

Tumours of Infancy and Childhood

BY THE STAFF OF THE
ROYAL CHILDREN'S HOSPITAL
MELBOURNE

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BY THE STABLESH TH

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Foreword

Nowhere in the field of paediatric surgery has individually guided treatment been dispersed more widely than in the care of the paediatric patient with a malignant tumour. In the most advanced paediatric centres this dispersal has been greatest. This collective form of treatment control has been named, in some parts of the world, the 'Combined Therapy Clinic' in other parts of the world, the 'Tumour Board'.

A 'Combined Therapy Clinic' may be comprised of fourteen or more members, each individual having expertise in some area of patient care. When this body of specialists functions well, it represents the most advanced form of care for the cancer patient. A 'Tumour Board' can create or adhere to a treatment protocol, and it can collect, store and report the hard data that are so necessary to further progress in this field.

In many areas on this earth, indeed in many universities and children's hospitals, paediatric physicians and surgeons, medical students and ancillary personnel do not have access to a 'Tumour Board' at all, or at best only occasionally, and it appears to me that this is the void which this new book fills so adequately, and for so many people

Peter Jones and Peter Campbell, in editing not only their own major contributions to the text, but also the thoughts and writings of the many members of the staff of The Royal Children's Hospital, Melbourne, have succeeded, unquestionably, in producing a lucid, well-stylized adequately illustrated edition.

The title has been well chosen, for the book contains not only information about the benign tumour masses so characteristically encountered in the paediatric patient but includes statistically-based data relating to the original working title of the book, 'Malignant Disease in Childhood'.

It is a no-nonsense book, clearly delineating the differential diagnoses and hopefully raising the index of suspicion for the early diagnosis of malignant tumours in infants and children.

This much needed, clinically-oriented text places its reader on a plateau from which he will be better able to grasp and understand the innovations in cancer therapy which must inevitably appear in the not too distant future.

HARVEY E. BEARDMORE MD, CM

Preface

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The certain working title, Matterant Discuss in Childhood, remains the certail through but it became apparent that if inflictential internosis was to be covered advantedly find in proper perspective, a less of much more common non majorant or non-neoplastic swalled a hould be included, and the original case could be the audit to be misleadous.

In the last two decades the medical profession has gradually realized the implications of the changing order of causes of death in children; in many parts of the world malignant disease is now the second commonest cause of death (after accidents) in children more than one year old.

Even when taken as a whole, the three major categories, brain tumours, leukaemias and 'solid tumours', are still uncommon enough to engender a low index of suspicion in clinical practice. Delays in investigation and diagnosis make the outlook worse, and survival rates in some malignancies could be significantly improved by earlier diagnosis and prompt action.

No other kind of illness requires the participation of so many in such a variety of fields, or makes greater demands on their humanity or their time. The family doctor is often the first (and not infrequently the last) to be involved; the paediatrician or paediatric surgeon, the radiologist, clinical biochemist, histopathologist, immunologist, radiotherapist, chemotherapist, nurses, medical social workers and, depending on the type of disease, the haematologist, neurosurgeon, orthopaedic surgeon or other specialist: each has a contribution to make.

Regular and frequent meetings of a multidisciplinary consultative clinic make it possible for the patient to derive maximum benefit from their expertise in planning and carrying out a carefully integrated regime of treatment. Such a team functions most effectively when each member plays his part at the appropriate time, while one doctor retains complete responsibility for the overall care of the child, and for close and continuing contact with the parents.

The publisher's invitation to compile this book was the stimulus to review the experience of the Combined Therapy Clinic established at the Royal Children's Hospital in 1964. Data from earlier cases have also been reviewed, and histological material from more than 1600 children has been re-examined, and reclassified where necessary, in the light of current diagnostic criteria.

We have attempted to bring together and summarize information scattered in journals and textbooks, and continually augmented by developments in many diverse fields. As a compilation, no claim is made that it is encyclopaedic, nor a comprehensive review of the literature in all the related fields, nor simply a report of some 1600 cases. Where our experience is limited or nonexistent, the lacuna has been partially filled by data from recent articles; where our experience differs significantly from the usual, this is noted and

individual patients whose history illustrates particular points are briefly described.

The original working title, 'Malignant' Disease in Childhood', remains the central theme, but it became apparent that if differential diagnosis was to be covered adequately and in proper perspective, a host of much more common non-malignant or non-neoplastic swellings should be included, and the original title could be thought to be misleading.

The fields represented by brain tumours and leukaemias are disciplines in their own right, and these have been broadly surveyed by senior clinicians of great experience.

The 'solid' tumours of infancy and childhood, although collectively the largest category comprising 45% of the total, have, perhaps, been covered less than adequately in some books on cancer in childhood. The greater part of this book is devoted to tumours which may arise anywhere in the broad field of general paediatric surgery, or in what might be considered 'special' areas such as the thorax, the eye, or the nose and throat.

