	Estimate According to Population and Manchester Children's Tumour Registry Figures	Cancer Registrations 1961	Estimate According to Population and Manchester Children's Tumour Registry Figures
Birmingham ..	4,754	50	45	5	5
*Manchester ..	4,395	—	41	—	5
Sheffield ..	4,378	46	41	6	5
†N.W. Metropolitan	3,288	36	31	4	4
Metropolitan boroughs ..	3,195	28	30	4	4
Leeds ..	3,103	26	29	4	4
Newcastle ..	3,017	29	28	0	3
South-western ..	2,875	29	27	6	3
†N.E. Metropolitan	2,709	34	25	2	3
†Liverpool ..	2,709	28	22	3	3
†S.E. Metropolitan	2,366	27	20	4	2
†S.W. Metropolitan	2,232	26	20	2	3
‡Wales ..	2,109	26	20	4	2
Wessex ..	1,664	19	16	3	2
Oxford ..	1,593	14	15	3	2
East Anglia ..	1,500	20	14	5	2

* In 1961 the Manchester Region was not participating in the National Cancer Registration Scheme.

† Excluding the Metropolitan Boroughs.

‡ For cancer registration purposes Anglesey, Caernarvon, Denbighshire, Flint, and Merioneth are included in Liverpool and not Wales.

It will be realized that non-leukaemic malignant extracranial tumours can be divided into at least 10 main groups, and, as an example, the regional incidence of Wilms's tumours is also shown in Table IV.

Thus, by either method of calculation, no hospital region has more than 50 children with non-leukaemic malignant extracranial tumours or more than six children with Wilms's tumours each year; furthermore, in analysing the results of treatment, patients with each type of tumour must be divided into groups according to age and stage. Thus if these children were all treated in the regions in which they lived it would never be possible to assemble enough cases to assess the value of any particular treatment technique.

The following example shows that the danger of failing to use efficient new methods is a very real one.

By 1953 the antifolics (Farber, 1949), steroids (Pearson and Eitel, 1950), and 6-mercaptopurine (Burchenal *et al.*, 1953) had all been shown to have an established place in the treatment of children with leukaemia. However, an analysis of 87 cases in the Manchester Region between 1953 and 1957 showed that the advent of these drugs had caused practically no improvement in the survival time compared with that of children who had had leukaemia prior to 1950 (Tivey, 1952). This was due to the fact that no paediatrician in the region saw enough children with this disease to be able to gain sufficient experience of the effective use of these drugs. In order to work out a satisfactory treatment technique these patients were to a certain extent centralized during 1957–8. After this the survival time was doubled. As leukaemia is the commonest childhood tumour new methods of treatment can be learned comparatively quickly. Failure to do so merely results in shortening the survival time of patients with a fatal disease, but failure to assess and use new methods of treating

children with non-leukaemic tumours may well have much more serious consequences.

Organization of Paediatric Cancer Research

So far only patient-care has been discussed and the need for a team approach to expedite the implementation of therapeutic advances has been stressed. But the responsibility of the medical profession does not end here. Numerically the children who will develop tumours are much more important than those who suffer from them to-day. In cancer research there is a need for scientists who are trying to discover the essential nature of the neoplastic change, but there must also be a place for those who want to study more specifically the behaviour of particular tumours. Tumours in children differ in so many ways from those in adults that paediatric cancer research must be a separate yet integrated part of general cancer research and there is a need to attract workers to it. As yet in Britain there are only a handful of full-time paediatric oncologists.

Why is the British research effort in this field so inadequate? Significant contributions can be made to some medical problems by individuals working on their own, but children's cancer research requires more organization. If any worthwhile progress is to be made the first essential is to bring three groups of people together. (1) The research workers, many of whom will be experts in non-medical subjects and who need financial stability so that they can give their whole time to the problems involved. (2) The clinicians, who must see enough children's tumours to know their natural history and to be able to put the right problems to the research workers. (3) Enough patients collected together in one centre to provide the research workers with sufficient material on which to work. Both lack of research and inability to evaluate treatment methods are caused by the same factor. Children with tumours are treated in too many scattered hospitals, and until they are concentrated into special centres progress in paediatric cancer research will always remain difficult. Admittedly children are sometimes collected in units in radiotherapy hospitals which are associated with excellent research institutes. These arrangements have failed, however, because in such hospitals the children are outnumbered by adults to such an extent that their particular problems appear correspondingly less important—and, in any case, only about half of the children with tumours require radiotherapy.

