

ADRENOMEDULLARY DYSPLASIA AND HYPOFUNCTION IN PATIENTS WITH CLASSIC 21-HYDROXYLASE DEFICIENCY

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ABSTRACT

Background Glucocorticoids are essential for the normal development and functioning of the adrenal medulla. Whether adrenomedullary structure and function are normal in patients with congenital adrenal hyperplasia is not known.

Methods We measured plasma and urinary catecholamines and plasma metanephrines in 38 children with congenital adrenal hyperplasia due to 21-hydroxylase deficiency (25 children with the salt-wasting form and 13 with the simple virilizing form), 39 age-matched normal subjects, and 20 patients who had undergone bilateral adrenalectomy. Adrenal specimens obtained from three other patients with 21-hydroxylase deficiency who had undergone bilateral adrenalectomy and specimens obtained at autopsy from eight other patients were examined histologically.

Results Plasma epinephrine and metanephrine concentrations and urinary epinephrine excretion were 40 to 80 percent lower in the patients with congenital adrenal hyperplasia than in the normal subjects ($P < 0.05$), and the values were lowest in the patients with the most severe deficits in cortisol production. Urinary epinephrine excretion and plasma epinephrine concentrations were at or below the limit of detection of the assay in 8 (21 percent) of the patients with congenital adrenal hyperplasia and in 19 (95 percent) of the patients who had undergone adrenalectomy. In the group of patients with congenital adrenal hyperplasia, plasma epinephrine and metanephrine concentrations and urinary epinephrine excretion were approximately 50 percent lower in those who had been hospitalized for adrenal crises than in those who had not. In three patients with congenital adrenal hyperplasia who had undergone bilateral adrenalectomy, the formation of the adrenal medulla was incomplete, and electron-microscopical studies revealed a depletion of secretory vesicles in chromaffin cells.

Conclusions Congenital adrenal hyperplasia compromises both the development and the functioning of the adrenomedullary system. (N Engl J Med 2000; 343:1362-8.)

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CONGENITAL adrenal hyperplasia is characterized clinically by prenatal virilization and genital ambiguity in newborn girls, postnatal virilization in both boys and girls, and adrenal insufficiency with or without salt wasting.¹⁻³ Biochemically, the disorder is characterized by impaired production of cortisol with or without impaired production of aldosterone, chronic stimulation

of the adrenal cortex by corticotropin, and overproduction of cortisol precursors and androgens. The most common cause of congenital adrenal hyperplasia is 21-hydroxylase deficiency, with an incidence of approximately 1 case per 15,000 live births worldwide.¹ Despite adequate treatment with glucocorticoid and mineralocorticoid replacement, children with the classic or severe form of 21-hydroxylase deficiency remain prone to adrenal crises, hypoglycemia, and cardiovascular collapse in response to febrile illnesses or other stressful circumstances, even when their serum electrolyte concentrations are normal.^{4,5}

The two adrenal stress systems, the cortisol-producing cortex and the catecholamine-producing medulla, are closely linked ontogenetically, anatomically, and functionally.⁶⁻¹⁰ Glucocorticoids are important in the development and regulation of the adrenal medulla. We evaluated adrenomedullary function in patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency, in age-matched normal subjects, and in patients who had undergone bilateral adrenalectomy. We performed histologic evaluation of adrenal specimens obtained from three patients with congenital adrenal hyperplasia who underwent bilateral adrenalectomy and specimens obtained at autopsy from eight age-matched patients.

METHODS

Study Subjects

From November 1998 through April 2000, we studied 38 patients (24 boys and 14 girls; age range, 4 to 16 years) with classic 21-hydroxylase deficiency, 39 normal subjects (20 boys and 19 girls; age range, 5 to 17 years), and 20 patients (5 men and 15 women; age range, 26 to 66 years) who had undergone bilateral adrenalectomy because of familial pheochromocytoma (9 patients) or Cushing's syndrome (11).

