70 T.A. WILSON*, D.L. KAISER*, E.M. WRIGHT*, E.M. ORTT*, A.E. FREEDLENDER*, M.J. PEACH*, AND R.M. CAREY*(intro. A.J. Johanson). Importance of Plasma Angiotensin Concentrations in a Longitudinal Study of Responses to Angiotensin in the Maturing Newborn Lamb. Charlottesville, Virginia, U.S.A.

Plasma angiotensin concentrations were measured in a longitudinal study of the vascular and adrenal responses to intravenous infusions of angiotensin II in lambs from birth to 8 weeks of age maintained on a high sodium intake. Basal plasma concentrations of angiotensin increased with age and correlated with the rising arterial pressure that occurred with maturation. However, age was a stronger determinant of arterial pressure than was plasma angiotensin concentration. At any given dose of angiotensin II infused per kilogram of body weight, the actual plasma angiotensin concentration achieved increased as the lambs matured. Therefore, a comparative study of biologic responses to angiotensin II in growing animals must be based on actual plasma angiotensin concentration achieved rather than on dose of angiotensin II infused per kilogram.

When analyzed on the basis of actual plasma angiotensin concentration, the increase in arterial pressure in response to increasing plasma angiotensin concentrations did not differ significantly as a function of age as the lambs matured. However, the increment in plasma aldosterone concentration was diminished in lambs less than 18 days of age in comparison to the aldosterone response in the same lambs at older ages. Therefore, although the adrenal response to angiotensin II appears to change with maturation, an increase in the pressor response to angiotensin II cannot account for the rise in blood pressure occuring with maturation.

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Circumstantial evidence for a role of the secretory pattern of growth hormone in control of body growth.

The effect of frequency of growth hormone (GH) administration on longitudinal bone growth and body weight was studied in hypophysectomized rats, given replacement therapy with corticosteroids, thyroxin and GH, with start of therapy on the day of surgery. Longitudinal bone growth, as determined by the tetracycline method, was measured during the last 5 days of the 9 day long replacement period. The daily replacement dose of GH (200 µg bGH-17:NIH) was divided on 1, 2, 4, or 8 occasions. Longitudinal bone growth was enhanced when GH was given on 2 or more occasions compared to one injection. The most pronounced response was seen when GH was given four times per day. Changes in body weight during the injection period showed similar changes. Similar results were observed in hypophysectomized rats given only GH, a daily dose divided on 1, 2, 4, or 8 occasions per day, over a 5 day long period starting two weeks after surgery. The results of the present study show that the administration frequency of GH is important for the growth rate in hypophysectomized rats receiving replacement therapy of other hypophyseal hormones or not. The findings suggest that the secretory pattern of GH is an important factor for optimum growth.

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Optic Nerve Hypoplasia with Hypopituitarism, Hyperprolactinemia, and Normal Growth in Infancy.

Of 12 children ages 5 months to 16 years with optic nerve hypoplasia (ONH), 2 of 6 lacked septum pellucidum, 9 of 9 had GH deficiency, 5 of 12 TSH deficiency, and 5 of 10 ACTH deficiency. Seven patients 5 months to 2 1/2 years old were at the 10-50th% for height and 25-90th% for weight when diagnosed to have GH deficiency; somatomedin C (SmC) levels were 0.10-0.26 U/ml. In two patients with hypothalamic TSH deficiency basal prolactin (PRL) levels were 27 and 94 ng/ml and peak PRL after TRH were 62 and 111 ng/ml. In 8 others who were clinically and chemically euthyroid PRL levels before and after IV TRH were significantly higher than in children with idiopathic hypopituitarism (IHP):

	SERUM PROLACTIN (mean ± SEM) (ng/ml)				
TIME (min.)	0	15	30	60	120
ONH (n=8)	19.8±1.4	57.2±5.1	55.7±6.0	40.5±6.1	28.0±3.7
IHP (n=17)	10.3±1.9	24.7±2.9	23.9±2.7	16.7±2.1	12.3±2.3
p<	.005	.0005	.0005	.005	.005

All patients with optic nerve hypoplasia tested with oral L-dopa had normal suppression of basal PRL levels.

These results suggest that optic nerve hypoplasia is associated with: 1. High incidence of hypopituitarism, 2. Normal growth in infancy in the absence of GH, and 3. Hyperprolactinemia which may have a growth promoting effect possibly not mediated by SmC.

