Tumours in Children

Edited by

H. B. Marsden and J. K. Steward

Second, Revised Edition

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With 295 Figures

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Henry Basil Marsden
University of Manchester, Department of Child Health,
Christie Hospital, Withington, Manchester M20 9BX,
Great Britain

James Kenrick Steward †

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Foreword

Cancer in childhood is a rare disease, but for many reasons attracts interest out of proportion to its frequency. There is, of course, the parental anguish associated with a catastrophic illness in a son or daughter — anguish shared in large measure by the physician. This aspect no doubt has spurred on clinicians and investigators in their race to develop more effective means of treatment. The rewards are great. Not only is there the human element, but there is also the fact that survival of the successfully treated child is measured in scores of years rather than the ordinary five to ten year survival rates cited for the adult. Associated with this aspect of paediatric oncology is the responsibility to make those many years as trouble-free as possible. The challenge to the team organizing the care of children with cancer is clear. Cure is to be obtained, but not at the cost of progressively more severe somatic or psychic lesions as the child develops through adolescence to maturity. The cured child of today must not become the chronically ill adult of tomorrow.

The spectrum of malignant diseases in childhood is not so varied as that of older patients. The kinds of tumour seen in children are relatively few in number; therefore, concentrated attention can be focussed on each entity, and specific strategies developed for clinical management. It was in the field of paediatrics that the extraordinarily successful and fruitful concept of the oncology team was first developed in full measure. Effective collaboration between surgeons, chemotherapists, radiation therapists, and pathologists has led to gratifying improvements in survival rates for many of the tumour types. In many instances, they are now at levels that were scarcely believable a decade ago. Efforts to go beyond this point continue. Equally important is the increasing, albeit, subtle change in emphasis from improvement in survival rates as an end in itself to the study of the late complications of successful therapy given in childhood. This has led to a search for refinements in treatment. For example, two of the major American clinical trials were designed to test whether routine postoperative radiation therapy is needed for early cases of Wilms' tumour and rhabdomyosarcoma. Treatments not truly essential for improvement in survival rates are being identified, and eliminated from the routine for each specific entity. This entails a greater understanding of the individual

malignant diseases of childhood. Proper classification according to histology, extent of disease at diagnosis, age factors, and the like must be and are being defined with greater clarity. Better estimates of prognosis will result. This, in turn, will lead to the abandonment of comprehensive and therefore unnecessarily radical routines of treatment, now too commonly in use without regard to stage and histological discriminants. The happy result will be specific treatment directed to the particular problem of each individual child.

Tumours in Children takes these many factors into consideration. General aspects of the problem, such as aetiology, epidemiology, and the delivery of medical care are first presented. Then, individual chapters pursue treatment recommendations, and include pertinent comments regarding clinical and laboratory investigations underway for the elucidation of each type of cancer discussed.

The authors review the problem of tumours in childhood from a unique standpoint. They have at their disposal one of the few all-inclusive population-based compilations dealing with cancer in children, the justly renowned Manchester Registry. They, therefore, are able to provide data with respect to the frequency with which each type of cancer is found in children. They go beyond this, however, and courageously address themselves to the problem of how best to provide care for these unfortunate children. This is done by first defining the clinical needs, and then evaluating the available resources, including the number of specialists. They then draw logical and provocative conclusions and make recommendations with respect to what is required to provide the specialized care which is essential for these patients. It is to be hoped that governmental and medical authorities in Britain and elsewhere in the world will take notice.

It is a tragedy that Dr. Steward succumbed to a prolonged illness before this volume appeared in press. He leaves a rich legacy in the Registry, to which he gave so many years of devoted service, and in the first and second editions of this work. It remains for clinicians and investigators around the world to continue the advances in which he shared. Surely, the task will not be complete until the causes of malignant disease — be they environmental or genetic — are identified and eliminated, and the harsh note of cancer is no longer heard in the joyous rhapsody that is childhood.

New York G. J. D'Angio

Preface

The aim of this book is to describe the clinical, epidemiological, and pathological manifestations of tumours in children and to discuss methods which are available for their treatment. Since the first edition was published in 1968, the need for special centres where children with tumours are treated by teams experienced in paediatric oncology has been widely accepted. Furthermore, collaborative therapeutic trials with improved clinical staging and pathological grading have resulted in many better methods of treatment. Consequently the preparation of a second edition has meant virtually rewriting the book.

