Abnormalities of growth and gonadal function in children treated for malignant disease: a review[1]

S M Shalet MD MRCP
Department of Endocrinology
Christie Hospital and Holt Radium Institute, Manchester M20 9BX

In recent years there has been increasing interest in the abnormalities of growth that occur in children treated for brain tumours and acute lymphatic leukaemia. The brain tumours include gliomas, ependymomas and medulloblastomas, all lesions which do not directly involve the hypothalamic-pituitary axis. Short stature is an extremely common complication following the treatment of such tumours in childhood (Bamford *et al.* 1976, Onoyama *et al.* 1975). The treatment of these tumours may include neurosurgery, cranial or craniospinal irradiation and chemotherapy. Poor growth in children receiving whole central nervous system (CNS) irradiation was not too surprising as it has been recognized for a number of years that spinal irradiation may impair spinal growth (Probert *et al.* 1973). However, some children who were small had received only cranial irradiation, suggesting that other adverse factors which affected growth were important. Several years after treatment, many of these children were found to be biochemically growth hormone (GH) deficient, although hypothalamic-pituitary function was normal immediately after surgery and before radiotherapy (Shalet *et al.* 1975). Subsequently it was shown that a strong correlation (Shalet *et al.* 1976*a*) existed between the dose of irradiation received by the hypothalamic-pituitary axis and the GH response to a standard pharmacological stimulus (insulin tolerance test). Furthermore, Czernichow *et al.* (1977) described a high incidence of GH deficiency in patients receiving a significant radiation dose to the hypothalamic-pituitary axis during radiotherapy for extracranial tumours.

It should be emphasized that the biological effect of a given radiation treatment regime will depend on the method of irradiation, total dose, number of fractions, fraction size and duration of irradiation. Therefore a threshold total radiation dose to the hypothalamic-pituitary region, above which GH deficiency ensues and below which no pituitary dysfunction follows, cannot be defined for certain. However, it appeared that a radiation dose in the 2500–3000 cGy range (over 3 weeks) was required to impair the GH response to insulin hypoglycaemia in childhood. To delineate the time course of radiation-induced GH deficiency we prospectively studied 14 children with brain tumours, each of whom received a radiation dose of 2700 cGy (3 weeks) or greater to the hypothalamic-pituitary region (Shalet *et al.* 1978*a*). Initially a normal GH response to an insulin tolerance test (ITT) was present in all, but one year later 7 out of 13 and two years later 5 of the remaining 6 showed a subnormal GH response to an ITT. The fourteenth subject was particularly interesting as he showed a normal GH response to an ITT when first tested three years after irradiation but a very poor GH response six and seven years post-irradiation (Figure 1). Clearly, if the radiation dose is sufficient then the majority of such patients will show biochemical evidence of GH deficiency within two years; however, an occasional patient may not become GH deficient for several years after radiotherapy.

In considering the degree of radiation-induced hypothalamic-pituitary damage after radiotherapy, the radiation dose as well as the time that has elapsed since treatment are critical. Shalet *et al.* (1977) tested pituitary function in 20 adults irradiated between 8 and 32 years earlier for brain tumours during childhood. Most patients received a radiation dose of 4000 cGy or less (3 weeks) to the hypothalamic-pituitary axis. Nine patients had an impaired

[1]Paper read to joint meeting of the Section of Oncology and the Section of Endocrinology, 10 February 1982. Accepted 26 April 1982

