

# NIH RELAIS Document Delivery

NIH-10091524

NIH -- W1 J0828H

PAMELA GEHRON ROBEY  
CSDB/NIDR/NIH Bldng 30 Rm 228  
30 CONVENT DRIVE MSC 4320  
BETHESDA, MD 20892

ATTN:	SUBMITTED:	2001-12-14 11:11:48
PHONE: 301-496-4563	PRINTED:	2001-12-18 07:48:04
FAX: 301-402-0824	REQUEST NO.:	NIH-10091524
E-MAIL:	SENT VIA:	LOAN DOC 5296851

---

NIH	Fiche to Paper	Journal
TITLE:	JOURNAL OF PEDIATRICS	
PUBLISHER/PLACE:	Mosby-Year Book St. Louis Mo	
VOLUME/ISSUE/PAGES:	1975 Dec;87(6 Pt 1):917-21	917-21
DATE:	1975	
AUTHOR OF ARTICLE:	Danon M; Robboy SJ; Kim S; Scully R; Crawford JD	
TITLE OF ARTICLE:	Cushing syndrome, sexual precocity, and polyostoti	
ISSN:	0022-3476	
OTHER NOS/LETTERS:	Library reports holding volume or year 0375410 171361	
SOURCE:	PubMed	
CALL NUMBER:	W1 J0828H	
REQUESTER INFO:	AB424	
DELIVERY:	E-mail: probey@DIR.NIDCR.NIH.GOV	
REPLY:	Mail:	

NOTICE: THIS MATERIAL MAY BE PROTECTED BY COPYRIGHT LAW (TITLE 17, U.S. CODE)

-----National-Institutes-of-Health,-Bethesda,-MD-----

## Cushing syndrome, sexual precocity, and polyostotic fibrous dysplasia (Albright syndrome) in infancy

*The sexual precocity of polyostotic fibrous dysplasia is occasionally accompanied by other endocrine disorders, but in only two previous instances has Cushing syndrome been reported. The history of a 6-month-old girl is presented, in whom this syndrome was complicated by congenital Cushing syndrome. Although the endocrinopathies of polyostotic fibrous dysplasia have usually been ascribed to a central (hypothalamic) origin, the findings in this patient suggest autonomous hyperfunction of the peripheral endocrine glands, with the Cushing syndrome caused by hyperplastic nodules in the adrenal glands and the precocity by luteinized follicular cysts of the ovary.*

Marco Danon, M.D., Stanley J. Robboy, M.D.,\* Samuel Kim, M.D., Robert Scully, M.D.,  
and John D. Crawford, M.D.,\*\* Boston, Mass.

ALBRIGHT SYNDROME (also known as McCune-Albright syndrome) is characterized by the triad of polyostotic fibrous dysplasia, skin pigmentation (café-au-lait spots), and sexual precocity.<sup>1</sup> Additional endocrine disorders observed have been hyperthyroidism,<sup>2</sup> acromegaly,<sup>3</sup> hyperparathyroidism<sup>4</sup> and, in two instances, Cushing syndrome.<sup>5, 6</sup> The present report concerns a girl with Albright syndrome in whom Cushing syndrome due to nodular hyperplasia of the adrenal glands and sexual precocity due to luteinized follicular cysts of an ovary developed in infancy. The evidence suggests that the hyperfunction of both the adrenal cortices and the ovary was autonomous rather than under the control of the pituitary gland.

*From the Children's Service, the James Homer Wright Pathology Laboratories, and the Division of Pediatric Surgery of the Massachusetts General Hospital, the Departments of Pediatrics, Pathology, and Surgery of Harvard Medical School, and the Shriners Burns Institute.*

*Supported in part by a Training Grant from the United States Public Health Service T01-HD00033 and the Children's Medical Research Fund.*

*\*Junior Faculty Fellow of the American Cancer Society.*

*\*\*Reprint address: Children's Service, Massachusetts General Hospital, Boston, Mass. 02114.*

### CASE REPORT

Patient H. K. (MGH No. 177-63-18), a 6-month-old girl, was referred because of sexual precocity, growth failure, and the appearance of an "infant hercules." The mother was 24 years old and gravida 2, para 1. The pregnancy and delivery were uneventful. The infant was born three weeks before term but weighed only 1.6 kg (normal 2.8 kg), and the length was only 40 cm (normal 47 cm) (Fig. 1). At birth, several café-au-lait spots were noted on the back and chin. She was discharged from the hospital after six weeks weighing 2.4 kg (Fig. 2, A). Growth during the next five months was subnormal. One month before admission she had a single episode of vaginal bleeding. Subsequently both breasts began to enlarge symmetrically, and moderate amounts of pubic and perianal hair appeared.

