0031-3998/85/1906-0543$02.00/0
PEDIATRIC RESEARCH

Vol. 19, No. 6, 1985
Printed in U.S.A.

Growth Hormone Secretion in the Stunted Head-Irradiated Rat

H. DAVID MOSIER, JR., REGINA A. JANSONS, KARL F. SWINGLE, CHARLES A. SONDHAUS, LYLE C. DEARDEN, AND LESLIE C. HALSALL

Departments of Pediatrics, Radiological Sciences, and Anatomy, University of California, Irvine, California 92717 and the Long Beach Veterans Administration Medical Center, Long Beach, California 90822

ABSTRACT. Pulsatile secretion profiles of pituitary growth hormone (GH) and size and number of cells of brain, heart ventricles, liver, kidney, and gastrocnemius muscle were determined in male Long-Evans rats which received 600 rad x-irradiation to the head only at 2 days of age. Controls consisted of sham-irradiated littermates. The irradiated rats showed significant stunting of body weight and tail length beginning prior to weaning and lasting throughout the period (64 days) of observation. In irradiated rats at 20–21 days of age, just prior to weaning, organ weight was significantly reduced in all organs studied. Brain showed a decrease in organ/body ratio ($p < 0.0005$) and in total DNA content ($p < 0.0005$), but these values were not significantly changed in the other organs. DNA/organ ratio was increased significantly in heart ($p < 0.025$) and gastrocnemius muscle ($p < 0.025$); brain, liver, and kidney had nonsignificant increases. Protein/DNA ratios were decreased significantly in brain ($p < 0.005$), heart ($p < 0.01$), and gastrocnemius muscle ($p < 0.05$); liver and kidney had nonsignificant decreases. Blood samples were removed for GH determination from cannulated undisturbed irradiated and control rats at 15-min intervals for 18-h periods (9 h light and 9 h dark) at 47–64 days of age. Irradiated rats had normal periodicity of bursts of GH secretion. The area under the curve of GH concentration *versus* time of the irradiated rat was decreased in light ($p < 0.025$) and in dark ($p < 0.05$). Assessments of cell size and cell number suggest that neonatal hypopituitarism and/or undernutrition are unlikely causes of the delayed growth of the head-irradiated rat, and the GH results show that brain controls of rhythmic secretion of GH are intact in this model. The finding of reduced GH secretion, is compatible with the hypothesis that the head irradiation has altered a centrally located control of catch-up growth. (*Pediatr Res* 19: 543–548, 1985)

Abbreviation

GH, pituitary growth hormone

X-irradiation to the head only of the neonatal rat with a single dose of 350 rad or greater results in stunting of body weight (1–4), tail length (3), and tibial length (5). The role, if any, of GH in the stunting produced by head x-irradiation is not clear. The pituitary gland is reduced in size in the head-irradiated rat (3). On the other hand, measurement of pituitary concentration of GH (6), assay of somatomedin activity in serum (Wright JC, Mosier HD, Jr, unpublished results), measurement of tibial epiphyseal width (3, 7), treatment with GH (3), and results of irradiation with the pituitary shielded from the beam (8), have failed to produce evidence that GH deficiency accounts for the growth impairment.

The growth pattern in the head-irradiated rat is characterized by lack of catch-up growth in males, and only a slight degree of catch-up growth in females (3). GH has been linked to the catch-up growth mechanism by the the finding of increased GH levels in sacrificed rat plasma during recovery after transient growth arrest produced by undernutrition (9, 10), glucocorticoid treatment (9), or hypothyroidism (11), and of increased pulsatile secretion of GH during recovery after fasting (12) and glucocorticoid treatment (13). Recently we have shown that head-irradiated rats are still capable of undergoing catch-up growth after a period of starvation, but only to their new, smaller body size (7). This observation suggests that the new size results from resetting a putative control for body size by the head irradiation. In this case one would not expect GH secretion to be augmented. The present experiments were carried out to test that possibility. Profiles of pulsatile GH secretion were carried out in stunted head-irradiated rats and controls. In addition, cell size and cell number were determined in selected organs just prior to weaning in order to assess the significance of the observed change in GH secretion.

METHODS

The experiments were carried out on male Long-Evans rats bred from stock obtained from Simonsen Laboratories, Gilroy, CA. The animals were maintained in fresh filtered air, 35–70% relative humidity, at 21.1–23.3° C. The daily light/dark cycle was 14/10 h. Purina Lab Chow (St. Louis, MO) and tap water were provided *ad libitum*. Animal handling and all measurements were carried out by the same individual.

