Second primary tumours

The quality of survival after treatment for cancer in childhood is a matter of increasing concern to clinicians. Approximately 50% of children newly diagnosed with cancer will be alive at five years from diagnosis and a large proportion of these will survive to adulthood. The considerable optimism engendered among clinicians by these improvements in survival, however, has been tempered by a growing awareness that children who have been successfully treated for one cancer seem to be at risk of developing a second malignancy.¹⁻³ The problem of second malignancies is most pertinent to those children who have a relatively good prognosis, for example children with retinoblastoma, Wilms' tumour, and Hodgkin's disease. Subsequent, however, to the introduction of effective treatment for children with other types of malignancy such as leukaemia and non-Hodgkin's lymphoma, diseases which until recently were associated with a very poor prognosis, there has been an increase in the number of children with these diagnoses who develop second tumours. Unfortunately no tumour type seems to be immune from the problem of second malignancy.

Patterns of second tumours

Bone sarcomas are the most frequently observed second neoplasms in children. Leukaemias, tumours of the central nervous system, and soft tissue sarcomas are also commonly encountered. A frequently observed association of tumours is that of retinoblastoma with either osteosarcoma or soft tissue sarcoma, accounting for about 20% of the total cases in a population based British study. Recently several children with leukaemia or lymphoma and a tumour of the central nervous system have been described, and it has been suggested that they may represent a new genetic syndrome.⁴ The development of acute non-lymphocytic leukaemia after treatment for Hodgkin's disease in adults is well documented, with an incidence as high as 6% at 10 years in patients receiving a combination of chemotherapy and radiotherapy.⁵ After the introduction of intensive combination chemotherapy into treatment programmes for childhood Hodgkin's disease, the development of acute non-lymphocytic leukaemia now seems to be an increasing problem in children. The latent interval to the development of a second neoplasm is variable and second malignan-

cies have been described at intervals ranging from less than a month to more than 40 years, with a peak incidence between five and 15 years after the diagnosis of the first tumour. 'Simultaneous' tumours, that is those developing within a period of a few months, occur more frequently in children with cancer predisposing conditions.

Incidence of second tumours

Two major epidemiological studies, one, an international study by the Late Effects Study Group initiated in the USA and the other, a national population based study by the Childhood Cancer Research Group in Oxford, have been set up to monitor the incidence of second tumours and to establish the magnitude of the problem. In an analysis of the American data,³ Mike *et al* reported that children with one malignancy have a 10 fold increased risk of developing a second cancer when compared with age matched population controls and that up to 12% will do so within 20 years of the diagnosis of the first tumour. Preliminary results from the Oxford group suggest a somewhat lower incidence with a relative risk of approximately 6% at 10 years from diagnosis of the first tumour.

The greatest risk of developing a second neoplasm is seen in children with the genetic form of retinoblastoma. For these children the risk may be as high as 15%,⁶ although studies by the Oxford group have indicated a smaller risk with an actuarially calculated cumulative risk of approximately 9% at 18 years.

Aetiological factors

Although the occurrence of multiple primary tumours may reflect an inherent predisposition to cancer, it seems likely that the therapies given for the first tumour are important factors in the pathogenesis of the second tumour. Most children with cancer are treated with either radiation or cytotoxic agent and many receive a combination of these two modalities of treatment.

Radiation

The carcinogenic potential of ionising radiation is well recognised, and the risk estimates per unit dose for certain radiation induced cancers such as

leukaemia, thyroid, skin, and breast carcinoma have been summarised in an extensive report prepared by the United Nations Scientific Committee on the Effects of Atomic Radiation.⁷ In this report it was concluded that the minimum latency period for radiation induced leukaemia is two years and for solid tumours about 10 years. Therefore, to determine the true incidence of radiation induced solid tumours, cohorts of patients must be observed for several decades.

There is a paucity of data relating the risk of radiation carcinogenesis to the age at exposure but the evidence that has accumulated indicates that those exposed at younger ages tend to be at greater risk than those exposed later in life, at least for solid tumours. In 1977, Li reporting a series of 36 second tumours in children,⁸ stated that 28 of the total could be attributed to prior radiation. The basis for this assumption was that the second tumour developed within the radiation field. In a recent analysis of the Late Effects Study Group data,⁹ 208 (67%) of 308 second tumours were classified as radiation associated. One observation of particular interest is that a significant proportion of radiation associated second tumours develop on the edge of a radiation field.

Chemotherapy

Animal studies with cyclophosphamide have shown that the main target organs for oncogenesis are the haemopoietic system, bladder, and nervous tissue. The problem of the carcinogenic activity of antineoplastic drugs in humans is complex. For patients treated with a combination of drugs it may be difficult to identify the specific carcinogenic agent, and assessment is frequently complicated by the fact that many patients treated with cytotoxic drugs have also received radiation at some stage during their illness. In a review of the double tumour cases in the published reports, where chemotherapy was considered to have been an aetiological factor in the induction of the second malignancy, Schmahl *et al*¹⁰ found that an alkylating agent was implicated in most cases. Cyclophosphamide, chlorambucil, and melphalan were the drugs most frequently cited. In the recent analysis of the Late Effects Study Group data,⁹ 49 children developing second malignancies had been treated with chemotherapy alone and all but two of these had been treated with at least one alkylating agent.

Genetic factors

Recently, clinicians have become aware that second

tumours occur more frequently in children with known cancer predisposing diseases. A number of genetically determined conditions such as Von Recklinghausen's disease, tuberose sclerosis, and the basal cell naevus syndrome are frequently associated with the development of multiple primary neoplasms.¹¹ In Meadows' report of the Late Effects Study Group data,⁹ 73 (25%) of a total of 292 patients had a known cancer prone condition, a much higher percentage than in the overall population of children who develop cancer.

One of the more interesting childhood tumours to study in this respect is retinoblastoma. This tumour is genetic in approximately 40% of patients, and it seems that the increased risk of second tumours is confined to children with the genetic form of the disease. The most commonly observed second tumour in children with retinoblastoma is osteosarcoma and the risk of developing osteosarcoma seems to be many hundred times greater than for the general population. The retinoblastoma gene has been mapped to band 14 on the long arm of chromosome 13 and of considerable interest, therefore, is a recent report that the genes for osteogenic sarcoma and retinoblastoma may have a common chromosomal origin.¹² During the past decade it has been recognised that some patients with Wilms' tumour carry a genetic predisposition and a specific deletion of band 13 on the short arm of chromosome 11 has been described in a small proportion of patients. In the American series,⁹ 30% of the children with Wilms' tumour who developed a second tumour had characteristics compatible with the genetic form of the disease, for example bilaterality, positive family history, or specific congenital anomalies.

In conclusion, while most cases of second malignancy seem to be associated with radiotherapy, genetic disease, chemotherapy, or combinations of these factors, there is a small proportion of patients with no identifiable risk factor. In these children unrecognised predisposition or indeed chance may play a role. Unfortunately, the problem of second primary tumours is likely to increase as the number of long term survivors of childhood cancer grows. Therefore, it behoves clinicians to identify factors such as genetic susceptibility and specific modalities of therapy, including ionising radiation and alkylating agents, that may contribute to the development of second tumours. Awareness of the risk factors may make it possible to modify treatment programmes and thereby minimise the risk of second neoplasms. It is evident that continuous surveillance of patients treated for cancer during childhood is essential to monitor the problem of second malignancy.

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