---

See related articles, pp. 922 and 1018.

---

The infant measured 51 cm in length and weighed 3.2 kg (average values for normal newborn infants). She had a cushingoid appearance with a rounded face, ballooned cheeks (Fig. 2, B), and hirsutism of the forehead. Extremities were short and the ratio of the crown-pubis, pubis-heel measurements was 1.7:1 (normal 1.7:1 at birth and 1.6:1 at 6 months). Although the subcutaneous tissue of the arms and legs was abundant, the muscle mass was abnormally small. Sharply but irregularly outlined pigmented macules (café-au-lait spots), measuring 4 cm in greatest diameter, were present on the neck, back, and anterior

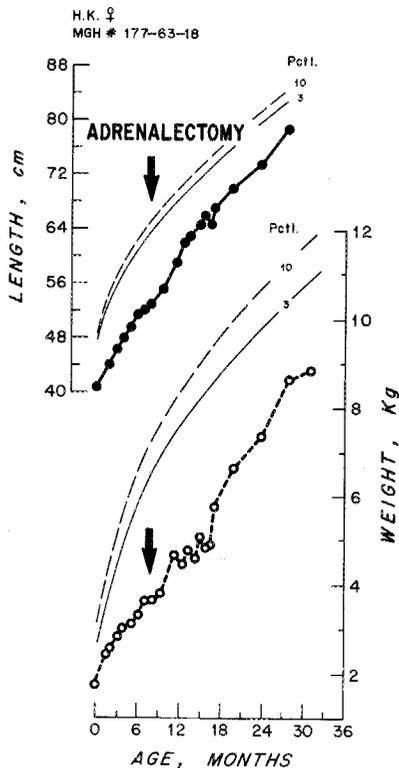


Fig. 1. Growth curves.

Table I. Adrenal function studies

	17-Keto steroids (mg/24 hr)	17-Hy- droxy steroids (mg/24 hr)	Cortisol ( $\mu$ g/dl)		Deoxy- cortisol ( $\mu$ g/dl)
			AM	PM	
No therapy	1.5 1.3	0.9 0.8	24	23	0.2
Dexamethasone					
0.2 mg, midnight			24		
0.5 mg, midnight			22		
0.5 mg, every 6 hr $\times$ 4 doses			32		
Metapyrone					
50 mg, every 6 hr $\times$ 4 doses			5		2.9
ACTH					
Control			22		0.2
1 hr after 25 U intravenous- ly	2.6	4.8	71		0.5
24 hr after 25 U intramuscu- larly	7.1	22	107		0.7
Normal	< 1.0	0.7	5-25	< 8	0.2

