57 LONGITUDINAL STUDY OF GH SECRETION, SOMATOMEDIN AND GROWTH IN THE TWO YEARS FOLLOWING CRANIAL IRRADIATION
R. Brauner, P. Czernichow, C. Prévot, H.J. Guyda, R. Rappaport. INSERM U30, Paris and Mc Gill University, Montreal.

In order to define characteristics and timing of GH deficiency after cranial irradiation a longitudinal study was performed on 16 children (2 to 15 yr) after > 3000 rads for medulloblastoma (n=9) or other posterior fossa tumors (n=7). At onset (TO), after 1 (T1) and 2 yr (T2) GH secretion was assessed by 1) GH peak response to AITT, 2) sleep GH peak, 3) plasma SmC/IGF I (RIA) and Sm (bioassay) expressed as % of normal values based on age and pubertal standards. At TO and T1 the mean (n=13) GH (AITT) peak values were respectively 21.8 ± 12.2 (SD) and 12.2 ± 5.7 ng/ml ($p < 0.02$). In 7 cases fully evaluated at T1 and T2 the frequency of GH secretion abnormalities were as shown below (GH, ng/ml)

	GH AITT peak <8	GH sleep peak <10	SmC/IGF I <50%
at 1 yr	2	3	5
at 2 yr	5	3	4

At time T2 3/7 children had complete GH deficiency. The mean SmC/IGF I values at T1 and T2 were respectively 0.54 ± 0.26 and 0.57 ± 0.35 %. Sm by bioassay did not show any clear correlation with RIA. From TO to T2 the mean height loss was 1.21 ± 0.4 SD (- 0.8 to - 1.8 SD) at T2 in this group. In conclusion, this study demonstrated the early occurence of various GH secretory disturbances and growth retardation. It should provide further information on the mechanism of radiation induced GH deficiency and help to define therapeutic strategies (supported by INSERM grant, 1982).

58 GROWTH HORMONE DEFICIENCY: INTERLEUKIN 2 (IL2) AND IMMUNE FUNCTION. Robert Rapaport, James Oleske, Selva Schenkman, Jeanne Churchill, Charles Kirkpatrick. UMDNJ-New Jersey Medical School, Newark, NJ, Dept. of Pediatrics and National Asthma Center, Denver, CO

IL2 production in response to phytohemagglutinin (PHA) was measured in 5 patients with growth hormone deficiency (GHD)(ages 7.8-14.5). In 3 patients IL2 was determined before and 24 hrs after the first dose (2 units) of human growth hormone (HGH) administration. In 2 patients IL2 was measured after 1 and 16 months of HGH treatment. At no time could IL2 production be identified in these patients. In contrast 1 patient (age 14) with short stature and normal GH responses to standard stimulatory tests on treatment with exogenous HGH for 6 months did produce IL2 normally.

We have previously presented data (Society Pediatric Research 1984) demonstrating that continuous treatment with HGH for 1 year resulted in transient decrease in % B cells, T helper/suppressor (T H/S) ratio and PHA responsiveness in 8 GHD patients. When treatment was interrupted for 1-2 month intervals, restarting HGH resulted in a fall in % B cells in 5/7 patients, mean 17.6% (range 12-20) to 7.8% (range 6-11) and a fall in T H/S ratio in 4/7 patients, mean 1.83 (range 1.5-2.0) to 1.20 (range 1.0-1.4) after 1-2 months of treatment. Serum immunoglobulins and polymorphonuclear leukocyte function was not affected by HGH treatment for up to 24 months in any patient.

In conclusion Interleukin 2 production, unlike other immune parameters, is impaired in growth hormone deficient patients and is unaffected by human growth hormone treatment.

59 PRECOCIOUS PUBERTY AND GROWTH HORMONE DEFICIENCY (GHD) FOLLOWING CRANIAL IRRADIATION (CI). Robert Rapaport, Selva Schenkman, Jeanne Churchill, Beverly Ryan, Maria I. New. UMDNJ-New Jersey Medical School, Newark, NJ and Cornell Medical College, New York, NY, Depts. of Pediatrics

GHD and pubertal delay are known to occur following CI in children. We report 3 girls who developed precocious puberty and GHD after receiving CI. The clinical data are shown below.

Pt #	Diagnosis	CI Dose*	Age*	Age*:onset puberty - current Breast	PH†	Menarche	CA	HA	BA
1	Astrocytoma	4500	1.75	6.5	2	8.5	14	10	16
2	Astrocytoma	5040	5.5	7.2	7.5	9.7	10	9.5	13
3	Rhabdomyo-sarcoma(ear)	2000 +2500 ear	1.75	6	6.25	-	6.5	6	7.4

*Age in yrs;dose in rads; †pub hair

Patients #1 and #2 grew at annual growth rates of 6.5 and 6.3 cm before menarche. GHD was diagnosed after menarche in both. Pt #1 received human growth hormone between the ages of 9.5 and 11.8. Their predicted adult heights (PAH) (method of Greulich and Pyle) were 141 and 142 cm. Pt #3 evaluated at the age of 6.5 was growing at 6.7 cm/yr. Her serum estradiol was 1.0 ng/dl and her peak serum LH and FSH following LHRH administration (100 μg) were 11.9 and 17.1 mIU/ml. Her PAH was 149 cm. No demonstrable cranial, adrenal or ovarian cause for precocious puberty was found in any of the patients.

We report here evidence that CI can result in both hypothalamic pituitary hypofunction and hyperfunction in the same individual. Finding "normal" growth rates in such patients does not obviate the need for evaluating their growth hormone dynamics.