Pregnant rats were kept, one to a cage, in hanging wire-mesh cages, until the 14th day of gestation when each was transferred to a box-type cage containing a dustless wood shaving bed. At 2 days postpartum the litter was reduced to eight pups. There was a deliberate attempt at that time to provide the same mean and variance of body weight between controls and irradiated rats. When there were less than eight males the litter was completed using females also matched in weight in order to minimize variation in competition for milk. The 2-day-old rats were x-irradiated with only the head exposed to the beam or were sham irradiated for controls as described previously (7). At weaning, the young rats were transferred to individual cages. During the 1st wk after weaning the irradiated rats were provided a Petri dish containing a mash of powdered Purina Lab Chow and water

Received October 30, 1984; accepted January 30, 1985.
Reprint requests Dr. H. D. Mosier, Jr., Department of Pediatrics, University of California, Irvine, CA 92717.
Supported by National Institutes of Health Grant HD 07074.

in addition to Purina Lab Chow pellets; the mash was changed daily. In the event an irradiated weanling felt cool to touch during the 1st wk after weaning it was given a cage companion of equivalent size for warmth or provided gauze squares for nesting during that week only. Mothers were rested for 14 days before rebreeding and were discarded after the fourth litter. Breeder males were discarded at 17 months of age. From 2 days of age measurements were made at intervals of 1 wk or less of body weight to the nearest 0.1 g and tail length to the nearest 0.1 cm using the method of De Groot (14).

At 41–49 days a catheter was implanted into the superior vena cava (15) of the irradiated and corresponding sham-irradiated controls. Sampling was carried out from ages 47–64 days, inclusive. Before sampling the rats were habituated 2 h on two different days in insulated chambers (Small Universal Cubical BRS/LVE, Tech Serv Inc., Beltsville, MD) provided with fresh air flow and the routine light/dark cycle. Only one rat, within its storage cage with food and water, was placed in each chamber. In addition, actual sampling followed, with no interruption, 18 h of presampling habituation. In order to eliminate bias due to the order of light and dark periods two groups were established. One of these consisting of six controls and six irradiated rats had sampling from 1100–0500 h (9 h dark, then 9 h light) and the other group consisting of seven controls and eight irradiated rats were sampled from 2100–1500 h (9 h dark, then 9 h light). Sampling was at 15-min intervals.

Plasma GH concentration was determined in duplicate by radioimmunoassay (10). The initial assay was carried out with a reference range of 10–250 ng/ml. Samples with values above or below that range were reassayed at a plasma concentration corresponding to ranges of 40–1000 or 1.25–31.25 ng/ml in order to more precisely determine peak height and trough level, respectively. The within assay variation is 3.50% and the between assay variation is 5.59% for the last seven assays. Area under the curve of plasma GH concentration plotted against time was calculated by the trapezoid rule using a program which eliminates intervals following missing values. The incidence of missing values did not differ significantly between irradiated and control rats. Area is expressed as the mean of all the interval values of GH concentration and is reported as area units per interval. The period of GH surges was determined by averaging for each rat the time between every first value above 50 ng/ml after a previous value below 50 ng/ml and the succeeding such value in the record.

Tissue analyses were carried out in a group of seven head-irradiated and seven control rats sacrificed prior to weaning by decapitation at 20–21 days of age. The tissues consisted of whole brain with brain stem sectioned at the level of the caudal edge of the cerebellum, heart ventricles, whole liver, both kidneys, and the right gastrocnemius muscle. The organs were promptly dissected free of adjacent tissue, weighed, and frozen in liquid nitrogen. Biochemical determinations were carried out as previously described (9) using a diphenylamine method for DNA (16) and the method of Lowry *et al.* (17) for protein. Differences between means were tested for significance by one-tailed t test.

RESULTS

Body weight and tail length. Body weight at the time of irradiation, 2 days of age, was 7.69 ± 0.17 g (mean ± SE) (n = 13) in controls and 7.59 ± 0.16 g (n = 14) in irradiated rats (NS). By 7 days of age irradiated rats were significantly lighter than controls ($p < 0.025$), this difference remained significant at all subsequent points at the $p < 0.005$ level. Tail length at 2 days of age was 1.99 ± 0.02 cm (n = 13) in controls and 2.05 ± 0.02 cm (n = 14) in irradiated rats ($p < 0.05$). The first significantly smaller value of tail length in irradiated rats occurred at 14 days of age ($p < 0.025$); all subsequent means of tail lengths in irradiated rats were significantly less than those of controls at the level of $p < 0.005$ before cannulation. The level of significance was $p < 0.05$ thereafter because of reduction in number of animals due to sacrifices after sampling (Fig. 1).

GH. Both the irradiated and the control rats displayed normal pulsatile patterns of plasma GH concentration (Fig. 2 *A* and *B*). The periodicity of the clustered bursts of GH secretion was not significantly different between controls and irradiated rats. The intervals were 3.32 ± 0.15 h (mean ± SE) in controls and 3.16 ± 0.16 h in irradiated rats.