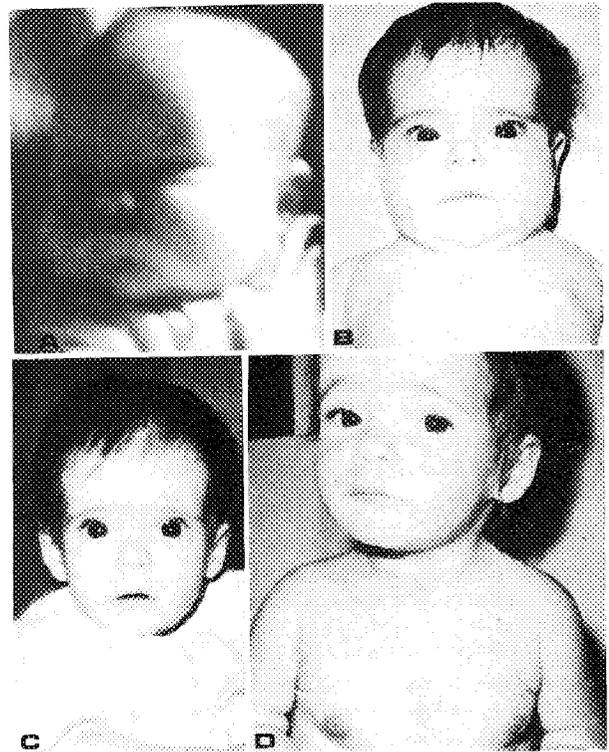


Fig. 2. A, Ballooned cheeks producing appearance of cushingoid facies, shortly after birth. B, Cushingoid facies and prominent breasts, age 6 months. C, Two weeks after bilateral adrenalectomy the cheeks had thinned, age 8 months. D, The breasts, having regressed after adrenalectomy, regrew greatly in size, while the face remained thin. Café-au-lait spots are present on the chest, age 20 months.

chest. Both breasts were enlarged and the areolae were deeply pigmented. Long, straight, dark hairs were present on the pubis, labia, and in the perianal region (Fig. 3). The vaginal mucosa was succulent and covered by abundant white mucus. No abdominal or pelvic masses were felt. The ovaries were not palpable on bimanual rectoabdominal palpation.

The hematocrit value was 35% and the white blood cell count was 16,800/mm<sup>3</sup> with a normal differential including 1% eosinophils. The total eosinophil count was 123/mm<sup>3</sup>. Concentrations of serum electrolytes, urea nitrogen, creatinine, and glucose were normal. A vaginal smear disclosed 4% superficial and 96% intermediate cells. Generalized demineralization with coarse trabeculation of the metaphyses and stippling of the epiphyses were evident on roentgenograms of the skeleton. Small, irregular lucencies were present in both ilia and ischia. The calvarium and sella turcica were unremarkable, and the skeletal maturation was that expected in a newborn infant. An intravenous pyelogram was normal. A split-skin preparation made from a café-au-lait spot and incubated with L-dopa disclosed fine pigment granules in the melanocytes of the type characteristic of Albright syndrome.<sup>7</sup>

The plasma cortisol was 24  $\mu$ g/dl at 8 AM (normal 5 to 25  $\mu$ g/dl) and 23  $\mu$ g/dl at 8 PM (normal less than 8  $\mu$ g/dl). The 17-

hydroxysteroids were 0.9 mg (normal 0.7 mg) and 17-ketosteroids were 1.5 mg/24 hours (normal less than 1 mg). The plasma 17-hydroxyprogesterone was 0.5  $\mu\text{g}/\text{dl}$  (normal less than 1  $\mu\text{g}/\text{dl}$ ) and the plasma testosterone 0.09  $\mu\text{g}/\text{dl}$  (normal less than 0.05  $\mu\text{g}/\text{dl}$ ). The urinary free cortisol was 72  $\mu\text{g}/24$  hours (normal less than 40  $\mu\text{g}/24$  hours) and the rate of pregnanetriol excretion was 0.2 mg/24 hours (normal less than 0.5 mg/24 hours). The plasma ACTH,<sup>8</sup> FSH,<sup>9</sup> and LH<sup>10</sup> were not detectable; the urinary FSH<sup>11</sup> was 0.8 IU/24 hours (normal less than 2 IU/24 hours). The plasma estradiol<sup>12</sup> was 806 pg/ml (normal prepubertal less than 7 pg/ml; menstrual 100 to 300 pg/ml), and the estrone<sup>12</sup> was 149 pg/ml (normal prepubertal less than 30 pg/ml). The serum thyroxine, free T<sub>4</sub>, and TSH values were 7.6  $\mu\text{g}/\text{dl}$ , 1.2 ng/dl, and 1.7  $\mu\text{U}/\text{ml}$ , respectively, all within normal limits.

The administration of dexamethasone had no effect on the levels of plasma cortisol (Table I), whereas the intravenous administration of ACTH resulted in a rise from 22 to 71  $\mu\text{g}/\text{dl}$  one hour later. The metyrapone test resulted in a blockade of cortisol production with no increment in plasma deoxycortisol levels, suggesting suppression of ACTH production.