Much of the material used is included in the files of the Manchester Children's Tumour Registry and most of the chapters have resulted from collaboration between Manchester contributors. In addition, we have been fortunate in drawing on the experience of six other contributors: Dr. R. W. Miller has discussed epidemiology, Professor J. N. P. Davies has described variations of incidence in different parts of the world, Dr. C. H. G. Price has discussed malignant bone tumours, Dr. J. Lindley Smith and Mr. M. A. Bedford have written the chapter on retinoblastomas and Dr. N. J. Brown has discussed testicular tumours.

Many of the chapters can be divided into two parts. Firstly, the pathological, clinical, and prognostic features of each tumour are described from a study of the cases included in the Registry during the 15 years up to the end of 1968 when, in Manchester, surgery and radiotherapy were nearly always the only methods used in trying to cure children with non-leukaemic tumours and chemotherapy was, almost exclusively, reserved for terminal palliation. Secondly, an attempt has been made to review the more important literature and to describe the treatment methods used at the present time. We are very conscious that any literature review must be incomplete and the therapy used while this book is being written will be, to a certain extent, out-of-date by the time it is published. Undoubtedly the great surge forward of that form of children's cancer research which is concerned with the assessment of new therapeutic agents will continue to produce many more effective chemotherapy schedules, but it is to be hoped that the era when reliance is placed mainly on cytotoxic drugs in treatment will only be transitory. Ultimately, there must be a

better understanding of the factors which determine the development and progress of tumours in children. So far, much of the knowledge in this field has come from epidemiological studies but many questions can only be solved by bringing together the methods and skills of basic laboratory cancer research and the particular problems of paediatric oncology. In this sense children's cancer research has hardly started. An attempt is made in the first and last chapters of this book to analyse the reasons for this and to suggest ways of overcoming the organizational difficulties.

Although therapeutic improvement must be our main goal, its achievement will bring further problems. For many years a large number of children with retinoblastomas have been cured and some of these survivors have passed the disease on to their progeny. There is now evidence that the retinoblastoma is not the only children's tumour which may be inherited and as therapy improves, an increasing number of other familial neoplasms will be seen in paediatric practice. It is appalling that anyone who has survived cancer as a child should discover, quite unexpectedly after marriage, that the disease was familial. There is an urgent need to start looking now for ways of recognising those survivors who are at risk in this way.

To many people paediatric oncology must appear one of the most disheartening branches of medicine. Admittedly the majority of affected children still die, but an increasing number are being cured, and for the rest much can be achieved by palliation. As one learns more about the natural history of these tumours, many fascinating research problems become apparent. Unless we are prepared to make the effort to tackle them, the future will remain as black as the present — and we shall have nobody to blame but ourselves.

Manchester, March 1975

HENRY BASIL MARSDEN
JAMES KENRICK STEWARD

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Contributors to the Second Edition

M. A. Bedford M.B., B.S., F.R.C.S., Consultant Eye Surgeon, St. Bartholomew's Hospital, London; Consultant Surgeon in charge of the Oncology Clinic, Moorfields Eye Hospital, London

N. J. Brown M.B., Ch.B., F.R.C.P., F.R.C.Path., Consultant Pathologist, Southmead Hospital, Bristol

J. N. P. Davies D.Sc., M.D., F.R.C.Path., Professor of Pathology, Albany Medical College, New York

B. H. Dawson M.D., F.R.C.S., Consultant Neurosurgeon, Royal Manchester Children's Hospital and Salford Royal Hospital

D. I. K. Evans M.B., M.R.C.P., D.C.H., Consultant Haematologist, Royal Manchester Children's Hospital, Monsall Hospital and Booth Hall Children's Hospital; Honorary lecturer, Manchester University

C. B. Freeman M.A., B.M., Ch.B., M.R.C.P., Research Fellow, Department of Medical Genetics, Manchester University

E. M. Hammond B.Sc., Principal Biochemist, Royal Manchester Children's Hospital

A. Jolleys M.D., F.R.C.S., Consultant Surgeon, Royal Manchester Children's Hospital; Honorary Lecturer, Manchester University