0141-0768/82/080641-07/$01.00/0

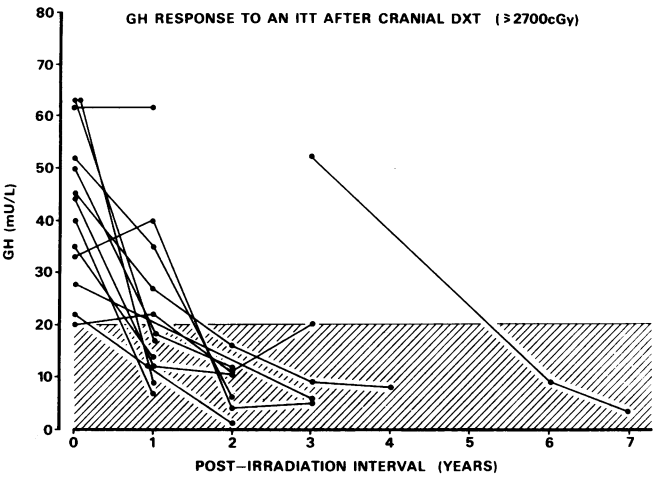

Figure 1. Growth hormone responses to insulin hypoglycaemia in 14 children with brain tumours, each of whom received a radiation dose of 2700 cGy (3 weeks) or greater to the hypothalamic-pituitary region

GH reponse to an ITT, but the rest of pituitary function was essentially intact. However, Samaan *et al.* (1979) have observed a significant incidence of panhypopituitarism in patients with nasopharyngeal cancer treated by external irradiation, which involved a radiation dose to the hypothalamic-pituitary region of between 5000–8500 cGy (5–6 weeks).

Growth and GH secretion in children treated for acute lymphatic leukaemia (ALL)

Following the observation that radiation-induced GH deficiency may complicate the treatment of brain tumours in childhood, various groups studied GH secretion in children who had received prophylactic cranial irradiation several years earlier as part of their therapy for ALL. Initially there was disagreement about whether or not GH secretion was blunted in such children, but it soon became apparent that an important variable in these studies was the effective biological dose of radiation reaching the hypothalamic-pituitary axis. This point was emphasized by Shalet *et al.* (1979), who showed that 14 out of 17 children (group 1) receiving cranial irradiation in a dose of 2500 cGy over $2\frac{1}{2}$ weeks (2900 cGy over 3 weeks) had a subnormal GH response to an ITT, whereas only one of 9 children (group 2) who received a dose of 2400 cGy (4 weeks) (2250 cGy over 3 weeks) showed an impaired response to the same stimulus.

The children in both groups were studied several years after their chemotherapy had been completed and at a time when they were in clinical and haematological remission. Those in group 1 showed a normal growth velocity, serum somatomedin activity, and no evidence of bone age retardation, which suggested that the normal physiological requirements of GH secretion had been met despite the blunted GH responses to certain pharmacological stimuli. Only one child in that study was clinically GH deficient and required treatment with GH therapy. Since then only a further two out of 60 previously irradiated long-term survivors of childhood leukaemia in the Manchester region have required a trial of GH therapy. More recently it has been shown that the dose of cranial irradiation required to prevent CNS leukaemic infiltration can safely be lowered from 2400 cGy to 1800 cGy (Nesbitt *et al.* 1981), a dose which should not impair GH secretion either physiologically or in response to pharmacological stimuli.

Children treated for ALL have been shown to be significantly smaller than their normal contemporaries. The loss in potential height is small but definite and the author (Shalet & Price 1981) attributes this to the effects of cytotoxic drugs and steroids received by these

patients. More recent work (Price *et al.* 1981) clearly shows that certain anti-leukaemic drugs may have a profound effect on somatomedin production and cartilage responsiveness to somatomedin *in vitro*. However, other workers (Griffin & Wadsworth 1980) believe that the small loss in height is due to radiation-induced transient GH deficiency.

Growth impairment in children treated for brain tumours

There are various possible adverse factors, apart from radiation-induced GH deficiency, which may contribute to impaired growth in children treated for brain tumours. Some receive spinal irradiation, others have recurrent tumour and many receive chemotherapy which may affect growth. In addition, many of these children have a poor appetite for the first year or two after their definitive treatment with surgery and irradiation. The importance of these adverse factors was illustrated by a prospective study (Shalet *et al.* 1978*a*) of growth rate and GH secretion in children with brain tumours before radiation and chemotherapy, and then at various time intervals afterwards. Twelve of the 13 children in whom growth could be assessed in the first year after irradiation grew very poorly. Children whose GH secretion appeared to remain adequate over the first year of study grew just as poorly as those in whom biochemical evidence of GH deficiency appeared. This suggested that poor growth within one year of treatment of a brain tumour was unlikely to be due to GH deficiency. However, in the years that follow, the development of clinical GH deficiency may become a significant adverse factor in the poor growth of children similarly treated. In 6 such children with radiation-induced GH deficiency who were treated with GH between three and ten years after cranial irradiation, the mean growth during the pretreatment year was 3.7 cm and during the first year of GH therapy was 7.9 cm (Shalet *et al.* 1981). Similar increases in growth velocity with GH therapy have been described in 5 other children with radiation-induced GH deficiency (Shalet *et al.* 1979, Perry-Keene *et al.* 1976, Richards *et al.* 1976).