At the age of 8 months, laparotomy was performed; both adrenal glands were enlarged and nodular and were removed in toto (Fig. 4). The ovaries were inspected and judged to be normal. Subsequently the infant was given 10 mg of cortisone acetate and 0.05 mg of fluorocortisone acetate daily. Two months postoperatively the cushingoid appearance was gone (Fig. 2, C), and the breasts had decreased in size. The vaginal smear contained 1% superficial and 99% intermediate cells.

Four months postoperatively, vaginal bleeding reappeared. Initially, the periods were irregular, occurring at intervals of one to three months and lasting two to five days, but within a year they had become monthly. Multiple determinations of plasma progesterone at various times between the cyclic bleeding always yielded levels less than 0.4 ng/ml, indicative of anovulatory cycles.

One year after the adrenalectomy, the breasts enlarged to a diameter of 5 cm (Fig. 2, D). Her appearance differed strikingly from that at the time of the first admission in that the cushingoid features and hypertrichosis were absent. Although her height was less than that of a normal girl, the skeletal maturation had increased rapidly. Thus the bone maturation (2 9/12 years) had exceeded the chronologic age (2 3/12 years) by six months. The weight age (8 months) and length (1 3/12 years) lagged behind.

Poor growth and the recurrence of signs of precocity led to a search for adrenal remnants or ectopic adrenocortical tissue. After cortisone therapy was briefly omitted the plasma cortisol levels became undetectable while estradiol levels remained very high. ACTH stimulation during a period when dexamethasone (0.4 mg daily) was substituted for cortisone produced no change in the plasma cortisol, testosterone, or elevated estrogen levels (Table II). These results and the lack of detectable FSH and LH in the plasma suggested that the ovaries rather than adrenal rests were the source of the hormones causing the sexual precocity and the inappropriately advancing skeletal maturation. Accordingly, laparotomy was performed; the left ovary was cystic and the right ovary appeared normal (Fig. 5). The left tube and ovary were

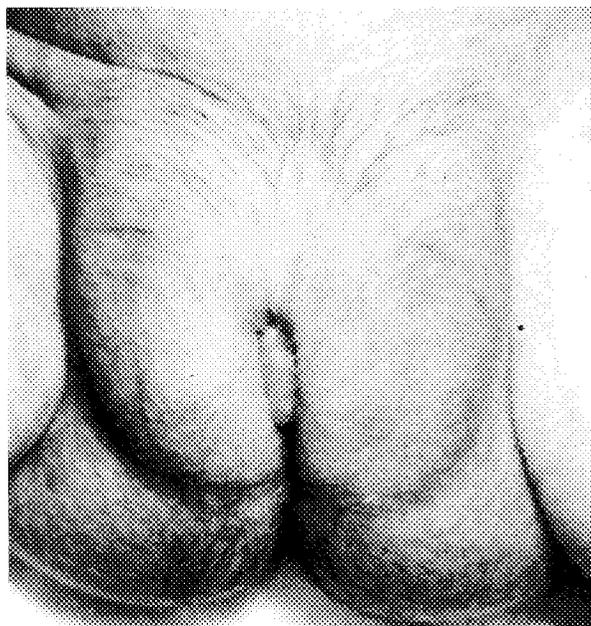


Fig. 3. Pubic hair, age 6 months.

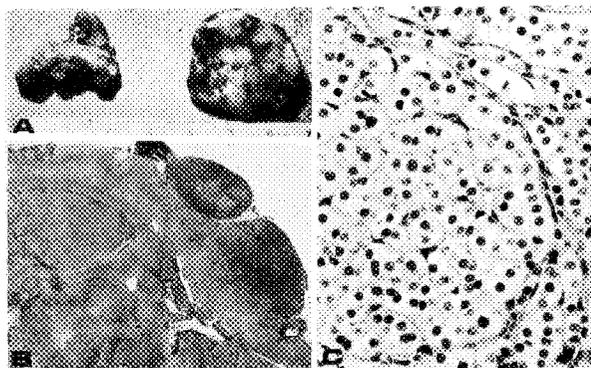


Fig. 4. A and B, Enlarged, multinodular adrenal glands. (Hematoxylin and eosin  $\times 4$ .) C, The hyperplastic nodules are composed of a uniform cell population of polygonal cells with a small central nucleus and copious granular cytoplasm. (Hematoxylin and eosin  $\times 320$ .)

