Current topic**Endocrine consequences of treatment of malignant disease**

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Cancer is a major cause of morbidity and mortality in childhood and affects about one in 650 children by the age of 15 years. When survival during the three decades 1954–63, 1964–73, and 1974–83 was compared striking improvements were observed.¹ For all childhood cancers, five year survival increased from 21% in the first decade to 49% in the third decade. During the first and third decades five year survival rates for acute lymphoblastic leukaemia increased from 2% to 47%, for Hodgkin's disease from 44% to 91%, for Wilms' tumour from 31% to 85%, and for medulloblastoma from 25% to 41%.

The improved chances of survival have stimulated great interest in the effects on the endocrine system and the impairment of growth after radiotherapy and cytotoxic chemotherapy for childhood cancer.

Radiation may directly impair hypothalamic, pituitary, thyroid, and gonadal function, or alternatively it may induce the development of hyperparathyroidism, thyroid adenomas, or carcinomas. Cytotoxic chemotherapy may damage the gonad and both irradiation and cytotoxic chemotherapy may interfere with the normal growth of bone. These complications of treatment may lead to various clinical presentations including short stature, failure to undergo normal pubertal development, precocious puberty, hypothyroidism, thyroid tumours, hyperparathyroidism, gynaecomastia, and varying degrees of hypopituitarism.

Brain tumours**GROWTH**

Short stature is a common complication after the treatment of brain tumours in childhood. These brain tumours include gliomas, ependymomas, and medulloblastomas—all lesions that do not directly affect the hypothalamic-pituitary axis. The treatment of these tumours may include operation, cranial or craniospinal irradiation, and chemo-

therapy. The final height achieved by the patients may be adversely influenced by a number of factors including growth hormone deficiency, impaired spinal growth, precocious puberty, chemotherapy, malnutrition, and occult tumour.

The impact of malnutrition and residual tumour on growth has not been studied in these children and there are few studies of cytotoxic chemotherapy and growth retardation.

GROWTH HORMONE DEFICIENCY

Irradiation of the hypothalamic-pituitary axis may produce a range of pituitary hormone deficiencies ranging from isolated growth hormone deficiency to panhypopituitarism.² Of the six anterior pituitary hormones, the first to be affected by radiation damage is always growth hormone, followed by gonadotrophin and adrenocorticotrophic hormone secretion. The extent of hypothalamic-pituitary dysfunction is dose dependent, growth hormone deficiency occurring at lower doses of irradiation, and panhypopituitarism after higher doses. The speed with which individual pituitary hormone deficiencies occur is also dose dependent. The higher the radiation dose, the earlier growth hormone deficiency will develop after treatment. In children irradiated for a brain tumour, a radiation dose to the hypothalamic-pituitary axis of between 2700 and 3500 cGy over three weeks is sufficient to produce subnormal growth hormone responses to standard provocation tests in most patients within two years of radiotherapy. In an occasional patient, however, growth hormone deficiency may not occur for three to six years after irradiation.

Both the hypothalamus and the pituitary may be directly damaged by irradiation. There are a number of studies, however, which indicate that the hypothalamus is more vulnerable to such damage than the pituitary. Therefore the primary pathological defect in such children is likely to be

subnormal endogenous production of growth hormone releasing hormone rather than inadequate growth hormone secretion by pituitary somatotrophs. Thus if an intranasal or depot preparation of a suitable growth hormone releasing hormone analogue becomes available, it may prove ideal for the treatment of children with radiation induced growth hormone deficiency.

SPINAL IRRADIATION AND GROWTH

Children treated for medulloblastomas, ependymomas, and certain other brain tumours receive spinal as well as cranial irradiation. After a dose of spinal irradiation of 2700 to 3500 cGy over 22 to 27 days spinal growth may be appreciably impaired.³ The younger the child at the time of irradiation, the greater the loss in growth potential—from 9 cm if irradiated at 1 year of age, to 5.5 cm at 10 years of age. It is likely that these estimates of eventual loss in height are conservative figures and furthermore, in centres where the spinal irradiation dose is greater than that used in the above study, even more potential growth may be lost. Much of the impairment in spinal growth occurs during puberty, irrespective of the age at irradiation. Consequently, the prognosis for spinal growth in an irradiated child who is still prepubertal should not be too optimistic.