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Continuous subcutaneous infusion of growth hormone (CSIGH) in GH deficiency.

In contrast to the sustained acceleration of growth observed in pituitary hypersecretion in GH, full catch-up growth is rarely attained in GH deficiency with conventional GH Rx (0.1 U/kg IM 3x/wk). Since circulating GH levels are very low for all but 24-30 hr per wk during conventional Rx, we examined the feasibility and metabolic effects of CSIGH using a small infusion pump. Somatomedin-C (SM-C), oral glucose tolerance (GT) and free fatty acids were determined in 7 untreated deficient children before and after 85 hrs of CSIGH (2.1 µU/kg/hr ≈ 0.3 U/kg/wk). CSIGH maintained serum GH at 3-9 ng/ml and produced a modest increase in fasting (0 min) G and I. Glucose tolerance was impaired despite 2-fold higher I levels (*p<0.05).

Plasma G:	0 min	60 min	120 min	I: 0 min	60 min	120 min
Pre-CSIGH	82±9	123±11	100±5	15±4	65±11	60±10
Post-CSIGH	97±10	153±11*	133±12*	27±6	133±23*	102±19*

FFA rose sharply after 12 hr CSIGH (1021±151 vs 605±87 µU,p=0.05) but later returned to baseline values. SM-C rose in only 2 subjects. In a 14 y.o. on IM GH injections for 7 yrs, CSIGH Rx (maintaining GH levels between 9-11 ng/ml for 2 mos) resulted in a 2-fold increment in growth velocity (6 vs 12 cm/yr).
Conclusions: CSIGH in standard doses produces sustained increases in GH levels sufficient to alter lipid fuel metabolism and induce hyperinsulinemia even in the absence of change in SM-C.

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Penile and testicular size in isolated GH deficiency (IGHD) and response to hGH treatment.

The response of genital and gonadal growth during the first year of treatment with hGH was studied in 20 boys with IGHD (11 of hereditary origin and 9 sporadic cases). Prior to hGH treatment 13 of the 15 prepubertal boys had a penis length below the normal mean, 3 of them more than 2 SD below the mean. The boys with hereditary IGHD had a greater deficit in penile size than did the sporadic cases. hGH treatment improved the penile length in all but 2 boys aged 14 and 15 years, and led to normal size in the 3 boys with very small penises. Three of the hereditary IGHD patients had subnormal testes and all of the other prepubertal boys had a testicular volume in the normal range. hGH treatment increased testicular size, particularly in the prepubertal boys. Of 3 untreated adults with IGHD one had a subnormal sized penis and 2 a penis of low normal size. Our findings constitute further evidence that hGH deficiency decreases penile and to some extent testicular size and that hGH treatment improves the growth of the genitalia and gonads. Since this was also observed in prepuberty it seems that not all the hGH or rather somatomedin effect on sex organs is androgen-mediated.

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Evolution of the genes for growth hormone (GH) and Prolactin (Prl).

Chorionic somatomammotropin (CS), GH, and Prl are a family of polypeptide hormones related by structure, function and evolution, and are encoded by a set of structurally related genes. As these genes are hormonally regulated, they constitute an excellent system for studying eucaryotic gene expression. We studied the structure and evolution of these genes by cloning cDNA complementary to the mRNA's for bovine, rat, and human (h) GH and Prl, and hCS, and compared their nucleotide sequences. All three GH mRNA's: i) have a high G+C content in codon third positions; ii) use UAG as the stop codon; iii) have very similar 3' untranslated regions; iv) are more homologous with one another than with the Prl mRNA of the same species. As hCS mRNA shares all these features and is 92% homologous with hGH mRNA, and as hCS and hGH are closely linked on chromosome 17, the CS gene is clearly a duplicated, slightly variant GH gene. Prolactin mRNA's: i) have little G+C preference in codon 3rd positions; ii) use UAA as the stop signal; iii) have similar 3' untranslated regions unlike GH's; iv) are less homologous with one another than are the GH mRNAs. Comparision of nucleotide sequences indicates GH and Prl arose from a common ancestral gene 350-400 million years ago, but that GH and Prl are now evolving by different mechanisms, and at different rates. GH evolves by "concerted evolution", where unequal crossover events among multiple GH genes slow the accumulations of mutations.