The Long-Term Effects of Therapy for Malignant Disease in Childhood

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The improved survival rate for children with malignant disease, which has occurred over the last twenty years, has led to an increased awareness of the late deleterious effects of the therapy necessarily used to achieve these cures. The centralisation of treatment for such patients has also developed. Groups of children with the same malignancy treated in the same way have been followed in a single clinic and symptoms and signs previously considered coincidental have been shown to occur with significant frequency, which has led to investigations of their cause.

Leukaemia accounts for 32 per cent of all childhood malignancy, solid tumours of the reticuloendothelial system for 10 per cent and tumours of the central nervous system for 23 per cent. Some of the less common malignancies such as retinoblastoma (3 per cent) and nephroblastoma (8 per cent) have had high cure rates of many years, and more recently the soft tissue sarcomas have been shown to be responsive to multi-modal therapy. It is, therefore, in these six categories that the majority of long-term survivors are found. Most children who have survived for more than 20 years have been cured by surgery alone, or surgery and radiotherapy, and in many cases the radiotherapy was given with orthovoltage apparatus that produced more damage to skin and superficial tissues than modern mega-voltage machines. On the other hand, more recent survivors have received chemotherapy and most cytotoxic agents produce enhancement of radiation effects that may necessitate reduction in radiation dose if severe and irreparable tissue damage is to be avoided.

The long-term effects can be divided into: surgical, radiation and chemotherapeutic damage, the effects of combined treatments, second primary neoplasms and the effects of chronic disease.

Surgical Damage

In order to achieve complete cure by surgery alone, wide excisions and extensive clearance are necessary, hence children may well have had pelvic exentoration, total cystectomy, orbital exentoration or amputation. The first three of these procedures are now less common, but the increasing success of the management of osteogenic sarcomas and the possible usefulness of amputation in soft tissue sarcomas and Ewing's tumours of the limbs means that the number of young amputees will increase. Early and sympathetic rehabilitation is essential.

Radiation Damage

Radiation effects on the skin include permanent epilation, telangiectasia with thinning and poor healing, and a tendency to malignant change in some instances where there is an underlying predisposition such as the basal cell naevoid syndrome[1]. Loss of normal soft tissues is particularly obvious following head and neck irradiation, and these patients have very thin necks and often require specially tailored shirts and jackets. There may also be permanent damage to the salivary glands, with reduction in production of saliva; this, associated with direct effects on the teeth and secondary tooth buds, means that dental caries develop very readily. Regular preventative dentistry is essential. Dental extractions and other dental procedures should not be carried out under local anaesthesia, as the vasoconstrictors included in the anaesthetic agents may further impair the precarious blood supply and delay or prevent healing.

The bone changes following irradiation are two-fold. When the epiphyseal plates are included in the irradiation field there is an interference with growth and subsequent shortening of the treated limb. Similar changes occur in the vertebrae[2]. The second type of change is caused by damage to the matrix with an increased tendency to fracture, and this damage and the associated flattening of the acetabulum leads to an increased frequency of slipping of the capital femoral epiphysis.

The effects of radiation on the endocrine glands and the gonads of children have recently received considerable attention. Therapeutic doses to the neck lead to damage of the thyroid gland, which seems more common in the young patient[3] and has been shown to be enhanced by prior lymphangiography[3, 4]. Many of these patients show raised levels of thyroid stimulating hormone in the absence of clinical hypothyroidism, suggesting that greater stimulation of the gland is required to maintain normality. This chronic stimulation may be an aetiological factor in the development of malignant change in the thyroid[5].

Investigation of the poor growth rates of children receiving cranial irradiation for intracranial tumours has shown that this is due to deficient growth hormone production. Studies have shown that growth hormone responses are normal prior to irradiation[6]. Other hormones produced by the hypothalamic pituitary axis are not shown to be affected.