PRECOCIOUS PUBERTY

Early⁴ or precocious⁵ puberty has been reported in some children who have received cranial irradiation. The onset of puberty at a very young age is, however, rarely seen. Puberty starts at appreciably earlier chronological and bone ages in children with radiation induced growth hormone deficiency compared with children who have idiopathic growth hormone deficiency.² The radiation induced shift in the onset of puberty may affect both sexes. The clinical implication for the treatment of children with radiation induced growth hormone deficiency and early puberty is to foreshorten the time available for treatment with growth hormone.

TREATMENT WITH GROWTH HORMONE

Data about final height in children with radiation induced growth hormone deficiency after the treatment of brain tumours indicate that their growth in response to treatment is less impressive than that seen in children with idiopathic growth hormone deficiency. I have already discussed some of the factors such as spinal irradiation and early puberty which prevent a better growth response. None the less, in the group with cranial irradiation alone, treatment with growth hormone prevented further loss in height SD scores,⁶ while in the children who received craniospinal irradiation growth hormone

restricted the amount of further loss in height SD scores.⁷

A further important adverse factor in the height prognosis of these children was the time interval between irradiation and initiation of treatment with growth hormone, which averaged between 5.5 and 6.7 years.^{6,7} There is little doubt that better results would have been achieved if treatment with growth hormone had been started earlier. This leads on to the fundamental question of when should treatment with growth hormone be started?

There has been a tendency to wait until the child exhibits a poor growth rate. Adverse factors, however, such as impaired spinal growth and cytotoxic chemotherapy, may lead to poor growth and—alternatively—early puberty may be associated with an ‘apparently normal’ growth rate that may give rise to false optimism about the child’s height prognosis.

What, if any, tests of growth hormone secretion should be carried out? Lannering and Albertsson-Wiklund suggested that 24 hour spontaneous growth hormone profiles provide the most useful information.⁸ For pragmatic reasons, however, I believe that the 24 hour growth hormone profile is likely to remain a research investigation, as the demands on the laboratory and clinical team make it unacceptable as a routine method of investigation in paediatric endocrinology. Furthermore, discordancy between physiological growth hormone secretion and growth hormone responses to pharmacological stimuli is uncommon after the higher doses of cranial irradiation used in the treatment of brain tumours. The majority of such children will therefore show a subnormal growth hormone response to an insulin tolerance test as well as blunted physiological growth hormone secretion. If tests of growth hormone secretion are carried out, the insulin tolerance test remains a particularly useful investigation in the child who has received cranial irradiation.

The chances of recurrence of a brain tumour are greatest within two years of the primary treatment of the tumour.² There is no evidence that treatment with growth hormone increases the risk of recurrence of a brain tumour in children with radiation induced growth hormone deficiency.⁹ One reasonable approach therefore would be to treat all the children with brain tumours treated by standard radiation schedules (including a dose to the hypothalamic-pituitary axis in excess of 2700 cGy) with growth hormone two years after their primary treatment. At this time they would no longer be receiving cytotoxic chemotherapy, the chance of recurrence of a tumour is low, and it is established that most will be growth hormone deficient by this

time. This policy would not require routine tests of growth hormone secretion. One drawback, however, is that a minority of the children would receive growth hormone at a time when they had not yet developed growth hormone deficiency.

In practice, I submit the children at our own centre to routine annual insulin tolerance test and arginine stimulation test from two years after irradiation until the decision is taken to start them on treatment with growth hormone. Other centres may choose different provocation tests and at least one centre does not carry out any tests at all, but treats all children irradiated for brain tumours with growth hormone two years after irradiation. Whatever policy an individual centre practices, the principle of administering treatment with growth hormone earlier in this group of children is central to the prognosis of their ultimate height.