It is contended, therefore, that children with tumours are best treated by teams consisting of paediatricians, paediatric surgeons, neurosurgeons, orthopaedic surgeons, radiotherapists, and pathologists. If possible all children with non-leukaemic tumours should be referred to such a team as soon as the clinical diagnosis is made. Although the team would mainly be concerned with treatment, help with diagnostic problems would also be provided. It might be arranged that once a week all the members of the team would combine in a special out-patient session so that they could follow up the patients together. These teams should not be based exclusively on the existing hospital regions, and there should be not more than six or seven of them in the whole country—that is, one centre for a population of one and a half million children. This would provide a service which would be used by clinicians who realized that they could never acquire a large experience in this field.

With such a service, research responsibilities could be discharged in two ways: (1) Collaborative trials of treatment methods should be undertaken. (2) In two or three of the larger centres cancer research institutes should be set up adjoining the hospitals where the children with tumours are collected; and here the workers should be able not only to carry out academic research in their particular specialties but

also to direct their investigations towards problems of the disease as it affects children.

Conclusion

It is realized that centralization makes visiting of children in hospital and out-patient attendance somewhat difficult, and for this reason a case can be made for treating children with leukaemia near their homes. But the initial treatment of those with non-leukaemic tumours rarely lasts more than six weeks, and follow-up need not be very frequent. Everyone realizes that these children are suffering from a desperate disease, and there must be few parents who would not put up with a reasonable amount of inconvenience so long as they believed that their children were getting good treatment; also, this inconvenience could be reduced to a minimum by the provision of accommodation for parents in hospital. It is much easier to collect patients together if they live in a densely populated area. For example, if one centre were set up for the treatment of children with tumours from the Metropolitan regions an enormous contribution could be made.

One thing must be accepted. Children's cancer research is a joint responsibility of paediatricians, radiotherapists, surgeons, and pathologists. If the treatment of children's tumours were reorganized new methods could be efficiently assessed and advantage be taken of the great research potential that is available.

Summary

Each year 100 children in the Manchester Hospital Region develop tumours, and 70% of these patients die. It is likely

that a significant improvement in the survival rate will come only when adjuvant treatment—for example, chemotherapy—is used to supplement surgery and x rays. The fact that children with tumours are treated in so many different hospitals hinders the assessment of new techniques and research. It is suggested that these patients are best treated in centres each serving a population of at least one and a half million children.

This work could not have been carried out without the ready co-operation of the clinicians and pathologists of the Manchester Region. The organization for treating children with tumours has been criticized in this article. It is hoped that nobody will interpret this as a criticism of any individual—such is certainly not my intention.

The Registrar-General kindly furnished data about the incidence of malignant tumours in the various hospital regions during 1961. Thanks are also due to Professor Wilfrid Gaisford, Professor A. C. P. Campbell, and Dr. Eric Easson for their help and encouragement, and to Mrs. N. Rowe for secretarial assistance.

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Review of Regional Limb Perfusion with Melphalan for Malignant Melanoma*

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Malignant melanoma, though often diagnosed at an early stage in its natural history, has a high mortality. Pack *et al.* (1952) reviewed over 1,000 cases and found that only 21.4% were free of disease after five years. The prognosis is much better when the regional lymph nodes are not involved, and Block and Hartwell (1961) reported a 50% five-year survival rate in the absence of involved regional nodes. Ackerman and del Regato (1954) reported a 30% five-year survival in the absence of node involvement, 15% survival with histological involvement, and 5% survival when the nodes are clinically affected.

It is characteristic of many melanomata that multiple cutaneous and subcutaneous metastases may be present in the limb between the primary tumours and the nodes draining the involved region. Removal of the primary lesion combined with block-dissection of the regional nodes consequently leaves an area of tissue between, which may contain viable malignant cells. Excision of the primary, together with the skin and sub-

cutaneous tissues in continuity with the regional lymph nodes, is therefore advised when practicable, as in the upper arm and upper leg. However, lesions below the knee and elbow are often associated with lymphatic spread along the deep vessels, and controversy exists about the place of prophylactic block-dissection of the regional nodes. Stehlin (1963) suggested that the lymphoedema which often follows block-dissection encourages the spread and growth of subcutaneous metastases, and Petersen *et al.* (1962) also found that skin metastases are more frequent when prophylactic block-dissection is carried out at the same time as excision of the primary. It is also argued that removal of the glands removes a filter against metastases in the lymphatic channels.

These opinions are supported by Vogler *et al.* (1958) and Sandeman (1965); on the other hand, prophylactic block-dissection has the theoretical advantage that it provides a greater chance of cure for patients in whom there is microscopical involvement of the nodes, and the procedure is advocated by Charalambidis and Patterson (1962), Meyer and Gumport (1953), and Southwick *et al.* (1962). Peterson *et al.* (1962) found it beneficial only if delayed for two to three weeks after

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