The 38 patients with congenital adrenal hyperplasia were classified as having the salt-wasting or simple virilizing form of the disorder (Table 1). The 18 patients who had had a neonatal crisis with documented hyperkalemia and hyponatremia were classified as having the salt-wasting form, and the 10 patients (8 boys and 2 girls) in whom early virilization was diagnosed at an older age (mean age at diagnosis, 4 years; range, 2 to 6) were classified as having the simple virilizing form. In 10 patients, treatment was

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started at birth, thus preventing confirmation of the salt-wasting phenotype. Seven of these patients were classified as having the salt-wasting form of the disorder on the basis of a history of markedly elevated plasma renin activity or a salt-wasting adrenal crisis; the other three were classified as having the simple virilizing form. The number of adrenal crises requiring hospitalization was obtained from parental reports and medical records.

We performed histologic studies of adrenal glands from three patients with congenital adrenal hyperplasia who had undergone bilateral adrenalectomy because of difficult-to-control hyperandrogenism, severe salt wasting, or both (a 3-year-old girl,¹¹ a 5-year-old boy, and a 16-year-old girl¹²) and from eight patients with no known adrenal disease who had died of sepsis or trauma (age range, 4 to 15 years). The weight of the adrenal glands from the 3-, 5-, and 16-year-old patients with congenital adrenal hyperplasia (5, 26, and 52 g, respectively) was greater than the normal weight for their age,¹³ whereas the weight of the adrenal glands from the other eight patients (range, 3 to 6 g) was appropriate for their age. Before undergoing adrenalectomy, the three patients with congenital adrenal hyperplasia had received doses of hydrocortisone ranging from 15 to 30 mg per square meter of body-surface area per day, and they had received multiple courses of higher doses of glucocorticoids in the year before surgery, in an attempt to control excess androgen secretion.

The study was approved by the institutional review board at the National Institute of Child Health and Human Development and at each participating center. Each patient or a parent gave written informed consent, and children over the age of seven years gave their assent.

Hormone Measurements

At approximately 8 a.m., samples of blood were drawn into 10-ml heparinized tubes through an intravenous cannula in the forearm. In the patients who had congenital adrenal hyperplasia or who had undergone adrenalectomy, the samples were obtained before the usual morning doses of hydrocortisone and fludrocortisone. All the subjects (or their parents on their behalf) had been instructed to avoid the use of acetaminophen, which interferes

with the plasma normetanephrine assay, for at least five days before the blood samples were obtained. Once the cannula had been inserted, the subjects rested in a supine position for a minimum of 15 minutes before the blood was collected. Plasma was stored at -70°C until the assays were performed. Plasma epinephrine, norepinephrine, metanephrine, and normetanephrine were measured by liquid chromatography with electrochemical detection, as described elsewhere.^{14,15} Twenty-four-hour urine specimens were obtained for catecholamine measurements while the patients were taking their usual doses of glucocorticoids and mineralocorticoids. Urinary epinephrine and norepinephrine were measured by liquid chromatography (Mayo Medical Laboratories, Rochester, Minn.).¹⁶

Endogenous cortisol production (which reflects the adrenocortical reserve) was evaluated by obtaining from the medical record the maximal plasma cortisol concentration recorded either 60 minutes after the intravenous administration of 250 μg of cosyntropin (in 28 patients) or when plasma corticotropin and 17-hydroxyprogesterone concentrations were elevated because hydrocortisone had been withheld (in 10). Plasma cortisol was measured by fluorescence polarization immunoassay (TDX-FLX, Abbott Laboratories, Abbott Park, Ill.). Plasma 17-hydroxyprogesterone and corticotropin were measured by radioimmunoassay (Hazelton Laboratories, Vienna, Va.).

Immunohistochemical Studies

The adrenal glands were fixed in 4 percent formalin and embedded in paraffin. Thin sections (6 μm) were cut from the largest diameter of the gland, so that they contained both cortex and medulla. The sections were deparaffinized in xylene and hydrated in ethanol. Endogenous peroxidase activity was stopped by incubating the sections with 1.5 percent hydrogen peroxide and 10 percent methanol in phosphate-buffered saline for 10 minutes.