THYROID DYSFUNCTION

Direct irradiation to the thyroid gland is a consequence of the spinal component of craniospinal irradiation. The two serious complications of radiation induced thyroid damage are hypothyroidism and thyroid tumours.¹⁰

Hyperparathyroidism may develop many years after neck irradiation in adults and, despite the fact that this specific complication has not been described after irradiation in children, it is clearly a possibility.

Radiation induced thyroid tumours may be benign or malignant. Typically there is a long latency period between irradiation and the clinical presentation with a thyroid swelling. In clinical practice any children who have received neck irradiation should have their thyroid glands palpated at least once a year. Routine use of isotope scanning is not recommended.

The degree of thyroid dysfunction after thyroid irradiation may range from frank hypothyroidism with increased concentration of thyroid stimulating hormone and low thyroxine concentration, to subtle disturbance with increased thyroid stimulating hormone, and normal thyroxine concentrations. A thyrotrophin releasing hormone test is unnecessary. An annual assessment of the basal thyroid stimulating hormone and thyroxine concentrations will suffice in children who have been irradiated.

In children with obvious biochemical hypothyroidism, thyroxine replacement is indicated. If the only abnormality in the thyroid function tests is an increase in the concentration of thyroid stimulating hormone, then interpretations in reports about adult patients vary between mild hypothyroidism and 'compensated thyroid dysfunction'. In the context of

children who have been irradiated, this is an academic discussion as treatment with thyroxine is indicated for a number of reasons. Firstly, there is strong circumstantial evidence that an increased concentration of thyroid stimulating hormone may increase the risk of thyroid tumours developing in an irradiated thyroid gland. Secondly, in a child who may be short for a number of reasons it is important to be certain that the child is euthyroid. These arguments weigh strongly in favour of early thyroxine replacement with a dose of thyroxine sufficient to restore the circulating concentration of thyroid stimulating hormone to within the normal range.

There is one report that suggests that the incidence of thyroid dysfunction is significantly greater in children who receive cytotoxic chemotherapy and craniospinal irradiation compared with craniospinal irradiation alone.¹¹ I know of no conclusive evidence, however, that cytotoxic chemotherapy alone may modify thyroid function.

GONADAL DYSFUNCTION

Both the adjuvant cytotoxic chemotherapy and the spinal fields of irradiation may damage the gonads in children treated for brain tumours. Long term follow up in 21 girls and 29 boys who had received a nitrosourea—carmustine (BCNU) or lomustine (CCNU)—with or without procarbazine has shown that there is a high incidence of primary gonadal dysfunction.^{12 13} Both sexes progressed through puberty normally with consistently raised basal concentrations of follicle stimulating hormone and occasionally increased concentrations of luteinising hormone. The girls achieved menarche at an appropriate age. As adults most of the boys had inappropriately small testicular volumes, which are likely to be associated with severe oligospermia or azoospermia, and infertility. In these children, as in those treated for other malignant diseases, gonadal damage in prepubertal life may not be associated with abnormal gonadotrophin concentrations either basally or after gonadotrophin releasing hormone stimulation; these develop during the peripubertal years.

A sex difference in the reversibility of damage was observed. The boys showed no evidence of recovery of germinal epithelial function and no deterioration in Leydig cell function in a follow up extended to 11 years. In contrast, several girls who had previously been shown to have ovarian damage have continued with regular menses and normal follicle stimulating hormone and oestradiol concentrations. Although it was not known whether these cycles were ovulatory, it is likely that these girls had recovered from the ovarian damage. The prospects for fertility among such girls are good in the early child bearing years.

As with other cytotoxic combinations, however, premature menopause remains a possibility.