P. H. M. Jones M.B., M.R.C.P., D.C.H., Senior Lecturer, Department of Child Health, Manchester University; Consultant Paediatrician, Royal Manchester Children's Hospital and the Christie Hospital, Manchester

S. Kumar Ph.D., M.V.Sc., Immunologist, Christie Hospital, Manchester

F. A. Langley M.Sc., M.D., F.R.C.O.G., F.R.C.Path., Professor of Obstetrical and Gynaecological Pathology, Manchester University

H. B. Marsden M.B., Ch.B., F.R.C.Path., D.Path., D.C.H., Consultant Pathologist, Royal Manchester Children's Hospital, Monsall Hospital and Booth Hall Children's Hospital; Honorary Lecturer, Manchester University

R. W. Miller M.D., Dr.P.H., Chief, Epidemiology Branch, National Cancer Institute, National Institutes of Health, Bethesda

M. K. Palmer B.Sc., M.I.S., F.S.S., Chief Medical Statistician, Christie Hospital

D. Pearson M.B., Ch.B., D.M.R.T., F.F.R., Consultant Radiotherapist, Christie Hospital, Manchester

C. H. G. Price M.D., F.R.C.Path., Research Fellow (Pathology) Bristol University; Honorary Secretary, Bristol Bone Tumour Registry

J. Roland M.B., Ch.B., Research Assistant, Manchester Children's Tumour Registry

J. Lindley S. Smith M.D., D.O.M.S., Consultant Pathologist, United Liverpool Hospitals

J. K. Steward † M.D., F.R.C.P., D.C.H., Senior Lecturer in charge of the Children's Tumour Registry, Departments of Child Health and Pathology, Manchester University; Honorary Consultant, the Christie Hospital

M. W. P. Wade M.B., Ch.B., Research Assistant, Manchester Children's Tumour Registry

M. Waghe Ph.D., B.V.Sc. and A.H., Research Fellow, Department of Immunology, Manchester University

P. O. Yates M.D., F.R.C. Path., Professor of Neuropathology, Manchester University

Contents

Chapter 1
Problems of Children's Tumours in Britain

With the steady improvement in the prevention and treatment of bacterial disease during the past 30 years, their importance as a cause of death in children has greatly diminished. During the same period the practical benefits resulting from cancer research have not been so striking and consequently neoplasms have assumed a relatively greater importance in paediatrics. In 1970 they were the second commonest cause of death between the ages of 1 and 15 years in England and Wales (Registrar-General), being exceeded only by accidents (Table 1).

Table 1. Commonest cause of death in children 1 - 15 years in England and Wales during 1970 (Registrar-General 1972)