At the risk of displeasing some who might prefer more orthodox taxonomy, solid tumours have been grouped on a clinical regional basis and, where possible, according to modes of presentation rather than a strictly anatomical or pathological plan.

This book has been written for paediatricians and paediatric surgeons, but realizing that specialized paediatric facilities for children with a tumour are not everywhere available, material has been included which may be useful to clinicians, radiologists, pathologists, chemotherapists and radiotherapists, whose practice is chiefly concerned with adults, and who may welcome information concerning the markedly different tumours and needs of children.

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December, 1975

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Chapter 1. Malignant disease in childhood

A. CAUSES, STATISTICS AND SURVIVAL

Although cancer is a rarity in childhood, it kills more children than any other disease, and is second only to accidents (of all kinds) as the commonest cause of death between one and fourteen years of age. Its lethal nature, insidious onset, emotional impact, and the increasing prospects of cure make it one of the most challenging aspects of paediatric practice.

The chief characteristic of a malignant tumour is the ability of its cells to grow and multiply in excess of the normal rate, free of controls normally concerned with maintaining tissue repair and limiting the rate and extent of tissue growth. Although these control mechanisms are not fully understood, their existence is obvious when one considers the body's ability to grow and to stop growing, to heal and to stop healing, and to replace cells dying of old age with new cells in such numbers as to maintain the *status quo*. Uncontrolled multiplication theoretically progresses more and more rapidly as each generation of cells continues to divide, leading to a 'cell doubling time' which would more or less halve with each generation. However, the growth of a tumour is an extremely complex biological phenomenon; increase in size depends on many factors, including the specific type of tumour, its rate of growth and the body's defence mechanisms.

The rate of growth depends upon the size of the fraction of cells (the growth fraction) in the process of active proliferation. The size of this fraction represents the number of cells vulnerable at any point in time, to cytotoxic agents, which exert their maximum anti-tumour effect on cells in the 'cell cycle', and specifically in different phases of the cycle (Fig. 6.1, p. 101). The rate of growth is also influenced by any factor which causes cell death, such as infarction following vascular accidents, and by the phenomenon of apoptosis whereby cells die and are removed.

An enlarging primary growth encroaches upon its environment and eventually produces, in most cases, a clinical picture determined largely by its site, or its size, or in some cases by substances it secretes. Sooner or later, clumps of cells leave the parent body and metastasize, by direct spread or via blood vessels or lymphatic channels, to establish secondary deposits elsewhere.

Metastasis may occur early in the life of a tumour, or late. The time relationship between the development of the primary and the occurrence of

metastasis is a critical factor affecting the results of treatment, and in many tumours tends to be one of its more constant features. In such cases both treatment and prognosis are less haphazard than they might otherwise be.

The histological and behavioural characteristics of individual tumours also tend to be reasonably consistent. Thus a therapeutic attack on a secondary deposit from a slowly growing tumour may be worthwhile, whereas it may not be warranted when the metastasis comes from a rapidly growing primary. Despite a general tendency to be consistent, there are examples of a very broad spectrum of behaviour within one type of tumour. Histologically, cells vary from the grossly anaplastic to the barely abnormal; cellular and biochemical function may be virtually normal or bizarre. The clinical features may also vary from the predictable to the extraordinary; the management is consequently difficult and the prognosis impossible to predict in cases which deviate markedly from the usual pattern.

ETIOLOGY

The etiology of cancer is complicated, usually multifactorial, and may never be fully understood. However, it is possible that some etiological factors are common to all forms of cancer; it is not unreasonable to expect that research may reveal that a particular biological process occurs as an indispensable part of the chain of causation in all forms of cancer, and that this process may be blocked, diverted or otherwise hindered by some means. We would then have a method of control which might effectively rid mankind of the disease. As an example, one possibility concerns the acquisition of a blood supply. Until a tumour reaches a diameter of 1 to 2 mm (varying with the cell type), it exists in an 'avascular' phase, the cells being nourished from tissue fluids. Beyond this critical size, a 'vascular phase' is essential for continuing growth, and solid tumours have been demonstrated to secrete an 'angiogenesis' factor (Folkman, 1975); without it, failure to convey nutrients and remove wastes limits growth to a few millimetres in diameter, a point of control which might be achieved by inhibiting angiogenesis.

Research into changes in the structure and constitution of nucleic acid in cancer cells may uncover a single cause operating at a molecular level which might then be attacked on a relatively narrow front. A new theory of oncogenesis, recently proposed by Comings (1973), links genetic and viral factors, and attributes neoplasia to inactivation of regulatory genes which normally prevent the action of growth-stimulating genes.