Adrenal chromaffin cells were stained with antibodies against chromogranin A (rabbit antihuman antiserum IgG antibodies, Dako, Hamburg, Germany) and tyrosine hydroxylase (Boehringer Mannheim, Mannheim, Germany), as previously described.⁷ Bound antibodies were detected by the linked streptavidin-biotin-peroxidase method (Dako), and the enzyme reaction was visualized

TABLE 1. CHARACTERISTICS OF CHILDREN WITH THE SALT-WASTING OR SIMPLE VIRILIZING FORM OF CONGENITAL ADRENAL HYPERPLASIA.*

CHARACTERISTIC	SALT-WASTING FORM (N=25)	SIMPLE VIRILIZING FORM (N=13)	P VALUE†
Female sex — no. (%)	10 (40)	4 (31)	0.58
Age — yr			
At diagnosis	0.03±0.03	2.8±1.9	<0.001
At enrollment	10.0±3.3	9.3±2.6	0.46
Hydrocortisone — mg/m ² /day‡	14.7±5.0	13.5±4.2	0.42
Fludrocortisone — μg /day‡	150±80	150±80	0.82
Maximal plasma cortisol — μg /dl§	2.1±0.8	3.6±1.2	<0.001
Adrenal crises requiring hospitalization — no.	1.8±2.0	0.3±0.6	0.002
Hospitalizations — no.¶	1.7±1.4	0.3±0.6	<0.001

*Plus-minus values are means \pm SD.

†P values were calculated with the use of a two-sided Student's t-test or the chi-square test.

‡The doses shown are the doses at the time of hormone measurements.

§The maximal plasma cortisol concentration was the value recorded either 60 minutes after the administration of cosyntropin or at a time when the plasma concentrations of corticotropin and 17-hydroxyprogesterone were markedly elevated (298±240 pg per milliliter [66±53 pmol per liter] and 7700±4700 ng per deciliter [231±141 nmol per liter], respectively). To convert the values for plasma cortisol to nanomoles per liter, multiply by 27.6.

¶The number of hospitalizations was the number that occurred during the first two years after the diagnosis of congenital adrenal hyperplasia.

with 3-amino-ethylcarbazole (Dianova, Hamburg, Germany). Monoclonal mouse antibodies against immunoglobulin were used as a negative control. All slides were counterstained with hematoxylin, rinsed in water, dehydrated, and mounted.

Electron-Microscopical Studies

Adrenal tissue was dissected and fixed with 2 percent formaldehyde and 2 percent glutaraldehyde in 0.1 M phosphate buffer at a pH of 7.3 for three hours. Tissue slices were then fixed for 90 minutes with 2 percent osmium solution in 0.1 M cacodylate buffer at a pH of 7.3, dehydrated in ethanol, and embedded in epoxy resin. Ultrathin sections were stained with uranyl acetate and lead citrate and were examined by electron microscopy.

Statistical Analysis

Two-sided Student's *t*-tests, chi-square tests, and analysis of variance with Scheffé's test were used to compare the results among the groups. Jonckheere's test was performed to analyze trends among the groups. Values are expressed as means \pm SD, unless otherwise specified.

RESULTS

Clinical Findings

At the time of the study, there were no significant differences in age or in hydrocortisone and fludrocortisone doses between the group of patients with the salt-wasting form of congenital adrenal hyperplasia and the group with the simple virilizing form (Table 1). In both groups, the adrenocortical reserve was markedly reduced, as assessed by the maximal recorded plasma cortisol concentration (normal value, $>18 \mu\text{g}$ per deciliter [497 nmol per liter]). However, the level of adrenal cortisol production was significantly lower in the patients with the salt-wasting form than in those with the simple virilizing form.

The mean number of adrenal crises requiring hospitalization and the mean number of hospitalizations during the first two years after diagnosis were significantly higher in the group with the salt-wasting form

than in the group with the simple virilizing form (Table 1). The distinction between the two forms of the disease was somewhat arbitrary, however, because two boys initially classified as having the simple virilizing form of congenital adrenal hyperplasia on the basis of their age at the time of diagnosis (two years and five months in one case, and three years in the other) subsequently had an adrenal crisis with documented hyponatremia and hyperkalemia during an acute viral illness.

Biochemical Findings

The patients with congenital adrenal hyperplasia and those with other disorders who had undergone bilateral adrenalectomy had significantly lower plasma epinephrine and metanephrine concentrations and urinary epinephrine excretion than the normal subjects (Table 2). The extent of the hormonal deficiencies was associated with the severity of adrenocortical dysfunction (the deficiencies were smallest in the group with the simple virilizing form, intermediate in the group with the salt-wasting form, and largest in the adrenalectomy group; $P < 0.001$). Values for plasma epinephrine and 24-hour urinary epinephrine excretion were at or below the threshold of detection in 19 of the 20 patients who had undergone adrenalectomy (95 percent) and in 8 of the 38 patients with congenital adrenal hyperplasia (21 percent); all the normal subjects had detectable values ($P < 0.001$ for the comparison of each group of patients with the normal subjects).