Table II. ACTH (10 units IM for 2 days) stimulation test (15 months postadrenalectomy)

	Prestimulation	Day 2
Plasma		
Cortisol ( $\mu\text{g}/\text{dl}$ )	0.0	0.0
Testosterone ( $\mu\text{g}/\text{dl}$ )	0.02	0.02
Estradiol (pg/dl)	680	696
Estrone (pg/dl)	140	149
Urinary		
17-Ketosteroids (mg/24 hr)	0.1	0.1
17-Hydroxysteroids (mg/24 hr)	0.1	0.1

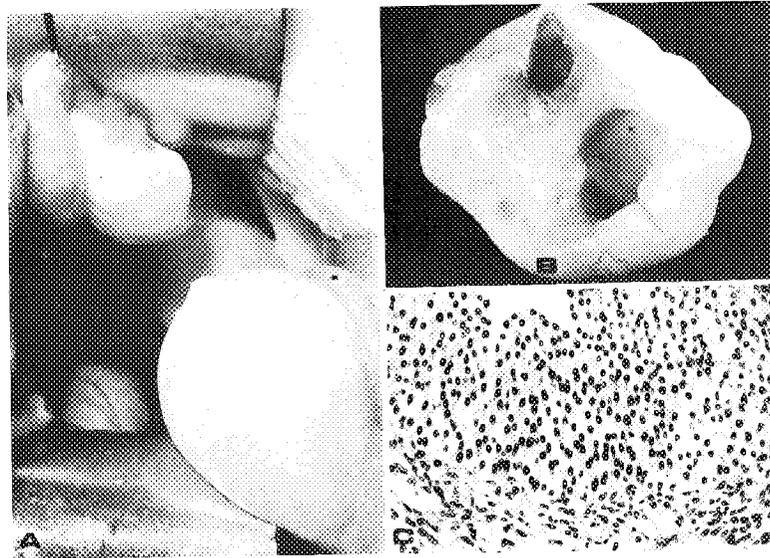


Fig. 5. A, Enlarged left ovary observed during laparotomy. B, Two cysts in bisected left ovary. C, The lining of the cysts is composed of a thick layer of luteinized granulosa cells and scattered clusters of luteinized theca cells. (Hematoxylin and eosin  $\times 230$ .)

removed and a wedge biopsy was taken from the right ovary. Postoperatively, the plasma estradiol levels fell to less than the lower limit of assay sensitivity (7 pg/ml) with a striking diminution of the estrogen effects on the vaginal epithelium, as reflected in cytologic smears. A significant increment in linear growth (1.9 cm) occurred in the 12 weeks after the operation.

#### **PATHOLOGY**

The left and right adrenal glands weighed 3.5 and 1.7 gm and measured  $2.5 \times 1.5 \times 1.5$  cm and  $2.5 \times 1.0 \times 1.0$  cm, respectively. Both were composed of numerous nodules 2 to 6 mm in diameter that microscopically were made up of a sheet of uniform polygonal cells (Fig. 4). The round to oval nuclei were small and the cytoplasm granular to eosinophilic. Neither mitoses nor pleomorphism was observed.

The left ovary measured  $2.8 \times 2.1 \times 1.6$  cm and contained two thin-walled cysts, 1 cm and 4 mm in greatest diameter (Fig. 5). The linings of their interiors were smooth and shiny with fine vascular markings; microscopically a layer of luteinized granulosa cells, 5 to 20 cells thick, and a deeper layer of luteinized theca cells lined both. The granulosa cells had central nuclei with single prominent nucleoli and large amounts of clear to eosinophilic granular cytoplasm. The theca layer was composed of small polyhedral cells with deeply staining cytoplasm interspersed among larger cells ballooned with vacuolated cytoplasm. Reticulin surrounded each theca cell. The granulosa and theca cells stained positively for lipids. The granulosa cells were larger in the small cyst, and the theca cells were more prominent in the larger cyst, but otherwise the two cysts were similar.