Many of these children have also received cranio-spinal irradiation, which results in scattered doses to the gonad. In the boys, this results in a small total dose to the testis (estimated at 46–120 cGy after a fractionated course of total spinal dose 3500 cGy in the Manchester centre). This is likely to contribute to testicular damage, as seen in individual boys treated with craniospinal irradiation but no chemotherapy who have developed testicular dysfunction.¹⁴ In girls, however, the dose of irradiation to the ovary may show greater variation. In the Manchester centre a total dose in the range 90–1000 cGy has been estimated to reach the ovary; this may contribute appreciably to ovarian dysfunction, which may be irreversible. The scattered dose to the ovary will differ among treatment centres depending on the method of giving the radiotherapy. Hence the individual contributions of spinal irradiation and cytotoxic chemotherapy to ovarian damage will vary.¹⁵

Acute lymphoblastic leukaemia

GROWTH

Much confusion and controversy have been generated over the growth patterns and growth hormone requirements of the child with acute lymphoblastic leukaemia treated with prophylactic cranial irradiation and combination cytotoxic chemotherapy for several years. Some groups have found no adverse effect on final height, while other groups (including our own) have noted a modest adverse effect on growth,¹⁶ but as final height is unknown in most of the children, the possibility of impaired pubertal growth may mean that final height loss is substantial in a proportion of children. Finally, there is a third group,¹⁷ who have studied children with acute lymphoblastic leukaemia and found a much greater retardation of growth. An analysis of the radiation schedules and chemotherapy protocols used in the different centres has led to some understanding of the explanation for the differences in height loss observed between groups.

There is *in vitro* evidence that cytotoxic chemotherapy may effect growth mechanisms and *in vivo* evidence of an effect on growth.^{16, 17} In the child with acute lymphoblastic leukaemia the duration and nature of the combination cytotoxic chemotherapy will influence the growth prognosis. After treatment with regimens used in the United Kingdom the effects of cytotoxic chemotherapy are likely to be minor, but more intense cytotoxic chemotherapy regimens have had a profound impact on growth.

Children irradiated prophylactically for acute lymphoblastic leukaemia rather than for a brain tumour tend to receive a lower radiation dose to the hypothalamic-pituitary axis. Most of the growth studies have been carried out in children who received a total cranial radiation dose of 2400–2500 cGy. The incidence of growth hormone deficiency in such children will depend on the number of fractions, fraction size, and duration of the radiation schedule.

For a number of reasons the demand for treatment with growth hormone is more difficult to predict after treatment for acute lymphoblastic leukaemia than after a brain tumour. I have already discussed the dissimilar growth patterns in children with acute lymphoblastic leukaemia studied by different groups. In the children with severe growth retardation, even though cytotoxic chemotherapy is a serious adverse factor, radiation induced growth hormone deficiency is common.¹⁷ It is appropriate therefore that most of these children are offered treatment with growth hormone whereas I have only treated a minority of the children with acute lymphoblastic leukaemia in Manchester.¹⁶ The clinical dilemma is how to identify the few who should receive treatment. We have suggested that those children who are below the tenth centile or whose growth rate is persistently poor after completion of cytotoxic chemotherapy, and who have growth hormone deficiency, should receive a therapeutic trial of growth hormone.¹⁶ It should be understood, however, that this is an arbitrary definition of growth hormone requirement.

Moëll *et al* have studied the growth patterns of children with acute lymphoblastic leukaemia during different phases of childhood.¹⁸ Their girls treated for acute lymphoblastic leukaemia lost very little standing height SD score during prepubertal life, as in other studies, but had an attenuated pubertal growth spurt. The contribution of growth hormone deficiency to the disturbed pubertal growth and the effect of treatment with growth hormone to improve it, with or without the addition of a gonadotrophin releasing hormone analogue to delay the rather early pubertal onset in some of the girls, are under investigation.¹⁹

Since 1980 the total dose of cranial irradiation for acute lymphoblastic leukaemia has been reduced to 1800 cGy. There are, however, few detailed studies of growth hormone secretion after this dose and the growth data available cover only the first four to five years after irradiation.²

THYROID DYSFUNCTION

In the past the prophylactic irradiation of the central nervous system for acute lymphoblastic leukaemia

included spinal as well as cranial fields. The possibility of radiation induced thyroid tumours or thyroid dysfunction, therefore, exists as previously discussed. In recent years children with acute lymphoblastic leukaemia have not received spinal irradiation, and so thyroid damage should not occur.