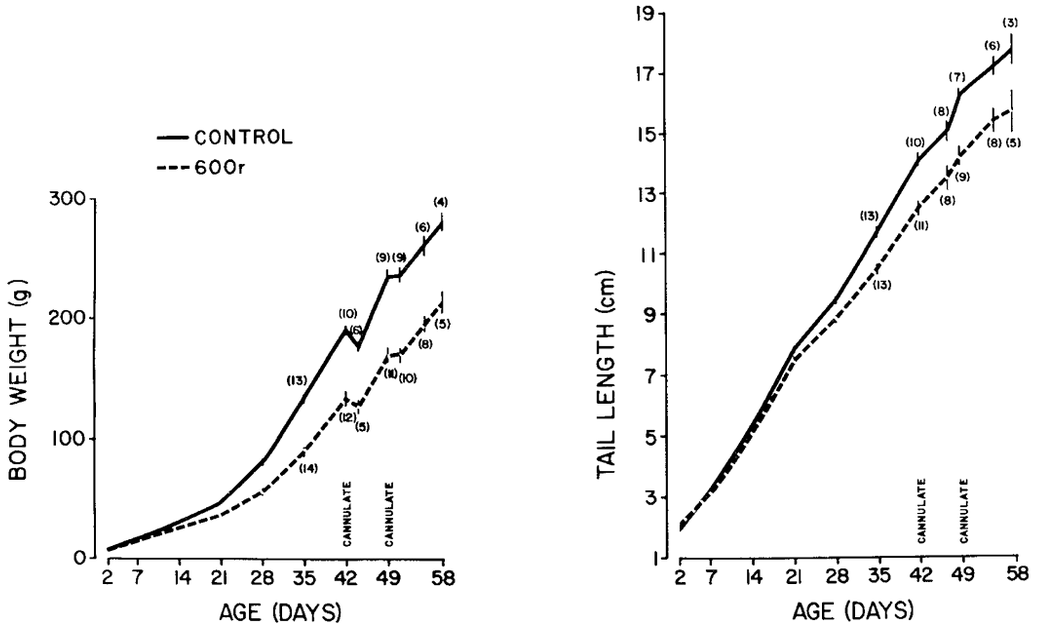

Fig. 1. Growth curves of body weight and tail length of head-irradiated rats and controls extending from the time of irradiation at 2 days of age through 58 days of age. The data of all rats of the two groups, those bled first in light and those bled first in dark, were combined in these curves. The body weight and tail length are most representative before the first cannulation. Although cannulations were carried out at different ages the curves closely approximate those previously reported for unoperated irradiated and sham-irradiated rats (3). It is evident that body weight growth is affected by operation similarly in irradiated and control rats. Full recovery of body weight after surgery occurs within 7 days.