Unfortunately, there are no long-term studies of the effects of GH therapy in a large number of children with radiation-induced GH deficiency. In the Manchester Growth Clinic over the last six years we have treated 18 such children with GH therapy for varying lengths of time (unpublished). Our data suggest that there has been a significant growth response to GH therapy in children who received cranial irradiation alone, but the growth response has been varied in those receiving craniospinal irradiation. The majority of the former children had received a radiation dose of 3500 cGy or greater (over three weeks) to the hypothalamic-pituitary axis. Nearly all the children who received craniospinal irradiation had been treated for a medulloblastoma. The radiation dose was usually lower in these children and, in several cases, it was in the region of 3000 cGy (over three weeks). The explanation for the varied growth reponses to GH therapy in this group may be that not all these children were clinically GH deficient, despite subnormal GH responses to pharmacological stimuli and a poor growth rate. Studies of the variation in GH secretion under different physiological circumstances, as well as assessment of somatomedin C status, should provide further information in this difficult area of clinical practice.

Gonadal function

The major cause of gonadal dysfunction in children treated for malignant disease is direct damage to the gonad by either radiation or chemotherapy. However, it should be remembered that irradiation to the hypothalamic-pituitary area may lead to gonadotrophin deficiency or hyperprolactinaemia, both of which may prevent normal pubertal development and impair subsequent reproductive function (Brauner *et al.* 1980).

Prepubertal and pubertal males

Chemotherapy: There are a number of reports (Lentz *et al.* 1977, Penso *et al.* 1974, Gueary *et al.* 1978) of testicular damage following single-agent cytotoxic drug therapy in childhood. The alkylating agents, in particular, may cause gonadal damage and the two drugs which have been incriminated most often are cyclophosphamide and chlorambucil. More recently, the

effects of combination chemotherapy on the gonadal function of children treated for ALL or Hodgkin's disease have been studied.

Lendon *et al.* (1978) examined testicular histology in 44 boys treated with combination chemotherapy for ALL. Nearly all of their patients had received their chemotherapy when prepubertal and the mean tubular fertility index (percentage of seminiferous tubules containing identifiable spermatogonia) was 50% of that in age-matched controls. The two drugs predominantly responsible for the testicular damage were cyclophosphamide and cytosine arabinoside (>1 g/m^2). However, Lendon *et al.* (1978) did find a significant improvement in testicular tubular morphology with increasing time after completion of chemotherapy. Investigation of testicular function in these 44 boys showed no evidence of Leydig cell dysfunction (Shalet *et al.* 1980), thereby implying that these boys would undergo normal pubertal development.