GONADAL DYSFUNCTION

The impact, both transient and permanent, of combination cytotoxic chemotherapy on gonadal function is totally dependent on the nature and dosage of the drugs received by the child.

In boys who received cyclophosphamide or cytosine arabinoside, or both, as part of their combination cytotoxic chemotherapy for acute lymphoblastic leukaemia, the germinal epithelial morphology was profoundly disturbed.²⁰ In others who did not receive alkylating drugs or methylhydrazines, the gonadotrophin and testosterone concentrations, and semen analysis, were normal. Lendon *et al* had indicated that the damage to the testicular germinal epithelium was likely to be reversible and therefore fertility a realistic prospect.²⁰

In girls the outlook is even brighter, in that cytotoxic chemotherapy induced ovarian damage has been reported only rarely. Morphological studies have shown that the main abnormality is inhibition of follicular maturation rather than severe depletion of primordial follicles, an observation more consistent with reversible rather than with permanent functional changes.²¹ Both boys and girls progress through puberty spontaneously indicating that gonadal steroidogenesis is adequate.

Most boys with leukaemic relapse of the testes receive direct testicular irradiation with a total dose between 2000 and 2400 cGy. The effects of the testicular irradiation are dependent on the age and pubertal stage of the boy.²²⁻²⁴ The young prepubertal boy seems most vulnerable to the development of severe and persistent testicular dysfunction. The germinal epithelium is completely ablated in all, and Leydig cell function seriously affected in most. Increased basal concentrations of follicle stimulating hormone and luteinising hormone will often first occur around the ages of 9 to 10 years. The serum testosterone concentration is usually low, which is of course normal for a prepubertal boy, but there is an inadequate or absent testosterone response to an acute bolus of human chorionic gonadotrophin. Most boys require androgen replacement to enable normal pubertal development to occur. Initiation of androgen replacement should be considered around 12 to 13 years of age, and the requirement will be permanent.

Girls are also susceptible to radiation induced gonadal damage during treatment of acute lympho-

blastic leukaemia.²⁵ In 97 girls treated for acute lymphoblastic leukaemia with identical regimens of cytotoxic chemotherapy but different modalities of irradiation, abnormalities of follicle stimulating hormone or luteinising hormone secretion, or both, were more commonly seen after craniospinal combined with abdominal irradiation, than after craniospinal irradiation alone. Not surprisingly, abnormalities of gonadotrophin secretion were rare in the group that received cranial irradiation alone. After craniospinal and abdominal irradiation, arrested puberty and delayed menarche occurred because of the ovarian damage.

Bone marrow transplantation

Marrow transplantation has become a life saving procedure for an increasing number of children and young adults with either non-malignant or malignant haematological disorders, in particular leukaemia. Follow up studies evaluating growth and development have shown that the delayed effects are related to the regimen used for preparation for marrow transplantation. Few endocrine abnormalities have been observed after regimens containing only high doses of cyclophosphamide, but growth disturbance and multiple endocrine abnormalities have been seen after regimens that include total body irradiation.²⁶

Total body irradiation has been given in single dose exposures of 750 to 1000 cGy, and more recently in fractionated exposures of total doses ranging from 1200 to 1575 cGy given over three to seven days. In a series of 116 children who received transplants for malignancy after preparation with cyclophosphamide and total body irradiation, 18% developed compensated thyroid dysfunction, 11% developed hypothyroidism and two children developed thyroid tumours four and eight years later.²⁶

As might be expected, there is a high incidence of gonadal dysfunction after total body irradiation with ablation of the germinal epithelium in the boys and irreversible ovarian failure in most of the girls. The degree of Leydig cell failure is dependent on the pubertal stage of the boy, and whether or not he has received previous testicular irradiation.

