16 S.L.BLETHEN* and V.V.WELDON*, Washington University St. Louis, MO. Kinetics of somatomedin C/insulin-like growth factor-I(SMC) response to hGH in GH deficient children.

Studies in animals indicate that the half-life ($t_{\frac{1}{2}}$) of SMC is longer (2-4 hrs) than that of other polypeptide hormones. This is believed to be due to the fact that SMC circulates as part of a binding protein complex. Studies of the $t_{\frac{1}{2}}$ of SMC in humans have not been possible due to the scarcity of purified SMC. We have estimated the $t_{\frac{1}{2}}$ of SMC in 11 children (8M, 3F) with GH deficiency. After 2 baseline serum samples were obtained, each child received 5 doses of NPA hGH (0.1 u/kg/dose) at 12 hr intervals. Serum samples were obtained at 24 hrs and 48 hrs of treatment and at 6 hr intervals after the last dose of hGH. Total SMC was determined on acid-ethanol extracted samples using an RIA specific for SMC. The $t_{\frac{1}{2}}$ for SMC disappearance was 18.7 ± 2.6 hrs (x ± SEM). $T_{\frac{1}{2}}$ was not correlated with age, bone age or peak SMC. However, the time elapsed from the last hGH injection to SMC = ½ peak SMC was correlated with bone age (r = 0.67, p 0.05). In 8 children, growth velocities on hGH are available (8.2 ± 2.5 cm/yr). Growth velocity was not significantly correlated with bone age, peak SMC or $t_{\frac{1}{2}}$. Conclusion: The $t_{\frac{1}{2}}$ of SMC in GH deficient children is considerably longer than the $t_{\frac{1}{2}}$ observed in small animals. The prolonged $t_{\frac{1}{2}}$ of SMC may partially explain the success of present GH treatment regimens in promoting skeletal growth.

17 R. RAPPAPORT, P. CZERNICHOW, C. PREVOT*
M.C. POSTEL-VINAY, H.J. GUYDA*, B.I. POSNER*
Hôpital des Enfants-Malades, INSERM U.30, Paris, France.
Discrepancy between the bioactivity and the binding activity of somatomedin in patients with abnormal growth hormone secretion after cranial irradiation.

The purpose of this study was to compare the bioactivity (SM) and the binding activity (ILA) of somatomedin in 11 children with growth retardation and persistent GH secretion after cranial irradiation for medulloblastoma or head and neck tumors. Children aged 6-12 yr, first seen 16-54 mo after irradiation were investigated over periods of 6-36 mo. Each patient at invervals of 3 mo or more underwent 2 to 4 arginine-insulin tests with determinations of GH, SM by the porcine cartilage bioassay and ILA by RRA after plasma acid gel filtration. GH peak values were distributed from severe (5 ng/ml n = 5), to partial (5-10 ng/ml n = 13) or normal range (10 ng/ml n = 7). All SM values were low (<0.5 U/ml). Mean ILA was lower than control but significantly higher than values obtained in idiopathic hypopituitarism (IH)

U/ml	Irradiated (n = 18)	IH (n = 5)	
SM	0.38 ± 0.04	0.27 ± 0.05	NS
ILA RRA	0.67 ± 0.09	0.31 ± 0.06	p < 0.02

In conclusion, in children with growth retardation after cranial irradiation impaired GH secretion was associated with SM in the hypopituitary range while ILA was only slightly decreased. This is another clinical example of the difficulty in evaluating somatomedin activities in growth retardation.

18 J.R. BIERICH, H. MOELLER and M. RANKE
Stunted growth due to peripheral resistance to somatomedin, a new syndrom.
Up to now small stature with high plasma-hGH is known only as Laron-type dwarfism, caused by insufficient response of somatomedin (SM)-production to hGH. Recently we observed a dwarf with constantly elevated levels of hGH and of SM as well. Methods: hGH acc. to Schönberg (1972), SM acc. to van den Brande & Caju (1974). - S.H. is a 15 mo. old girl of healthy parents who clinically resembles a pituitary dwarf. Length 60 cm (corresp. to age 3 mo.), weight 5.5 kg (~3 mo.), bone age 11 mo. With 5 mo., basal hGH was 36.4 ng/ml, after arginine max. 46.6 ng/ml. Blood glucose dropped to 26 mg% under arginine. With 10 mo. basal hGH was 58.2 and 65.5 ng/ml, resp.. Basal SM-levels were 1:99 and 2.03 u/ml (normal mean for age 0.41 u/ml). Stimulation with hGH caused no further rise.- Biological inactivity of the hormones measured seems improbable, because SM-activity was determined biologically and the high SM-levels presumably are the result of the elevated hGH-secretion. Two other patients who clinically exhibited delayed growth and adolescence showed normal basal hGH-levels but significantly increased spontaneous hGH-secretion by night and, in addition, high plasma-SM.
Conclusion. In the first case, a pseudo-hypopituitary dwarf with high plasma-hGH and -SM, absolute peripheral resistance against SM seems to be the most plausible explanation. In the 2 other cases, a certain degree of non-responsiveness to SM may play a rôle.