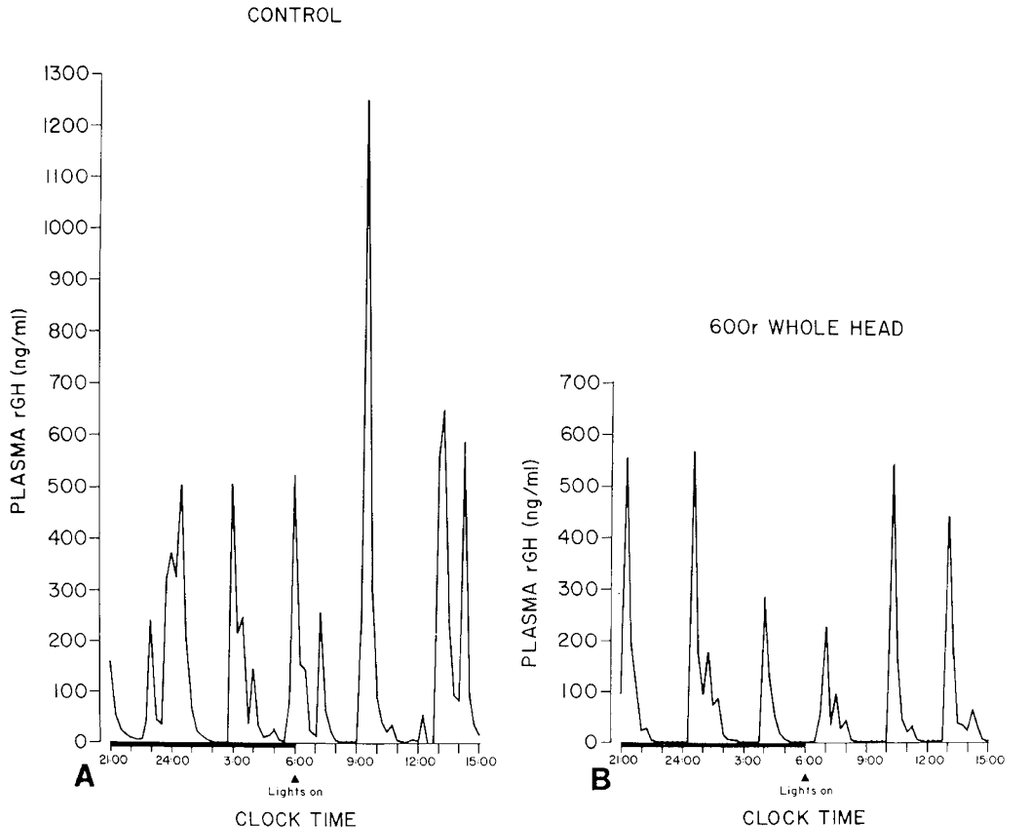

Fig. 2. *A*, control rat plasma GH concentrations determined at 15-min intervals beginning at 2100 h and ending at 1500 h the following afternoon. The first 9 h were in darkness and the second 9 h in light. The record shows a characteristic pulsatile pattern of GH secretion. *B*, a similar record of a stunted head-irradiated rat showing a normal pulsatile rhythm. The height of peaks are variable as in the control. The number of peaks in the ranges from 200 through 999 ng/ml and the area under the GH concentration curve were significantly reduced in irradiated rats (see text).

Table 1. *Number of values of GH concentration occurring within arbitrarily designated ranges of GH concentration in plasma in 13 controls and 14 irradiated rats**

	GH concentration (ng/ml)				
Experimental groups	50–99	100–199	200–499	500–999	>1000
Combined light and dark					
Controls	7.0 ± 1.0	6.5 ± 0.8	6.6 ± 0.7	2.9 ± 0.4	0.7 ± 0.4
Irradiated	7.7 ± 0.4	7.6 ± 1.0	4.8 ± 0.7	1.4 ± 0.3	0.2 ± 0.1
p			<0.05	<0.005	
Light					
Controls	3.9 ± 0.6	3.2 ± 0.5	3.5 ± 0.5	1.7 ± 0.4	0.3 ± 0.2
Irradiated	3.5 ± 0.4	3.7 ± 0.9	2.7 ± 0.5	0.9 ± 0.1	0.1 ± 0.1
p				<0.025	
Dark					
Controls	3.1 ± 0.5	3.4 ± 0.5	3.1 ± 0.4	1.2 ± 0.2	0.4 ± 0.3
Irradiated	4.2 ± 0.5	3.9 ± 0.4	2.1 ± 0.4	0.6 ± 0.1	0.1 ± 0.1
p			<0.05	<0.025	

* The data for light and for dark periods include all results irrespective of sequence of sampling. Data are given as mean ± SE.

The number of peak values of GH concentration in arbitrarily designated ranges of concentration, 50–99, 100–199, 200–499, 500–999, and 1000 or greater ng/ml, were counted. When all data for light and dark periods were combined the irradiated rats had significantly fewer peak values in the ranges covering 200–999 ng/ml. During the light period alone, the irradiated rats had significantly less peaks in the range 500–999 ng/ml; in the dark period the irradiated rats had less peaks in the ranges covering 200–999 ng/ml (Table 1).

The area under GH concentration plotted against time was significantly decreased in the irradiated rats in light and in dark phases when these sampling times were considered separately (Table 2). No significant difference existed between the groups sampled first in light and first in dark, or between the data of all samples in light and all samples in dark in either the controls or the irradiated rats.

Organ Weight, Cell Number, and Cell Size. The tissue results given below are described for the irradiated rats as compared with controls. The data are given in Table 2.

Brain. Organ weight, organ/body ratio, and total DNA were

significantly reduced indicating both decreased cell number and a decrease relative to body size (Table 3). DNA/organ ratio was increased, although not significantly, and protein/DNA ratio was decreased significantly indicating decreased cell size.

Heart. Organ weight was significantly decreased, but organ/body ratio and total DNA were not significantly changed. DNA/organ ratio was increased and protein/DNA ratio was decreased indicating preservation of cell number but reduction in cell size in the heart.

Liver. Organ weight was decreased but no significant changes occurred in the other measures.

Kidney. Combined organ weight was decreased. No significant changes occurred in the other measures.

Gastrocnemius muscle. Organ weight was significantly decreased but there was no significant change in organ/body ratio. Total DNA was unchanged indicating normal cell number. DNA/organ ratio was significantly increased and protein/DNA ratio was significantly decreased indicating reduced cell size.