Both the ovary and the testis are damaged by radiation, but investigation of these patients before puberty does not always reveal abnormalities. Nevertheless, doses of 2,500-3,000 rads in four weeks to the ovaries is usually associated with ovarian failure, poor breast development and infertility. In males much lower doses to the testes can produce oligo- or azospermia, but Leydig cell function is usually preserved unless higher doses of radiation are delivered to the testes. Replacement therapy in the female should include both oestrogen and progestogen preparations to allow for normal breast development and prevent osteoporosis in later years. This therapy will also protect against possible malignant change. Replacement hormones are probably not indicated in the males unless Leydig cell function is impaired.

Radiation damage to the brain is very difficult to assess and separate from the direct effects of tumour and neurosurgery. Retrospective analysis of long term survivors reveals a high incidence of patients with a low IQ who have been unable to obtain employment on leaving school. There is also evidence of increased frequency of significant psychological problems, including severe depression, suicide attempts, alcoholism, aggressive behaviour and agrophobia. Prospective studies indicate that these children show a normal pattern of IQ scatter before radiation. Whether the long-term effects seen in survivors are due to the direct action of radiation or to insufficient attention being paid to appropriate schooling and rehabilitation in the past remains to be resolved.

Chemotherapy Damage

Very few patients have been treated with cytotoxic chemotherapy alone and those who have have usually received various combinations, so single drug toxicities are difficult to delineate.

Methotrexate causes widespread damage even when used in low dosage, and these changes have been described in detail by Nesbit *et al*[7].

Cyclophosphamide is known to cause cystitis and also to produce gonadal damage. Some authors have suggested that this is reversible[8] but in other cases the damage appears to be permanent[9].

Combination Effects

Actinomycin D has been known to enhance the effects of radiation[10]. Severe skin reactions can occur when the two agents are used concurrently, and radiation damage to vital structures is also potentiated so that the dose of radiation must be reduced to prevent permanent sequelae such as lung fibrosis, liver damage and fibrosis, renal failure and retarded bone growth. Renal failure has an insidious onset and the children can show the first evidence of the problem as late as 18 years after radiation[11].

Methotrexate probably enhances radiation effects on the brain when it is given intrathecally, intravenously or intramuscularly, although the sequence of radiation to methotrexate may be important. Many children who have received intrathecal methotrexate and prophylactic cranial irradiation in the treatment of acute lymphoblastic leukaemia are now showing evidence of specific learning difficulties[12, 13], and computed tomography shows hypodense areas, intracerebral calcification and dilatation of the ventricles[14] in a significant proportion of cases. Many of these patients have a minor clinical abnormality at present but, nevertheless, the changes may indicate preclinical lesions that will progress.

Second Primary Tumours

The incidence of second primary neoplasms is higher in patients who have survived the first tumour than in the population as a whole[15]. Many of these second tumours can be related to previous radiotherapy, but there are also some types of neoplasia where host susceptibility plays a role. The association between retinoblastoma and osteogenic sarcoma within or without the radiation field has been well established[16] and with better survival rates other tumour associations are also becoming apparent[17].

Effects of Chronic Disease

The psychosocial effects of chronic diseases, associated with an unpredictable outcome are immense. The services available in the community for the support of these families are inappropriate and inadequate. There is a tendency for the confidence of parents and children in the hospital team dealing with them to be undermined by the over-pessimistic attitudes of the lay public and sometimes of other members of the profession. The stress is subtly increased by the isolation of the families, and the reluctance of neighbours and friends to provide practical help because of their fear of 'cancer'. The incidence of severe but undiagnosed depression in the parents is significant and often not appreciated because they make an effort to be seen to be coping when attending hospital with their child, for fear of detracting from the attention given to the patient. Some of these difficulties can be alleviated by repeated sympathetic discussions, and by parent groups led by an experienced social worker.

Conclusion

Mortality from childhood malignancy continues to show a gratifying fall, but it is essential for us to be constantly vigilant in following up these patients in order to diagnose and treat the long-term effects of intensive therapy. If these children are to be truly cured, society as a whole must accept that cure is possible. Only then will these patients cease to be at a disadvantage because they have survived cancer.

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