Accidents	1526
Tumours	772
Respiratory diseases	680
Congenital abnormalities	610

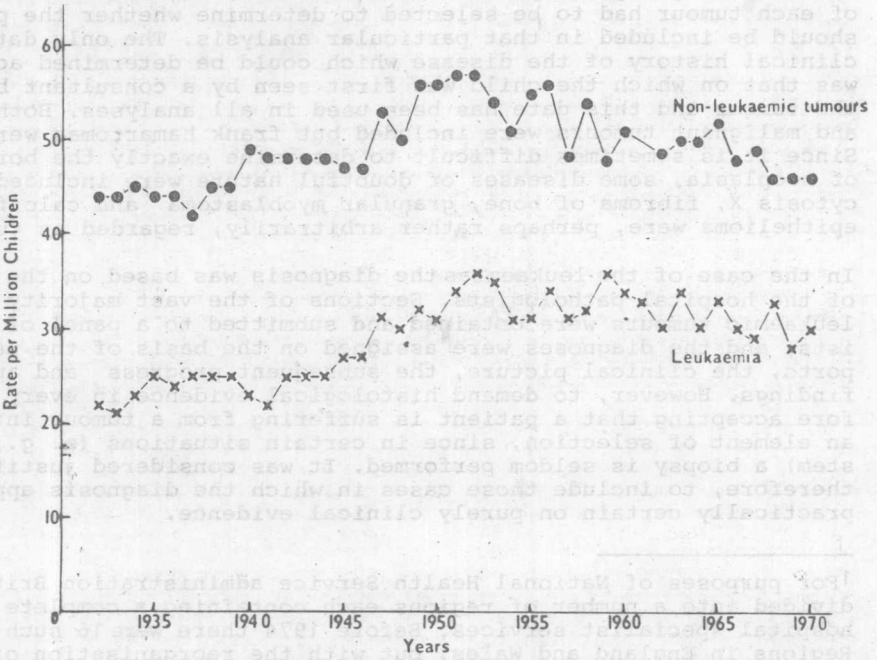

Fig. 1. Incidence of fatal tumours in children under 15 years in England and Wales 1932 - 1970 (Registrar-General)

Although it is easy to show that tumours have increased in importance relative to other children's diseases, it is more difficult to be certain whether there has been any absolute alteration in their frequency. The incidence of fatal tumours in children in England and Wales since 1932 is shown in Figure 1. There has been a rise in both leukaemia and non-leukaemic tumours but this was almost entirely confined to the period 1946 - 1953. It will be realised that these figures depend on the accuracy of the diagnoses given in death certificates. The fact that the apparent increase occurred during the time when the paediatric and pathological services in Britain were being greatly improved could easily be explained on the basis of greater diagnostic accuracy. Thus the Registrar-General's figures do not provide incontrovertible evidence that tumours in children have in fact become more frequent. On the other hand, they indicate that there has been no increase during the past 10 years.

Children with tumours are treated in many different centres and the value of reports from individual hospitals is limited by selective factors. To try to overcome this difficulty, information about these patients has been recorded in the Manchester Children's Tumour Register since January 1954. Patients were included in the Register only if the following conditions were fulfilled:

1. They were first seen by a consultant because of their tumour after 1st January 1954.
2. They lived in the Manchester Hospital Region which consisted of considerable portions of Lancashire, Cheshire, Derbyshire, and Westmorland and contained approximately one million children.[1]
3. They were under 15 years old.

The first condition was made because, if any analysis of cases collected during a given period was to be made, some date in the history of each tumour had to be selected to determine whether the patient should be included in that particular analysis. The only date in the clinical history of the disease which could be determined accurately was that on which the child was first seen by a consultant because of the tumour and this date has been used in all analyses. Both benign and malignant tumours were included but frank hamartomas were not. Since it is sometimes difficult to determine exactly the borderline of neoplasia, some diseases of doubtful nature were included. Histiocytosis X, fibroma of bone, granular myoblastoma and calcifying epithelioma were, perhaps rather arbitrarily, regarded as tumours.

In the case of the leukaemias the diagnosis was based on the reports of the hospital pathologists. Sections of the vast majority of non-leukaemic tumours were obtained and submitted to a panel of pathologists, and the diagnoses were assigned on the basis of the panel's reports, the clinical picture, the subsequent progress and any necropsy findings. However, to demand histological evidence in every case before accepting that a patient is suffering from a tumour introduces an element of selection, since in certain situations (e. g., the brain stem) a biopsy is seldom performed. It was considered justifiable, therefore, to include those cases in which the diagnosis appeared practically certain on purely clinical evidence.

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[1]For purposes of National Health Service administration Britain is divided into a number of regions each containing a complete range of hospital specialist services. Before 1974 there were 16 such Hospital Regions in England and Wales, but with the reorganisation of the National Health Service in April 1974 the boundaries of these regions were altered.

Three tests of the completeness of the survey were carried out:

1. The Medical Officers of Health provided lists of children who had died and on whose death certificates there was mention of neoplasms. According to these returns 284 children who lived in the Manchester Hospital Region died from tumours during the 4 years, 1954 - 1957, i. e., there were 71 fatal cases per year. During the 15 years ending 1968, 1589 cases were included in the Register and an assessment in 1972 showed that 1123 of these patients had died (Table 2), i. e., 74 fatal cases per year.

2. An analysis in 1959 (CAMPBELL et al., 1961), showed that the children in the Register were, on the whole, evenly distributed throughout the Region, indicating that cases were not missed because they were treated in hospitals distant from Manchester.