Table 2. *The area under the curve of GH concentration vs time expressed as units/interval**

Experimental groups	*n*	Area (units/interval)	*p*
Combined light and dark			
Control	13	91.7 ± 10.7	<0.025
Irradiated	14	64.9 ± 6.4	
Light			
Control	13	98.5 ± 11.9	<0.025
Irradiated	14	69.5 ± 7.3	
Dark			
Control	13	85.5 ± 11.6	<0.05
Irradiated	14	60.3 ± 7.0	

* The data for light and for dark periods include all results irrespective of sequence of sampling. Data are given as mean ± SE.

DISCUSSION

The irradiated rats in the present experiments showed diminished secretion of GH while maintaining a normal pulsatile pattern of GH secretion. Light or dark or the order of light and dark periods had no influence on the results. While total cell number was strikingly reduced in brain after irradiation there was only a slight and not significant reduction of cell number in heart, liver, kidney, and gastrocnemius muscle. DNA/organ and protein/DNA ratios were indicative of reduced cell size in all the organs tested, heart and gastrocnemius muscle having the most significant reduction in cell size. The growth patterns of body weight and tail length of the irradiated rats were similar to those previously reported in this experimental model (3, 8).

The role of GH in the growth stunting of the head-irradiated rat remains unclear. Previous experiments have indicated that GH deficiency may not be the cause of the growth failure in the head-irradiated rat. Treatment with GH, alone or combined with thyroxine, failed to improve the growth rate of the head-irradiated rat (3). We have found no difference in bioassayable somatomedin activity, a GH-dependent factor (18), between irradiated and control rats (Wright JC, Mosier HD, Jr, unpublished data). The irradiated rats have normal or increased tibial epiphyseal width at 70 days of age (7) instead of narrowing of the epiphyseal growth plate which would be expected in GH deficiency (19). In the present experiments total cell number in heart, liver, kidney, and gastrocnemius muscle was not significantly reduced. Hypopituitarism, on the other hand, is associated with reduced cell number (20).

Widespread use of cranial irradiation in the treatment of children with intracranial malignancies or acute lymphoblastic

Table 3. *Organ wt, protein, and DNA determinations in seven irradiated and seven control male rats at 21–22 days of age (mean ± SE)*

Organ	Organ wt (g)	Organ/body (mg/g)	Total DNA (mg)	DNA/organ (μg/mg)	Protein/DNA (g/g)
Brain					
Control	1.45 ± 0.02	33.8 ± 0.6	2.15 ± 0.08	1.48 ± 0.04	36.5 ± 0.5
Irrad	1.08 ± 0.01	29.0 ± 0.8	1.63 ± 0.04	1.55 ± 0.05	33.4 ± 0.9
p	<0.0005	<0.0005	<0.0005	NS	<0.005
Heart					
Control	0.191 ± 0.011	4.03 ± 0.54	0.490 ± 0.029	2.56 ± 0.05	41.4 ± 1.1
Irrad	0.164 ± 0.010	4.35 ± 0.19	0.455 ± 0.025	2.79 ± 0.07	36.6 ± 1.3
p	<0.05	NS	NS	<0.025	<0.01
Liver					
Control	1.55 ± 0.05	36.1 ± 0.7	5.22 ± 0.26	3.37 ± 0.11	35.9 ± 0.6
Irrad	1.34 ± 0.04	35.9 ± 0.8	4.83 ± 0.23	3.59 ± 0.14	35.1 ± 0.8
p	<0.005	NS	NS	NS	NS
Kidneys					
Control	0.466 ± 0.011	10.9 ± 0.2	2.91 ± 0.10	6.24 ± 0.08	13.3 ± 0.4
Irrad	0.425 ± 0.018	11.3 ± 0.2	2.75 ± 0.13	6.46 ± 0.12	12.5 ± 0.4
p	<0.05	NS	NS	NS	NS
Muscle					
Control	0.142 ± 0.005	3.31 ± 0.14	0.204 ± 0.006	1.45 ± 0.04	69.0 ± 2.4
Irrad	0.126 ± 0.007	3.34 ± 0.14	0.197 ± 0.011	1.57 ± 0.04	52.9 ± 1.6
p	<0.0502	NS	NS	<0.025	<0.05

Body wt (g)		Tail length (cm)	
control	42.7 ± 0.7	8.1 ± 0.1	
irrad	37.5 ± 0.9	7.8 ± 0.1	
$p < 0.0005$		$p < 0.01$	

leukemia has resulted in a number of reported observations of short stature, although considerable variability is found in the growth effect of cranial irradiation (21). Of the anterior pituitary hormones, GH appears the most likely to be deficient after cranial irradiation in children (22, 23). Reduced secretion of GH in response to pharmacologic challenges has been reported either as a common finding after cranial irradiation in the human (28) or as an infrequent complication (24). Although some stunted cranially irradiated children have responded to GH treatment by improved growth responses (21) others have shown blunted responses (28). The clinical inconsistencies may result from variations in the dose of radiation, area irradiated, age, and the combination of various regimes of chemotherapy (21). These variables limit comparisons between the existing human data and our present findings.