Plasma norepinephrine concentrations and urinary norepinephrine excretion were significantly higher in the patients who had undergone adrenalectomy than in the normal subjects. However, the patients with congenital adrenal hyperplasia did not have increased

TABLE 2. MEAN (\pm SD) PLASMA CONCENTRATIONS AND URINARY EXCRETION OF EPINEPHRINE, METANEPHRINE, NOREPINEPHRINE, AND NORMETANEPHRINE IN CHILDREN WITH CONGENITAL ADRENAL HYPERPLASIA (CAH), AGE-MATCHED NORMAL SUBJECTS, AND PATIENTS WHO HAD UNDERGONE BILATERAL ADRENALECTOMY.

MEASUREMENT*	NORMAL SUBJECTS	SIMPLE VIRILIZING CAH	P VALUE†	SALT-WASTING CAH	P VALUE†	ADRENALECTOMY	P VALUE†
Plasma epinephrine (pg/ml)	39 \pm 23	9 \pm 8	<0.001	8 \pm 7	<0.001	3 \pm 3	<0.001
Plasma norepinephrine (pg/ml)	187 \pm 45	174 \pm 98	0.98	170 \pm 81	0.95	290 \pm 188	0.008
Plasma metanephrine (pg/ml)	39 \pm 21	24 \pm 12	0.03	12 \pm 8	<0.001	2 \pm 2	<0.001
Plasma normetanephrine (pg/ml)	48 \pm 15	31 \pm 13	0.007	35 \pm 11	0.01	38 \pm 18	0.17
Urinary epinephrine ($\mu\text{g}/\text{day}$)	3.1 \pm 1.9	1.3 \pm 0.7	0.02	0.6 \pm 0.7	<0.001	Not detectable	<0.001
Urinary norepinephrine ($\mu\text{g}/\text{day}$)	23 \pm 6	23 \pm 8	0.99	18 \pm 8	0.60	42 \pm 39	0.02

*To convert the plasma values for epinephrine, norepinephrine, metanephrine, and normetanephrine to picomoles per liter, multiply by 5.46, 5.91, 5.08, and 5.46, respectively. To convert the urinary values for epinephrine and norepinephrine to nanomoles per day, multiply by 5.46 and 5.91, respectively.

†P values are for comparisons with the normal subjects and were calculated by analysis of variance with Scheffé's test.

values for plasma or urinary norepinephrine. Plasma normetanephrine concentrations were lower in the patients with congenital adrenal hyperplasia and in the patients who had undergone adrenalectomy than in the normal subjects, reflecting substantial production of the *O*-methylated metabolite in the adrenal medulla.^{17,18} The patients who had a history of an adrenal crisis requiring hospitalization had lower plasma catecholamine concentrations than the patients who had never been hospitalized for an adrenal crisis (plasma epinephrine concentration, 6 ± 4 vs. 12 ± 10 pg per milliliter [33 ± 22 vs. 66 ± 55 pmol per liter]; $P=0.05$; plasma metanephrine concentration, 13 ± 7 vs. 22 ± 13 pg per milliliter [66 ± 36 vs. 112 ± 66 pmol per liter]; $P=0.03$; and urinary epinephrine excretion, 0.6 ± 0.6 vs. 1.2 ± 0.9 μg per day [3.3 ± 3.3 vs. 6.6 ± 4.9 nmol per day]; $P=0.05$).

Histologic Findings

Light-microscopical studies of adrenal glands from three patients with 21-hydroxylase deficiency showed adrenocortical hyperplasia and poorly defined zones, with an irregular zona glomerulosa, zona fasciculata-like cells that reached the capsule, and extensive intermingling of cortical and chromaffin cells (Fig. 1A and 1B). Immunostaining with anti-chromogranin A showed that the formation of the adrenal medulla in the center of the gland was incomplete, with single cells and islets of chromaffin cells remaining within the adrenal cortex (Fig. 1B). Immunostaining with antibodies against tyrosine hydroxylase showed smaller amounts of the enzyme in chromaffin cells from the patients with 21-hydroxylase deficiency than in chromaffin cells from patients studied at autopsy (Fig. 1C and 1D).