3. LECK (1974) examined the cases included in the Registry from 1956 to 1968. Ten percent of the Manchester children suffered from conditions (e. g., Histiocytosis X) which are not included in the National Cancer Registration Scheme. After excluding these, he found that the annual incidence of tumours per million children during 1956 - 1968 according to the Manchester Children's Tumour Registry was 91.8, whereas the national incidence for 1968 of cases correctly registered under the National Cancer Registration Scheme was estimated to be 90.5.

These three tests indicate that the great majority of children with potentially fatal tumours were included in the Manchester Children's Tumour Registry, but it must be admitted that many cases of small benign tumours (e. g., fibromas and lipomas) were certainly not included, since the consultants concerned would not have considered them serious enough to notify. Nevertheless, it is probable that the cases in the Register give a fairly true picture of the frequency of children's serious tumours in the Manchester Region (Table 2).

Table 2. Manchester Children's Tumour Registry 1954 - 1968 (assessed 1972)

	Alive	Dead	Total
Leukaemias	11	454	465
Non-leukaemic reticuloendothelial	59	89	148
Gliomas	89	196	285
Sympathetic	25	89	114
Retinoblastomas	44	8	52
Connective tissues	88	103	191
Renal	28	59	87
Gonadal	8	6	14
Teratomas	35	16	51
Epithelial	38	25	63
Ewing's	2	28	30
Rare miscellaneous	31	18	49
Third ventricular (clinical diagnosis only)	5	4	9
Malignant unclassified	3	28	31
	466 (29%)	1123 (71%)	1589

It will be seen that rather over one-third of all the tumours were reticuloendothelial while a slightly lesser number arose in some part of the nervous system (glia, sympathetic, or retina). Connective tissue tumours accounted for one-eighth of all cases. Other neoplasms

were less common. Wilms' tumours made up 5% of the total, being only slightly more frequent than teratomas and epithelial tumours. There were 30 children with Ewing's tumours. In 31 patients it was not possible to make an accurate histogenetic diagnosis and these cases were designated as "malignant unclassified". The miscellaneous group was made up of tumours which were so uncommon that only a few examples of each were included in the Register. The fact that 1589 cases were included in the Register during 15 years indicates that 105 out of a population of a million children develop tumours each year and the frequency of the various neoplasms is most easily expressed as the average annual incidence (Table 3).

Table 3. Manchester Children's Tumour Registry 1954 - 1968 (assessed 1972)

Average annual incidence of children's tumours in the Manchester Hospital Region. (Total population 5,000,000; population <15 years 1,000,000)	
Leukaemia	31
Non-leukaemic reticuloendothelial	10
Gliomas	19
Sympathetic	8
Retinoblastoma	3
Connective tissue	12
Renal	6
Gonadal	1
Teratomas	3
Epithelial	4
Ewing's	2
Miscellaneous	4
Malignant unclassified	2
	105

Multiple Primaries

There have been 6 children in the Registry who developed two or more dissimilar tumours.

CTR.67/54. Boy, who had Hodgkin's disease at the age of 8 years in 1954 and then developed a leiomyosarcoma of the iris in 1959. He remained alive and well in 1972 (DUGMORE, 1972).

CTR.94/54. Boy, who had a fibrosarcoma of the scalp in 1947 at the age of 3 years. In 1954 he developed an osteogenic sarcoma of the right fibula and in 1957 an osteogenic sarcoma of the right ulna appeared. Lung secondaries were seen in 1958 and he died in 1959. He had a twin brother who was said to be identical. This brother had a son who presented with an embryonic sarcoma of the nasopharynx in 1972.

CTR.34/54. Girl, who in 1954 at the age of 10 years, had a teratoma of the ovary removed and a year later a mass in the upper lobe of the right lung was noted. This was irradiated without any effect and a benign teratoma of the lung was removed. In 1968 at the age of 24 she developed a carcinoma of the right breast from which she died.

CTR.79/57. A boy, who had a medulloblastoma treated successfully with irradiation in 1957 at the age of 2 years. During the 1960's he developed multiple basal cell carcinomas (naevoid-basal cell carcinoma syndrome). The child's father had a basal cell carcinoma of the neck in 1960 and died from a glioma in 1962.

CTR.33/60. Boy, who in 1960 developed ataxia, headache and squint at the age of 8 years. Ventriculograms showed a filling defect of the