Evidence from studies in head-irradiated primates suggests that the disturbance of GH function, when it occurs, is predominantly the result of disturbed hypothalamic control. Reduced pulse amplitude, which we have found in the present study in rats, has also been shown after cranial irradiation in both humans (21, 25) and rhesus monkeys (26). Cranial irradiation in monkeys has resulted in blunting of the GH response to insulin-induced hypoglycemia which could be overcome by increasing the insulin dose; however, the same animals had normal responses to arginine and L-dopa stimulation (26). Analysis of target volume in humans with disturbed pituitary function after irradiation indicates that direct pituitary irradiation is unlikely to be a factor, at least in some cases (27).

Decreased secretion of GH in the head-irradiated rat contrasts with the increased GH secretion found in rats recovering after fasting (9, 10, 12) or even after glucocorticoid treatment in which there is a failure of catch-up growth (9, 13). We have proposed, on the basis of those findings, that GH secretion is linked to the catch-up growth control (12, 13). In both experimental models the increased secretion of GH may serve as a marker for the positive (switched-on) phase of the catch-up growth control. The failure of catch-up growth in the glucocorticoid-treated rat has been attributed to other factors (13). Having recently shown that the head-irradiated rat is capable of catch-up growth after fasting (7), we interpret the absence of growth recovery and the lowered GH secretion after head-irradiation as indicative that the catch-up growth control is not called into play by the growth stunting of head-irradiation, alone. This suggests the hypothesis that a new body size has been established by the resetting of an age-dependent set-point for body size. The putative set-point constitutes part of a conceptual model for catch-up growth advanced by Prader *et al.* (29) and Tanner (30). The possibility that such a control exists and that it is located in the central nervous system is thus supported by these experiments.

In these and earlier experiments we have considered the possibility that undernutrition during the neonatal period contributed to the growth retardation and disproportionate growth of the head-irradiated rat. The disproportion consists of small body weight with respect to tail length appearing before weaning and extending into the postweaning period (31). It has been previously noted that undernutrition may interfere with cell proliferation of certain tissues (32). Williams *et al.* (33, 34) found that rats underfed during the suckling period and later rehabilitated displayed disproportionate growth of body weight, body length, and skull size during recovery. However, the head-irradiated rat has shown normal milk intake with respect to body weight prior to weaning (35) and normal laboratory diet intake with respect to body weight after weaning (Mosier HD Jr, unpublished observations). We have previously reported that undernutrition could not account for differences noted between head-irradiated and control rats in cartilage metabolism (5) and in light and electron microscopy of cartilage (36). There is further contrary evidence in the present experiments in the lack of significant reduction of cell number of heart, liver, kidneys, or gastrocnemius muscle, all of which would be expected to lose cells as a result of neonatal undernutrition (32). These findings leave open the possibility that disproportionate growth of the head-irradiated rat results from disturbance of a central control of proportionate growth.

Acknowledgment. Purified rat GH and the first antibody were generously provided by the Pituitary and Hormone Distribution Program, NIADDK.