Electron-Microscopical Findings

On the ultrastructural level, the normal adrenocortical cells contained ample smooth endoplasmic reticulum, with normal mitochondrial structure characterized by elongated tubulolamellar cristae in glomerulosa cells and round tubulovesicular cristae in zona fasciculata and zona reticularis cells (Fig. 2A). In the patients with 21-hydroxylase deficiency, the zona glomerulosa was irregular, and the subcellular adrenocortical structure was characterized by an abnormally large amount of cytoplasm with dilated smooth endoplasmic reticulum, large, round mitochondria, and poorly developed internal membranes (Fig. 2B).

The chromaffin cells in the normal adrenal glands had the typical ultrastructural features of neuroendocrine cells, with ample membrane-bound secretory vesicles and dense-core vesicles approximately 50 to 450 nm in their greatest diameter (Fig. 2C). In the normal adrenal medulla, there are two major types of vesicles: large, round or elongated, epinephrine-containing vesicles of medium density with a particulate substructure, and small, norepinephrine-containing

vesicles of high density within large, lucent vacuoles (Fig. 2C). In the patients with 21-hydroxylase deficiency, the secretory vesicles were depleted, and the remaining vesicles were primarily norepinephrine-containing, high-density vesicles within large, lucent vacuoles (Fig. 2D). The chromaffin cells were frequently intermingled with adrenocortical cells in the cortex.

DISCUSSION

We found that patients with classic 21-hydroxylase deficiency had both adrenomedullary dysfunction, characterized by reduced production of epinephrine, metanephrine, and normetanephrine, and major structural changes in the adrenal medulla, characterized by dysplasia, reduced expression of tyrosine hydroxylase, and depletion of epinephrine-containing secretory vesicles. The patients with the most severe phenotype, associated with salt wasting and a history of adrenal crises requiring hospitalization, had the lowest levels of adrenal production of epinephrine and metanephrine.

Chromaffin precursor cells start migrating into the adrenal anlagen in the sixth week of gestation and differentiate into mature chromaffin cells under the influence of adrenocortical steroids.¹⁹ High intra-adrenal glucocorticoid concentrations are necessary for the induction of phenylethanolamine *N*-methyltransferase, the enzyme that converts norepinephrine to epinephrine, and therefore for adrenal epinephrine synthesis.^{20,21} The low plasma and urinary epinephrine values in our patients with congenital adrenal hyperplasia may have been due to the lack of high intra-adrenal glucocorticoid concentrations at the time of the study or to faulty embryogenesis.

In normal adrenal glands, adrenocortical cells are frequently seen in the medulla, but outgrowths of chromaffin cells in the cortex are uncommon.^{6,7} In our study, the intermingling of the two types of endocrine cells was more pronounced in the patients with congenital adrenal hyperplasia than in the normal subjects, suggesting that congenital adrenal hyperplasia is caused by a developmental defect in the formation of the adrenal medulla.

In humans, epinephrine constitutes over 80 percent of adrenal catecholamine secretion,¹⁸ and epinephrine secretion can increase by a factor of more than 300 under stressful conditions.²² Patients with acquired secondary adrenal insufficiency have diminished basal epinephrine secretion, even with glucocorticoid-replacement therapy, suggesting that a high intra-adrenal glucocorticoid concentration is necessary for the maintenance of adrenal epinephrine synthesis.²³ Compensatory increases in sympathetic-nerve activity and norepinephrine secretion have been reported in patients with Addison's disease²³ and in those who have undergone bilateral adrenalectomy,¹⁷ but these changes did not occur in our patients with congenital adrenal hyperplasia.