60 Prolactin (Prl) Secretion in Long-term Survivors of Acute Lymphoblastic Leukemia (ALL).
Charles A. Sklar, Saul A. Rothenberg, Theodore W. AvRuskin, Aaron Rausen and Raphael David. New York University Medical Center and Downstate Medical Center, Depts. of Pediatrics and Medicine, New York, USA.

The therapy employed for the treatment of childhood ALL is known to cause disturbances in the neuroendocrine control of growth hormone (GH) secretion. Recent data suggest that this is due primarily to hypothalamic damage. Since Prl levels are frequently elevated and diurnal variation is lost when hypothalamic damage is present, we assessed Prl secretion in a group of long-term survivors of ALL. We studied 5 males between the ages of 11 8/12 - 20 5/12 yrs. The patients were euthyroid and had been off treatment for 2-10 yrs. 4 of 5 had received cranial radiation (2400 rads). 2 of 4 irradiated patients had demonstrated blunted peak GH levels (<7 ng/ml) during sleep. Prl levels were determined in PM prior to sleep (q 30 min) and q 20 minutes during sleep.

The awake PM Prl concentrations in patients (8.7 ± 1.0 ng/ml) were not different from controls (5.6± 0.8 ng/ml). The patients' mean Prl levels during sleep (13.9 ± 0.7 ng/ml) and mean Prl output (476 ± 98 area units) were not significantly different from those of the controls (9.0 ± 0.4 ng/ml and 333 ± 40 area units). All patients showed normal augmentation of Prl during sleep. These results suggest that the neuroendocrine mechanisms controlling Prl secretion are less sensitive to the toxic effects of ALL therapy than those controlling GH secretion.

61 PROPYLTHIOURACIL AND METHIMAZOLE PHARMACOLOGY IN CHILDREN AND ADOLESCENTS WITH GRAVES DISEASE. Akimasa Okuno, Daisuke Ueda, Koichi Yano, Fumie Inyaku, Nozomu Sasaki, Hironori Nakajima. Asahikawa Medical College and Chiba University School of Medicine, Dpt. of Ped., Asahikawa and Chiba, Japan

Concentrations of propylthiouracil (PTU) and methimazole (MMI) in plasma and thyroid glands were measured. A single oral dose of the drugs (100 to 280 mg/m^2 of PTU or 20 mg/m^2 of MMI) induced a rapid increase of plasma levels reaching a peak within 1 hr for both PTU and MMI. Peak PTU values ranged from 7.2 to 18 μg/ml with the administered dose. Its mean plasma half-life was 1.36 hrs, and its mean distribution volume was 326 ml/kg. Plasma levels of MMI showed a mean peak value of 1.03 μg/ml, a mean half-life of 4.56 hrs, and a mean distribution volume of 630 ml/kg. Intrathyroidal concentrations of PTU were measured in needle biopsy specimens and were 2.06 - 4.31 μg/g, 4.56 - 17.8 μg/g and 1.09 - 4.48 μg/g at 2, 12 and 24 hrs after 200 mg/m^2 of PTU respectively. Intrathyroidal MMI was measured in surgically obtained specimens and was 1.1- 2.3 μg/g and 0.78 - 1.40 μg/g at 5 and 18 hrs after 10 - 20 mg/m^2 of MMI respectively. These values far exceeded the plasma values at the respective times except for 2 hrs after PTU. Our results indicate: 1) elimination of PTU and MMI from the thyroid gland is much slower than from plasma, and 2) a single daily dose of PTU or MMI is adequate for the treatment of Graves disease.

62 FAMILIAL PARTIAL PERIPHERAL AND PITUITARY RESISTANCE TO THYROID HORMONE - A FREQUENTLY MISSED DIAGNOSIS? Nancy J. Hopwood, Sue E. Sauder, Brahm Shapiro, and James C. Sisson, University of Michigan Medical School, Depts. of Pediatrics and Int. Med., Ann Arbor, MI USA

Two boys, 7 and 9 yrs, and a girl, 11 yrs, presented with goiters and hyperthyroxinemia. The boys were treated with PTU/thyroidectomy or I^{131} for suspected thyrotoxicosis, but had poorly suppressible serum TSH post Rx. The girl had increasing goiter size on PTU 100 mg q 8 h x 1 mo. These findings led to re-evaluation of thyroid hormone dynamics in these patients and their families. The diagnosis of partial peripheral and pituitary resistance to thyroid hormone was made in the 3 index cases and 12 additional family members, ages 3-38 yrs, compatible with an autosomal dominant inheritance. All had elevated serum T_4 RIA (13.9-25.8μg/dl), T_3 RIA (205-396 ng/dl), and non-suppressed serum TSH (1.5-158 μU/ml). T_3 resin uptakes were N→sl↑. Reverse T_3, free T_4 and 24h I^{131} uptakes were ↑ in 6/6. Goiters were present in 10/11 (4 were post thyroid ablation). TRH (200 μg iv) given to 5 pts (from 3 families) showed exaggerated TSH responses (Δ μU/ml = 26, 31, 32, 34, 268). After incremental doses of L-thyroxine up to 0.3 mg/d, goiter size decreased, and TSH response to TRH was now normal (Δ 13,19 μU/ml) in 2 pts with intact thyroids and still exaggerated (Δ 96 μU/ml) in the pt with I^{131} Rx. Misdiagnosis in 6/15 members of 3 families has led to significant morbidity (hypothyroidism, delayed growth, Rx risk). Appropriate management for this condition should include L-thyroxine in order to decrease goiter size and normalize TSH responses to TRH. A non-suppressed TSH in a patient with suspected thyrotoxicosis should lead to suspicion of this disorder.