REFERENCES

1. Yamazaki JN, Bennett LR, McFall RA, Clemente CD 1960 Brain radiation in newborn rats and differential effects of increased age: I Clinical observations. Neurology 10:530–536
2. Yamazaki JN, Bennett LR, Clemente CD 1962 Behavioral and histologic effects of head irradiation in newborn rats. In: Haley TJ, Snyder RS (eds) Response of the Nervous System to Ionizing Radiation. Academic Press, New York, pp 57–73
3. Mosier HD Jr, Jansons RA 1967 Stunted growth in rats following X-irradiation of the head. Growth 31:139–148
4. Savković NY 1969 Effect of local irradiation of the head of 2-day old rats: morphological and functional disorders and genetic changes in their progeny. In: Sikov MR, Mahlum DD (eds) Radiation Biology of the Fetal and Juvenile Mammal. U.S. Atomic Energy Commission, Division of Technical Information, Publication CON-690501, Oak Ridge, TN pp 453–474
5. Mosier HD Jr, Sondhaus CA, Dearden, LC, Zuniga OF, Jansons RA, Good CB, Roberts RC 1983 Cartilage metabolism during growth retardation following irradiation of the head of the neonatal rat. Proc Soc Exp Biol Med 172:99–106
6. Mosier HD Jr, Jansons RA 1968 Pituitary content of somatotropin, gonadotropin and thyrotropin in rats with stunted linear growth following head X-irradiation. Proc Soc Exp Biol Med 128:23–26
7. Mosier HD Jr, Good CB, Jansons RA, Sondhaus CA, Dearden LC, Alpizar-S M, Zuniga OF 1983 The effect of neonatal head-irradiation and subsequent fasting on the mechanisms of catch-up growth. Growth 47:13–25
8. Mosier HD Jr, Jansons RA 1970 Effect of X-irradiation of selected areas of the head of the newborn rat on growth. Radiat Res 43:92–104
9. Mosier HD Jr, Jansons RA 1976 Growth hormone during catch-up growth and failure of catch-up growth in rats. Endocrinology 98:214–219
10. Sinha YN, Wilkins JN, Selby F, VanderLaan WP 1973 Pituitary and serum growth hormone during undernutrition and catch-up growth in young rats. Endocrinology 92:1768–1771
11. Mosier HD Jr, Dearden LC, Jansons RA, Hill RR 1977 Growth hormone, somatomedin and cartilage sulfation in failure of catch-up growth after propylthiouracil-induced hypothyroidism in the rat. Endocrinology 100:1644–1651
12. Mosier HD Jr, Jansons RA, Good CB 1983 Growth hormone release is increased in rats undergoing catch-up growth after fasting. Endocrinology 112(suppl):213(abstr)
13. Mosier HD Hr, Jansons RA 1985 Increase in pulsatile secretion of growth hormone during failure of catch-up growth following glucocorticoid-induced growth inhibition. Proc Soc Exp Biol Med 178:457–461
14. De Groot DA 1963 Tail growth in the thyroxine-treated hypophysectomized rat as a sensitive criterion for growth hormone activity. Acta Endocrinol (Copenh) 43:423–431
15. Tannenbaum GS, Martin JB 1976 Evidence for an endogenous rhythm governing growth hormone secretion in the rat. Endocrinology 98:562–570
16. Burton K 1968 Determination of DNA concentration with diphenylamine. In: Grossman L, Moldave K (eds) Methods in Enzymology: Nucleic Acids, vol 12. Academic Press, New York, pp 163–166
17. Lowry OH, Rosebrough NJ, Farr AL, Randall RJ 1951 Protein measurement with the Folin phenol reagent. J Biol Chem 193:265–275
18. Daughaday WH 1981 Growth hormone and the somatomedins. In: Daughaday WH (ed) Endocrine Control of Growth. Elsevier, New York, pp 1–24
19. Evans HM, Simpson ME, Mark W, Kebrick E 1943 Bioassay of the pituitary growth hormone. Width of the proximal epiphyseal cartilage of the tibia in hypophysectomized rats. Endocrinology 32:13–16
20. Winick M, Grant P 1968 Cellular growth in the organs of the hypopituitary dwarf mouse. Endocrinology 83:544–547
21. Romshje CA, Zipf WB, Miser A, Miser J, Sotos, JF, Newton WA 1984 Evaluation of growth hormone release and human growth hormone treatment in children with cranial irradiation-associated short stature. J Pediatr 104:177–181
22. Bajorunas DR, Fereshteh G, Jereb B, Sonenberg M 1980 Endocrine sequelae of antineoplastic therapy in childhood head and neck malignancies. J Clin Endocrinol Metab 50:329–335
23. Pomarede R, Czernichow P, Zucker JM, Schlienger P, Haye C, Rosenwald JC, Labib A, Rappaport R 1984 Incidence of anterior pituitary deficiency after radiotherapy at an early age: study in retinoblastoma. Acta Paediatr Scand 73:115–119
24. Uderzo C, Natale BD, Locasciulli A, Adamoli L, Nizzoli G, Mariani R, Rondanini G, Masera G 1982 Endocrine study after interruption of therapy in 41 children with acute lymphoblastic leukemia. Haematologica 67:642–645
25. Blatt J, Bercu BB, Gillin JC, Mendelson WB, Poplack DG 1984 Reduced pulsatile growth hormone secretion in children after therapy for acute