19 D.O. SOBEL*, J.P.GUTAI, B.S. RABIN*, B.J. MONDINO*, P. FIREMAN*. University of Pittsburgh School of Medicine, Pittsburgh, PA.
Cell mediated immunity to pituitary extracts in hypopituitarism.

To obtain evidence of autoimmunity in children with idiopathic hypopituitarism, lymphocyte reactivity to pituitary extract in 9 normal subjects and 3 children with idiopathic hypopituitarism was determined. Lymphocyte reactivity to thyroid extract was also studied. Standard lymphoblastic transformation testing by thymidine incorporation was performed with crude human pituitary extract at concentrations of 2.6 or 5.0 µg protein/ml & 26 or 50 µg/ml. For each set of replicate wells, the arithmetic mean of the square root counts per minute ($\Delta\sqrt{CPM}$) was calculated. Thymidine incorporation was recorded as the difference of the test counts from the control ($\Delta\sqrt{CPM}$). $\Delta\sqrt{CPM}$ to 2.5/5.0 µg/ml in 9 normal subjects was -6.0(SD+6.9). The $\Delta\sqrt{CPM}$ to 26/50 µg/ml extract was 0.66(SD+8.2). One child had $\Delta\sqrt{CPM}$=34 to the higher extract concentration which was >95% tolerance limits of normal subjects, 6 months later the $\Delta\sqrt{CPM}$=40 to the lower extract concentration (>95% confidence limits). This child had no significant $\Delta\sqrt{CPM}$ to thyroid extract. He has alopecia dystrophic nails and T and B cell dysfunction. $\Delta\sqrt{CPM}$ to pituitary extract to two other children were within normal limits. In conclusion we describe an invitro test to detect cellular hypersensitivity to pituitary extract for patients with hypopituitarism. We report 1 of 3 children tested with persistent lymphocyte reactivity which appears to be organ specific. Clinical and laboratory presentation suggests an autoimmune basis of his disease.

20 N. STEBBING, J.T. FENNO* and M. SANDA*
Genentech, Inc., So. San Francisco, California 94080 U.S.A.
Efficacy and pharmacokinetics of recombinant DNA derived human growth hormone in rats and monkeys.

Production of human growth hormone by bacteria harboring a plasmid gene increases the potential availability of the hormone for human clinical use. The efficacy of this material has been determined by growth promoting effects in rats and clinical chemistry parameters in rats and monkeys. Comparison of the pharmacokinetics of the hormone administered intramuscularly or sub-cutaneously indicates that essentially similar effects are achieved. Other biochemical properties also indicate that the sub-cutaneous route is not associated with potential adverse effects, supporting use of the material for a variety of clinical indications.

21 R.L. HINTZ, R. ROSENFELD,* D. WILSON* and A. BENNETT*
Dept. of Pediatrics, Stanford University Medical Center, Stanford, California USA.
Synthetic hGH causes both increased somatomedin levels and insulin resistance in humans.

The supply of human pituitary growth hormone (hGH) available has been limited by the number of donors. Recently, methionyl-hGH (Genentech) has been synthesized by recombinant DNA techniques. We have compared synthetic methionyl-hGH with pituitary hGH in twelve normal adult male volunteers. Each patient was given 4 daily doses of 16 U of each hGH with a 10 day period between hGH preparations. Somatomedin-C (SM-C) by RIA was determined daily. Glucose tolerance tests were done prior to the first and after the fourth injection. The SM-C by RIA increased from a baseline of 1.04 ± 0.07 U/ml to 2.95 ± 0.20 U/ml with methionyl-hGH and from 1.11 ± 0.06 U/ml to 3.08 ± 0.19 U/ml with pituitary hGH. The GTT glucose area increased from 348 ± 16 mg%-hr to 475 ± 30 mg%-hr and the insulin area increased from 133 ± 19 uU/ml-hr to 403 ± 55 uU/ml-hr with methionyl-hGH. The glucose area increased from 333 ± 14 mg%-hr to 435 ± 25 mg%-hr and the insulin area increased from 110 ± 12 uU/ml-hr to 324 ± 49 uU/ml-hr with pituitary hGH. The equal somatomedin responses are evidence that the synthetic methionyl hGH has full biological activity. The equal changes in glucose metabolism demonstrate that insulin resistence is linked to monocomponent synthetic hGH as well as pituitary hGH. These studies open the way for explorations of uses of methionyl-hGH in human disease states and developmental disorders.