The biopsy of the contralateral ovary contained numerous primordial follicles and a single atretic follicle; no corpora lutea or albicantia were seen.

#### **DISCUSSION**

The Cushing syndrome in this infant probably began prenatally, a rare but documented event.<sup>13</sup> Shortly after birth the cushingoid facies were already evident (Fig. 2, A). The low birth weight, short stature, and disproportionately high ratio of body length above and below the pubis also suggested that intrauterine hypercortisolism was the cause of the retarded body growth.<sup>14</sup> Documentation of osteoporosis at the age of 6 months was additional evidence of hyperactive adrenal glands during prenatal life since corticosteroid therapy for at least 9 months is usually necessary before osteoporosis can be detected radiologically.<sup>15</sup>

The failure of dexamethasone to suppress the elevated levels of plasma cortisol and the lack of a marked rise of the plasma deoxycortisol after metapyrone administration suggested the adrenal hyperfunction was autonomous by the time the patient was first seen at age 6 months. When Cushing syndrome is due to excessive release of pituitary ACTH, the levels of plasma cortisol decrease substantially when 1.1 mg/m<sup>2</sup>/day (2 mg test) and 4.7 mg/m<sup>2</sup>/day (8 mg adult dose) of dexamethasone are given. Our patient, whose level of plasma ACTH was undetectable, received over 6 mg/m<sup>2</sup>/day of dexamethasone without stimulating production of ACTH. Although the plasma concentration of cortisol rose after ACTH administration in this infant and in other patients with primary nodular hyperplasia of

the adrenal gland,<sup>16</sup> this has not been interpreted as a sign of ACTH dependence, since cortisol production in these cases cannot be suppressed or can be suppressed only partially.<sup>17</sup>

Although the normal-appearing ovaries at the first operation together with the remission of the precocity after bilateral adrenalectomy appeared initially to implicate the adrenal glands as the source of the abnormal findings, it is possible that some if not the major source of the estrogen had come from unrecognized cysts in the ovary. The recurrence of sexual precocity with high estrogen levels, suboptimal growth (failure to catch-up), and the inappropriately advanced skeletal maturation was not due to ectopic adrenal tissue, since the plasma cortisol fell to zero with discontinuation of steroid replacement therapy and ACTH stimulation did not affect the levels of plasma cortisol, testosterone, and urinary 17-hydroxy and 17-ketosteroids. The ovarian origin of the plasma estradiol and estrone was subsequently demonstrated when their values fell abruptly to prepubertal levels after the functioning ovarian cysts were removed, an observation recorded in a patient with Albright syndrome, in whom all signs of precocity disappeared during a follow-up period of eight years.<sup>18</sup>

Although the coexistence of Cushing syndrome and Albright syndrome is rare,<sup>5, 6</sup> other endocrinopathies have been described more frequently. However, the interrelationships of the adrenal hyperplasia, the other endocrine disorders, and Albright syndrome is unclear. Hypersecretion of hypothalamic hormones has been suggested as one causal mechanism<sup>19</sup> and in at least one case the hypothalamus was probably involved, since mature spermatozoa were identified in a biopsy of the testicle of a 2-year-old boy with precocious puberty<sup>20</sup>; the absence of a Leydig cell tumor in this child precluded that the spermatogenesis was caused by excessively high levels of androgens produced locally.<sup>21</sup> Although a central mechanism may have initially triggered the formation of the adrenal hyperplasia and the luteinized ovarian cysts, they were probably already autonomous by the age of 6 months, the time at which the medical attention was sought. A detailed review of autopsy findings in Albright syndrome has shown that most endocrine glands are hyperplastic,<sup>22</sup> suggesting that the syndrome complex which Albright and his associates described may, in fact, represent an entity in which multiple organs initially or subsequently function in an autonomous fashion.<sup>23</sup>

#### REFERENCES

1. Benedict PH: Endocrine features in Albright's syndrome (fibrous dysplasia of bone), *Metabolism* 11:30, 1962.
2. Hamilton CR, and Maloof F: Unusual types of hyperthyroidism, *Medicine* 52:195, 1973.