lymphoblastic leukemia. J Pediatr 104:182–186
26. Chrousos GP, Poplack D, Brown T, O'Neill D, Schwade J, Bercu BB 1982 Effects of cranial radiation on hypothalamic-adenohypophyseal function: abnormal growth hormone secretory dynamics. J Clin Endocrinol Metab 54:1135–1139
27. Wigg DR, Murray RML, Koschel K 1982 Tolerance of the central nervous system to photon irradiation. Acta Radiol Oncol 21:49–60
28. Winter RJ, Green OC 1984 Irradiation induced growth hormone deficiency: blunted growth response and accelerated skeletal maturation to growth hormone therapy. J Pediatr 106:609–612
29. Prader A, Tanner JM, von Harnack GA 1963 Catch-up growth following illness or starvation. J Pediatr 62:646–659
30. Tanner JM 1963 The regulation of human growth. Child Dev 34:817–847
31. Mosier HD Jr, Jansons RA 1971 Allometry of body weight and tail length after head X-irradiation in rats. Growth 35:23–31
32. Winick M, Noble A 1966 Cellular response in rats during malnutrition at various ages. J Nutr 89:300–306
33. Williams JPG, Tanner JM, Hughes PCR 1974 Catch-up growth in female rats after growth retardation during the suckling period. Pediatr Res 8:149–156
34. Williams JPG, Tanner JM, Hughes PCR 1974 Catch-up growth in female rats after growth retardation during the suckling period. Comparison with males. Pediatr Res 8:157–162
35. Schjeide OA, Yamazaki J, Haack K, Ciminelli E, Clemente CD 1966 Biochemical and morphological aspects of radiation inhibition of myelin formation. Acta Radiol 5:185–203
36. Dearden LC, Mosier HD Jr, Thai C, Brundage M 1984 Effect of neonatal head X-irradiation on growth of costal and tibial cartilage in rats: a histochemical and electron microscopic study. Basic Appl Histochem 28:117–136

0031-3998/85/1906-0548$02.00/0
PEDIATRIC RESEARCH

Vol. 19, No. 6, 1985
Printed in U.S.A.

Ovarian Hyperstimulation Syndrome in Preterm Infants

G. SEDIN, C. BERGQUIST, AND P. G. LINDGREN

The Departments of Paediatrics, Obstetrics and Gynaecology, and Diagnostic Radiology, University Hospital, Uppsala, Sweden

ABSTRACT. Estradiol-producing ovarian cysts were found in four very preterm females at a postconceptional age that slightly preceded the expected time of delivery. The serum concentration of estradiol was very high. In the first infant one cystic ovary was removed surgically. When cysts appeared in the other ovary, the girl was treated with medroxyprogesterone acetate. The serum concentration of estradiol then fell and the cysts disappeared. Medroxyprogesterone acetate treatment was given also to the second girl, who had a high and rising serum concentration of estradiol. In infants 3 and 4 the cysts disappeared and the serum estradiol normalized spontaneously. Measurements of serum concentrations of luteinizing hormone and follicle-stimulating hormone before and after an iv injection of luteinizing hormone releasing hormone showed that preterm girls with early estradiol-producing ovarian cysts have a postpubertal type of response to luteinizing hormone-releasing hormone. When the test is repeated some months later they have a prepubertal type of response, which is normal for their age. (*Pediatr Res* 19: 548–551, 1985)

Abbreviations

FSH, follicle-stimulating hormone
LH, luteinizing hormone
LHRH, luteinizing hormone-releasing hormone
CPAP, continuous positive airway pressure
MPA, medroxyprogesterone acetate
HFPPV, high-frequency positive-pressure ventilation

Received July 13, 1984; accepted February 6, 1985.
Reprint requests Dr. Gunnar Sedin, Department of Paediatrics, University Hospital, 75185 Uppsala, Sweden.
Supported by grants from the Swedish Medical Research Council (Project 19X-04998 and 19P-6716).

It has been demonstrated that the serum concentration of estrogens in full-term newborn infants decreases rapidly during the first hours after birth (1). A high serum level of estradiol is unlikely in newborn infants beyond the early neonatal period and few measurements have been made in early infancy. Recently high serum levels of FSH and LH have been found in preterm girls (2). Also, there have been few reports of estradiol-producing ovarian cysts in childhood; most reported cases have been associated with precocious puberty (3). As far as we know such ovarian cysts have not been reported during the neonatal period. Herein we report four cases of estradiol-producing ovarian cysts in preterm girls.

MATERIALS AND METHODS

Four preterm girls were found to have estradiol-producing ovarian cysts. All were born before the 30th wk of gestation. Symptoms, including swelling of the labia majora, appeared at a time corresponding to 1–4 wk before the expected time of delivery, ie, 34–37 wk postconceptionally, or at 36–39 completed gestational weeks. A brief description of each case is given below. Maturity was assessed in all cases from external characteristics and on the basis of neurological criteria (4, 5). Immunoreactive FSH and LH in serum were assayed by a radioimmunosorbent technique with indirectly coupled antibodies (6). Immunoreactive estradiol in serum was measured by a radioimmunological method using an antiserum to an estradiol-6-oxime-bovine serum albumin conjugate (7). For the LHRH test informed consent was obtained from the parents. Ultrasonic examination was performed with a dynamic sector scanner (ATL Mark 300, 7.5 MHz, ATL, Seattle, WA), and included both scanning for cysts and determination of uterine size. The latter was measured as the length of the uterus and this determination required that some urine was left in the bladder when the examination was made.

Infant 1 was born after 26 wk of gestation; birth weight was