Severe testicular damage is much more common following the use of combination chemotherapy for Hodgkin's disease rather than ALL. Presumably this is a reflection of the capacity of the individual drugs used in these combinations to inflict tubular damage. Sherins *et al.* (1978) found germinal aplasia and very high serum follicle-stimulating hormone (FSH) levels in boys who had received MOPP (mustine, vincristine, procarbazine and prednisolone) therapy for Hodgkin's disease when pubertal. They also studied 6 boys who received the same treatment but who were prepubertal when they received their chemotherapy and at the time of study, and found that serum FSH, luteinizing hormone (LH) and testosterone concentrations were appropriate for their age. Whitehead *et al.* (1982) also found evidence of severe damage to the germinal epithelium in patients who received MOPP therapy during childhood. Six patients provided semen for analysis between 2.4 and 8 (mean 5.3) years after completion of chemotherapy and were noted to be azoospermic. The 4 boys studied whilst still prepubertal showed normal basal gonadotrophin levels and gonadotrophin responses to luteinizing hormone-releasing hormone (LHRH). However, one subject treated when prepubertal showed normal serum gonadotrophin levels in prepubertal life but an evolving pattern of abnormally-elevated gonadotrophin levels in early puberty, despite the increasing length of time since the completion of chemotherapy. It has become clear that abnormalities of gonadotrophin secretion rarely allow the detection of testicular damage in prepubertal life. Therefore it is highly probable that the prepubertal boys in the two studies (Sherins *et al.* 1978, Whitehead *et al.* 1982), despite normal gonadotrophin levels following MOPP therapy, have sustained severe testicular damage.

Sherins *et al.* (1978) noted Leydig cell dysfunction, clinically manifested by gynaecomastia, in their pubertal boys who received MOPP. However, Whitehead *et al.* (1982) could not substantiate these findings. All their subjects who were in late puberty or young adulthood had basal testosterone levels within the normal adult range.

Radiation: It is known that the normal adult testis is extremely sensitive to the effects of external radiation (Rowley *et al.* 1974). The threshold dose of irradiation required to damage the germinal epithelium in childhood is unknown, although a little more information has become available in the last few years. Shalet *et al.* (1978*b*) studied testicular function in 10 men, aged between 17 and 36 years, who had received irradiation for a nephroblastoma during childhood. The dose of scattered irradiation to the testes ranged from 268 to 983 cGy (20 fractions over four weeks). Eight subjects had either oligo- or azoospermia (0 to 5.6 million/ml), and 7 of these had an elevated FSH level. One patient showed evidence of Leydig cell dysfunction, with a raised serum LH level and a low plasma testosterone concentration; but in retrospect it was apparent that he was the only one studied who showed evidence of renal impairment. Therefore the abnormal LH and testosterone concentrations may have been due to chronic renal failure rather than radiation-induced damage.

Subsequently we have studied testicular function in 6 boys who required testicular irradiation (2400 cGy over 21 days) for leukaemic infiltration of the testes (ALL relapse). Before irradiation the testosterone response to human chorionic gonadotrophin (HCG) stimulation was normal in those studied. After irradiation there was no testosterone response

to HCG stimulation. In addition to the testicular irradiation, these boys also received a further year's combination chemotherapy. Our earlier results (Shalet *et al.* 1980) had shown that such chemotherapy when used alone did not affect Leydig cell function; however, we cannot exclude the possibility that chemotherapy contributed to the Leydig cell damage by acting synergistically with testicular irradiation. Two of the boys required androgen replacement therapy to enable them to undergo normal pubertal development. The remainder have either died or are too young to require hormone replacement therapy.

These results suggest that a fractionated dose of irradiation to the testes of between 268 and 983 cGy (20 fractions over four weeks) does not impair Leydig cell function, whilst a much higher dose of 2400 cGy (21 days) causes Leydig cell failure.

Prepubertal and pubertal females

Chemotherapy: There have been relatively few studies on the effects of cytotoxic drugs on ovarian function in the prepubertal and pubertal female. The reports of Pennisi *et al.* (1975), Etteldorf *et al.* (1976) and Lentz *et al.* (1977) found no evidence of menstrual dysfunction in women who had received cyclophosphamide for renal disease during childhood. Less encouraging was the morphological study of Miller *et al.* (1971) in which the autopsy in a 13-year-old girl, who had received cyclophosphamide for 29 months, revealed ovaries totally lacking in follicles.