The activities of the molecular biologists and anti-smoking propagandists represent the outer edges of a broad approach to the control of cancer, which is based on knowledge of at least some of the facts related to etiology. Information already available indicates that environmental factors are varied and widespread, but potentially identifiable, and in many cases

removable. Research workers took a long time to realize that cancer of the lung was largely dependent on something which was inhaled (Doll, Muir & Waterhouse, 1970), and even longer to start looking for causes of intestinal cancer in things we eat. A great deal of current cancer research has its origins in simple epidemiological observations which showed that certain groups of people with a high incidence of certain types of cancer had specific habits or habitats. A high rate of lung cancer has been correlated with the habit of smoking (U.S. Public Health, No. 1696); a high rate of cancer of the stomach with residence in Japan (Haenszel & Kurihara, 1968); and cancer of the large bowel with residence in developed countries with a 'western' type of diet. Not many of the environmental causes of cancer so far identified (cigarettes excepted) are of a kind which public health measures could reduce appreciably. Nevertheless, some of the facts collected provide glimpses of the biological aspects of carcinogenesis.

Ionizing radiation to appendiction in reducing a profit eldicitories a good and lining

Information linking radiation to cancer has been available for centuries. The mining communities of Schneeburg (Germany) and Joachimstal (Czechoslovakia) were known to suffer from 'mountain sickness' since the sixteenth century, diagnosed as lung cancer at the end of the hineteenth century. In due course the disease was shown to be caused by radioactive materials present in the mines. Later it was noted that the pioneer radiologists were unduly prone to skin cancer and leukaemia, and later again that their patients were also at risk when large doses of x-rays were used therapeutically (International Atomic Energy Agency, 1969; Clemmesen, 1965).

The tragic experience of Hiroshima confirmed these effects, and established that whole body irradiation produced cancers in various tissues, such as thyroid (p. 370), bone and stomach. Observations of the effects of irradiation in utero suggest that the risk of cancer is directly proportional to the radiation dose, and there is probably no safe threshold (Stewart & Barber, 1971). The long term effects of nuclear fallout on the survivors of Hiroshima (Bizzozero, Johnson et al., 1966), have clearly demonstrated a specific leukaemogenic effect, as well as a general carcinogenetic effect. The National Research Council Report reveals a 1.48 fold excess over the expected rate of deaths due to cancers, other than leukaemia, in survivors who received 200 rads or more of ionizing radiation. In more recent years the excess has been even greater (×1.84), suggesting an increasing rate of carcinogenetic effects. An important finding is that there is a dose-response relationship which leads to the logical conclusion that even minimal doses of radiation may be harmful (Stewart & Barber, 1971). The possibility that nucleic acid repair mechanisms may counteract the effect of low doses should not allow the unnecessary use of any dose of radiation with confidence.

Diagnostic radiation during fetal life has recently been implicated as a

hazard causing an increased incidence of leukaemia and some other cancers in childhood.

Bross & Natarajan (1972) have reported variable susceptibility of children to intrauterine irradiation, with a higher incidence of leukaemia in those children who had asthma or hives. Eczema was not mentioned as a possible predisposing cause, but the association with hives and asthma is taken by the authors to reflect altered immunological surveillance which could render the subject more susceptible to mutations resulting in the emergence of cancer cells. However, as pointed out by Miller (1973) the leukaemic child might be predisposed to allergies rather than the allergic state predisposing to leukaemia, and more data are required.

Therapeutic irradiation in relatively large doses has long been used in the treatment of ankylosing spondylitis (Clemmesen, 1965), and this had led to a substantial increase in the risk of aplastic anaemia and myeloid leukaemia among patients so treated. In childhood, radiotherapy for 'thymic hyperplasia' has been responsible for a number of carcinomas of the thyroid gland (p. 370).

Nuclear 'accidents' have occurred and even well-designed colour television sets can deliver undesirably high doses. The use of radio-nucleides in the investigation of patients (p. 75), and in research, is increasing and requires careful control. It should also be remembered that careless use of x-rays is a major risk to the staff involved and is relatively common.

Sunlight

It has long been known that skin cancer occurs most frequently on the exposed parts of the body. Modern social custom has, to a degree, changed the patterns of body exposure and in the future we may see a wider distribution of skin cancers, but the face, arms and hands will presumably continue to be the major sites, as they are in xeroderma pigmentosum in children.

The incidence of all forms of skin cancer, including malignant melanoma, particularly in fair-skinned Europeans, in the clear, hot, dry air on the inland slopes of the Dividing Range in Queensland, is the highest anywhere in the world (Gordon, Silverstone & Smithurst, 1972), and increases progressively with cumulative exposure, and hence with age.

Ultraviolet radiations of wavelength 2900-3300 Å are carcinogenic in experimental animals, and probably in humans as well, for example in xeroderma pigmentosum (p. 839). Various sun-screening agents now freely available minimize the penetration of these rays and may be capable of reducing the incidence of skin cancer.

Environmental Hazards

The number of environmental factors known to be involved in the development of cancer is steadily increasing.