Severe growth disturbance is common and may be caused by various aetiological factors including growth hormone deficiency, thyroid dysfunction, radiation induced impairment of bone growth, or graft versus host disease and its treatment. Growth hormone deficiency may occur even if the child has not previously received prophylactic cranial irradiation.²⁷ It is, however, too early to draw conclusions about the beneficial effects of treatment

with growth hormone in growth hormone deficient children after total body irradiation, but there is room for optimism.

Abdominal tumours

In the past it was more common to find that children with malignancies such as Wilms' tumour received whole abdomen irradiation. Gonadal dysfunction was common, with azoospermia and infertility resulting from the scatter dose of irradiation to the testes, and ovarian failure caused by direct radiation damage to the ovaries. In the girls in whom ovarian function was preserved the reproductive outcome was still poor, presumably as a result of the effects of irradiation on the uterus or its blood supply.²⁸

Fortunately irradiation of the whole abdomen for Wilms' tumour is used much less often now. If radiotherapy is given then only the relevant flank is treated. Consequently the incidence of ovarian failure and azoospermia have been dramatically reduced.

Irradiation, both of the whole abdomen and of the flank, will include part of the vertebral column in the radiation field. Some degree of skeletal disproportion and height loss will therefore occur, but this is less than that seen after irradiation of the whole spine for brain tumours.

Lymphomas

Hypothyroidism, compensated thyroid dysfunction, and thyroid tumours may occur in children who have received neck or mediastinal irradiation for lymphoma.

In those boys treated with six or more courses of MVPP (mustine, vinblastine, procarbazine, and prednisolone) or MOPP (mustine, vincristine, procarbazine, and prednisolone) testicular dysfunction is inevitable.²⁹ The damage to the germinal epithelium is severe and seems irreversible, whereas Leydig cell dysfunction—if it occurs—is subtle and does not prevent the boys from progressing through puberty spontaneously.

Gonadal dysfunction is less common in girls than in boys but it may occur and, if so, then sex steroid replacement may be necessary for pubertal development. It is likely but not proved that ovarian function is less vulnerable to cytotoxic chemotherapy induced damage in young girls than in adult women in whom the incidence of ovarian failure is between 15 and 60%.

Conclusions

In this review I have concentrated on the growth and

endocrine results of the treatment of the more common childhood malignancies. Irrespective of the primary malignancy, however, the damage is caused if the radiation field includes an endocrine gland, or if a cytotoxic chemotherapy regimen contains gonadotoxic drugs. For instance, if a child is growing poorly after irradiation for a rhabdomyosarcoma of the orbit, consider the possibility that an appreciable amount of irradiation reached the hypothalamic-pituitary axis and caused growth hormone deficiency. Alternatively, if a boy has received combination cytotoxic chemotherapy for a bone tumour and has pathologically small testes, consider the possibility that the alkylating agent or cisplatin used in the cytotoxic chemotherapy regimen has caused severe damage to the germinal epithelium. The first boy may require treatment with growth hormone, while the second will need some advice and counselling about his potential infertility at the appropriate time.

All children attending an oncology centre should have their standing height, weight, and pubertal stage noted at each visit. The measurements should be recorded on standard Tanner growth charts. If all or part of the child's spine has been irradiated then the sitting height should be measured regularly. There are standard charts available for recording growth in leg length and sitting height.

The oncologist can screen for abnormalities of thyroid function and morphology, and many oncologists will feel competent to titrate the replacement dose of thyroxine against the clinical state, and thyroid stimulating hormone and thyroxine concentrations of the child.

Growth disturbance and the hormonal management of pubertal development are much more complicated and require expertise in endocrinology. The equipment required consists of standing and sitting height stadiometers and an orchidometer. The personnel must include an endocrinologist and an oncologist.

The numbers of patients recovering from cancer in childhood are growing, and for optimum management every major paediatric oncology service should offer a combined clinic at which both the paediatric oncologist and the endocrinologist contribute.

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