Siris *et al.* (1976) examined the effects of childhood leukaemia and combination chemotherapy on pubertal development and reproductive function in 35 girls and women. Twenty-eight patients underwent normal pubertal maturation in a median time of 74 months after diagnosis of leukaemia and 49 months of chemotherapy. Only 3 patients showed evidence of primary ovarian dysfunction. None of these three had received cyclophosphamide and, interestingly, only 9 out of the 35 females had received this drug. The main drugs used were vincristine, methotrexate, 6-mercaptopurine and steroids, although one of the 3 girls with primary ovarian dysfunction had also received busulphan. We have found definite biochemical evidence of ovarian failure (raised serum FSH level) in 4 out of 12 prepubertal girls who had received combination chemotherapy for ALL. All 4 had received cyclophosphamide. Three of the 4 have undergone normal pubertal development with the previously elevated serum FSH level dropping into the normal range, while the fourth girl remains prepubertal. This clearly suggests that ovarian damage has occurred in some of these patients but that recovery of ovarian function is not uncommon. A further difficulty in establishing the incidence of such damage was indicated by the studies of Conte *et al.* (1980). They found normal basal gonadotrophin levels and gonadotrophin responses to LHRH in 50% of girls with gonadal dysgenesis between six and nine years of age. Therefore in both sexes reliance on abnormal gonadotrophin levels for the detection of primary gonadal damage during prepubertal life will seriously underestimate the true incidence of such damage. The morphological evidence that such gonadal damage occurs is, however, just as convincing in the female (Himelstein-Braw *et al.* 1978) as in the male. The impairment in follicular maturation in such patients may prove reversible with time, but if a serious depletion of primordial follicles has occurred following exposure to cytotoxic drugs in childhood then a premature menopause may be a long-term sequel.

Radiation: When girls and adult women are irradiated, the response of the ovary involves a fixed population of cells which, once destroyed, cannot be replaced. Effects on fertility are most readily explained on the basis of reduction in this fixed pool of oocytes. Not unexpectedly, the dose of irradiation required to destroy all the oocytes in the ovary is larger in younger rather than older women. Rubin & Casarett (1968) concluded that acute ovarian doses of about 600 cGy are 100% effective in inducing permanent sterility in women of all ages. However, the threshold dose of irradiation required to induce such damage in the prepubertal female may be larger in view of the greater number of oocytes in this age group.

Shalet *et al* (1976*b*) studied ovarian function in 18 females treated for abdominal tumours in childhood. Treatment consisted of abdominal irradiation in each case (2000–3000 cGy over

25–44 days) and chemotherapy in 7 cases. Only one girl received a cytotoxic drug (cyclophosphamide) known to damage the ovary. All 18 showed very high FSH levels and low oestradiol levels typical of primary ovarian failure. Stillman *et al.* (1981) studied a much larger number of long-term survivors of childhood cancer. They found evidence of ovarian failure in 17 out of 25 patients who received an ovarian radiation dose of between 1200 and 5000 cGy, and in 5 out of 35 who received between 90 and 1000 cGy. The abdominal radiotherapy consisted of multiple fractions, but the number of fractions and duration of therapy were not stated. Himelstein-Braw *et al.* (1977) have studied the morphological changes in the irradiated ovaries from girls who died of malignant disease. The dose of irradiation received by these patients was similar to that received by the patients studied by Shalet *et al.* (1976*b*). Follicle growth was inhibited in all cases and the number of oocytes was markedly reduced in most.

The number of reports concerned with the effects of chemotherapy and irradiation in childhood on subsequent gonadal function remains small. It is still not known if the vulnerability of the gonad to radiation- or chemotherapy-induced damage varies with pubertal status or is age-dependent. Beck *et al.* (1982) have shown that induction chemotherapy (prednisone, daunomycin, vincristine and L-asparaginase) for ALL has profound but transient effects on gonadal function in children. Newer cytotoxic drugs or combinations of such drugs may damage the gonad, and only continued surveillance of gonadal function in these patients will allow such damage to be detected. More recently, primary ovarian failure has been described in girls who received spinal irradiation for medulloblastoma (Brauner *et al.* 1980). It is not yet clear if the ovarian damage is due to the irradiation or adjuvant chemotherapy or both. There is a need for accurate and unequivocal answers to these questions so that when paediatric oncologists and radiotherapists plan new protocols for future treatments the true endocrine morbidity from existing methods of therapy can be taken into account.

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