Concluding Remarks

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Over the past 2 days growth and endocrine data following cancer treatment in childhood have been presented. The symposium has provided a unique opportunity to meet with oncologists. In the concluding remarks I would like to take the endocrinologist's point of view because the clinical situations in which we have been working have provided us with quite a number of models of damage to endocrine systems.

If we consider growth hormone (GH) secretion, I would say that from a clinical point of view it is important to remember that growth is impaired and the impairment is related to the dose of cranial irradiation and to the age of the patients at treatment. Both growth and GH secretion may be greatly disturbed in puberty. We do not have enough data on final height in treated acute lymphoblastic leukaemic (ALL) children. The data that exist are controversial and this is because we are not all dealing with the same chemotherapy protocols and radiotherapy schedules. The complexity of the subject is demonstrated clearly in the prophylactic low-range cranial irradiation (2,400 cGy) applied in ALL treatment, where it is clear that during prepubertal life most of these children have some impairment of GH secretion but growth is relatively normal in many cases once chemotherapy is completed. The indications for GH therapy in the ALL child remain ill-defined. Biochemical evidence of GH deficiency is not a sufficient indication on its own to institute GH therapy. We need further information about the growth response to GH therapy in children with radiation-induced GH deficiency and how the growth response is modified by early puberty. The mechanism of the early sexual maturation and advanced bone age requires elucidation but cranial irradiation has a crucial aetiological role.

I believe that we should offer GH therapy only to carefully selected patients with radiation-induced GH deficiency. It is important to take into consideration the height of the patient before diagnosis. Obviously patients with genetic short stature will end up even shorter following therapy. We should consider treating patients who do not recover normal growth rate 2 years after irradiation, patients who experience early puberty and patients who have lost more than 1 SD in height. However, the problems associated with GH therapy will need to be balanced against the psychological impact of a small reduction in final height. Whichever criteria we consider important the prescribing of GH will require a separate decision for each individual child.

Apart from the clinical endocrine problems created by the cancer treatment, the iatrogenic damage to the hypothalamic-pituitary axis has prompted studies of the relationship between physiological GH secretion and GH responses to pharmacological tests. Although a 24-hour GH profile is time-consuming and cannot be used to investigate all patients it remains an interesting tool for clinical research. Therefore, there is still a place for pharmacological tests of GH secretion even though a discordance between the results of the pharmacological tests and the 24-hour GH profile may be seen in some patients.

A number of problems remain to be resolved. The long-term outcome of radiation-induced GH deficiency and the impact of the GH deficiency in adult life are unknown. The possibility of radiation damage to the pituitary as well as the hypothalamus must be explored if we are to consider treating these patients with GH-releasing factor preparations. Normal growth in the presence of very low circulating GH levels requires evaluation.

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tion. The circulating insulin-like growth factor-1 (IGF-1), IGF-2 and IGF-binding protein concentrations in these patients may shed some light on this phenomenon. By studying these unusual clinical situations we may gain a better understanding of the relationship between growth, GH secretion and circulating IGF-1 levels.

Following thyroid irradiation, thyroid tumours and thyroid dysfunction are significant problems which require lengthy clinical follow-up as the tumours may not present for 30 years or more after irradiation. We have not discussed the development of auto-immune thyroid diseases following thyroid irradiation nor the relationship between thyroiditis and cancer. Perhaps there are more generalised disturbances of the immune system in irradiated patients who have sustained damage to a variety of tissues including endocrine.

Treatment of haematological disorders with bone marrow transplantation (BMT), which includes total body irradiation (TBI), is likely to produce disturbances of skeletal growth, GH secretion, thyroid and gonadal function. GH deficiency is not a frequent occurrence after TBI in the absence of additional previous cranial irradiation. The presence of additional adverse growth factors such as skeletal lesions due to radiation is important as these may modify the growth response to GH therapy. There is a need to clearly define groups of patients undergoing BMT and treated in identical fashion. Only in this way will we truly appreciate the contributions of different treatment modalities. Gonadal function may be impaired by either chemotherapy or radiotherapy. Long-term studies are required in adults cured of a childhood malignancy. These will provide information

about the impact of treatment on fertility and the offspring of the treated patients. Leydig cell function may be severely damaged by direct high-dose testicular irradiation during prepubertal life, however, Leydig cell dysfunction after chemotherapy is rather subtle and does not interfere with spontaneous progression through puberty. In girls, longitudinal studies are necessary due to fluctuation of ovarian follicular activity with time. Such studies might shed some light on the possibility of premature menopause which has been postulated as a long-term complication of ovarian damage in childhood. Radiation-induced testicular damage is dose-dependent. After low irradiation doses, the germinal epithelium is damaged but only after much higher doses is severe Leydig cell damage seen. Damage to germinal epithelium may prove reversible with time but Leydig cell damage is irreversible. Methods of protecting the gonad from damage by chemotherapy and radiotherapy, using GnRH analogues, are now being explored in a number of animal models.

O. Our endocrine studies will contribute to the development of new oncological protocols which cure the malignancy and leave the quality of life of the survivor unimpaired. However the clinical studies must be restricted to relevant problems lest we forget that these children are considered 'cured'.