3. Scurry MT, Bicknell JM, and Fajans SS: Polyostotic fibrous dysplasia and acromegaly, *Arch Intern Med* 114:40, 1964.
4. Ehrig V, and Wilson DR: Fibrous dysplasia of bone and primary hyperparathyroidism, *Ann Intern Med* 77:234, 1972.
5. Aarskog D, and Tvetaraas E: McCune-Albright's syndrome following adrenalectomy for Cushing's syndrome in infancy, *J PEDIATR* 73:89, 1968.
6. Benjamin DR, and McRoberts JW: Polyostotic fibrous dysplasia associated with Cushing's syndrome, *Arch Pathol* 96:175, 1973.
7. Benedict PH, Szabo G, Fitzpatrick TB, and Sinesi SJ: Melanotic macules in Albright's syndrome and in neurofibromatosis, *JAMA* 205:72, 1968.
8. Berson SA, and Yalow RS: Radioimmunoassay of ACTH in plasma, *J Clin Invest* 47:2725, 1968.
9. Odell WD, Parlow AF, Cargille CM, and Ross GT: Radioimmunoassay for human follicle-stimulating hormone. Physiological studies, *J Clin Invest* 47:2551, 1968.
10. Odell WD, Ross GT, and Rayford PL: Radioimmunoassay for luteinizing hormone in human plasma or serum. Physiological studies, *J Clin Invest* 46:248, 1967.
11. Midgley AR: Radioimmunoassay for human follicle-stimulating hormone, *J Clin Endocrinol* 27:295, 1967.
12. Nagai N, and Longcope C: Estradiol-17 and estrone: studies on their binding to rabbit uterine cytosol and their concentration in plasma, *Steroids* 17:631, 1971.
13. O'Bryan RM, Smith RW, Fine G, and Mellinger RC: Congenital adrenocortical hyperplasia with Cushing's syndrome, *JAMA* 187:257, 1964.
14. Blodgett FM, Burgin L, Iezzoni D, Gribetz D, and Talbot NB: Effect of prolonged cortisone treatment on statural growth, skeletal maturation and metabolic status of children, *N Engl J Med* 254:636, 1956.
15. Murray RO: Radiological bone changes in Cushing's syndrome and steroid therapy, *Br J Radiol* 33:1, 1960.
16. Meador CK, Bowdoin B, Owen WC, and Farmer TA: Primary adrenocortical nodular dysplasia: a rare cause of Cushing's syndrome, *J Clin Endocrinol* 27:1255, 1967.
17. Cohen RB: Observations on cortical nodules in human adrenal glands; their relationship to neoplasia, *Cancer* 19:552, 1966.
18. Senior B, and Robboy SJ: Case records of the Massachusetts General Hospital (Case 4-1975), *N Engl J Med* 292:199, 1975. (See discussion for follow-up of Pray LG: *Pediatrics* 8:684, 1951.)
19. Hall R, and Warrick C: Hypersecretion of hypothalamic releasing hormones: a possible explanation of the endocrine manifestations of polyostotic fibrous dysplasia (Albright's syndrome), *Lancet* 1:1313, 1972.
20. Benedict PD: Sexual precocity and polyostotic fibrous dysplasia. Report of a case in a boy with testicular biopsy, *Am J Dis Child* 111:426, 1966.
21. Steinberger E, Root A, Ficher M, and Smith KD: The role of androgens in the initiation of spermatogenesis in man, *J Clin Endocrinol Metab* 37:746, 1973.
22. MacMahon HE: Albright's syndrome—thirty years later, in Somers SC, editor: *Pathology annual*, vol 6, New York 1971, Appleton-Century-Crofts, Inc, p 81.
23. Danon M, and Crawford JD: Peripheral endocrinopathy causing sexual precocity in Albright's syndrome, *Pediatr Res* 8:368, 1974.