Over 90 percent of circulating metanephrine and

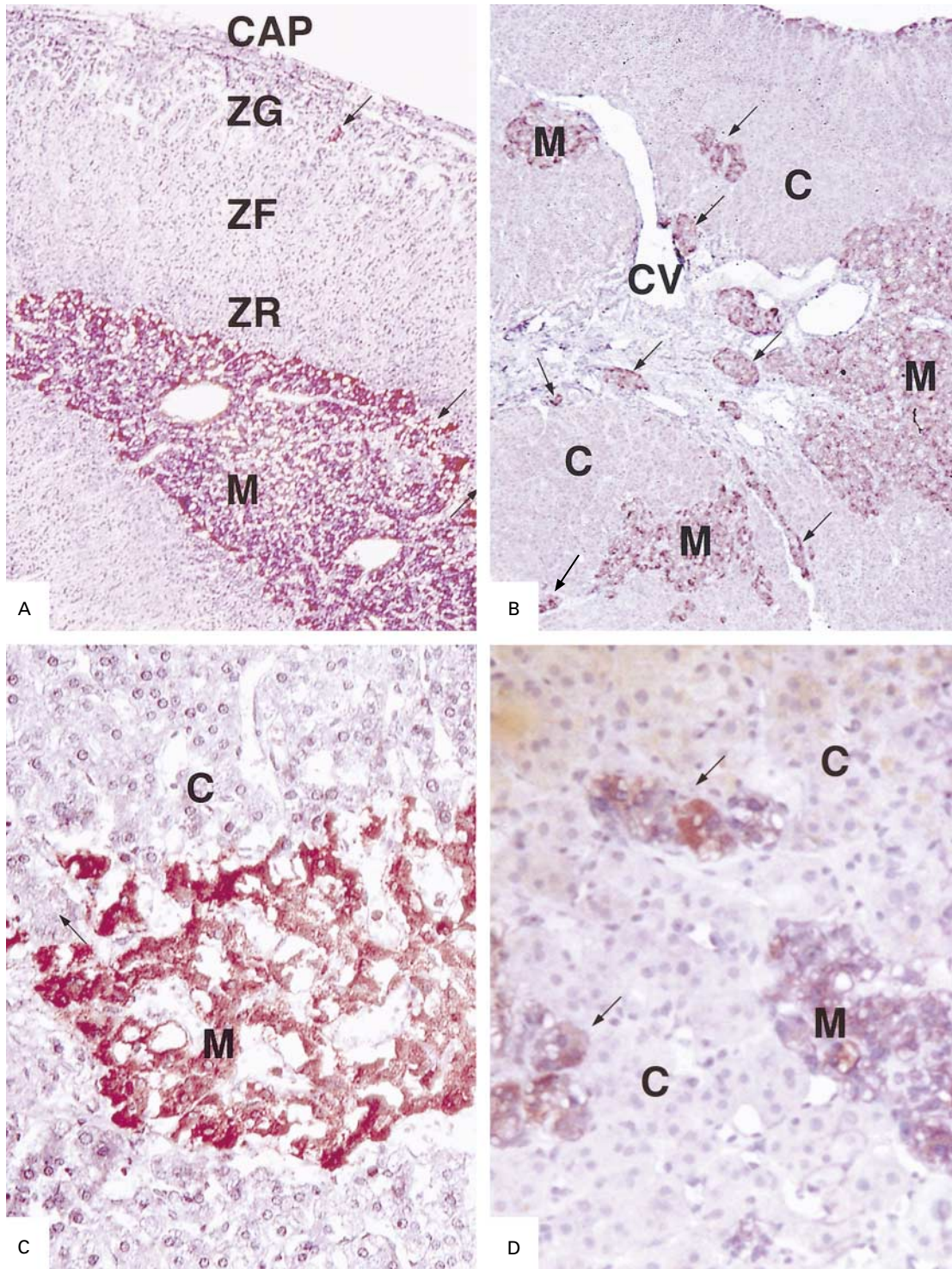


Figure 1. Immunostaining of Tissue from a Normal Adrenal Gland (Panels A and C) and an Adrenal Gland from a Patient with Classic 21-Hydroxylase Deficiency (Panels B and D).

Panel A shows well-defined zones as well as minimal intermingling of the chromaffin and cortical cells (arrows) in the normal adrenal gland ($\times 40$). Panel B shows hyperplasia, poorly defined zones, and pronounced intermingling of the chromaffin and cortical cells (arrows) in the adrenal gland from a patient with 21-hydroxylase deficiency ($\times 40$). Chromaffin cells were stained with anti-chromogranin A. Panel C shows staining with anti-tyrosine hydroxylase, with an irregular border between the adrenal cortex and the medulla (arrow), in normal adrenal medulla ($\times 400$), and Panel D shows reduced amounts of the enzyme in islands of chromaffin cells (arrows) from a patient with congenital adrenal hyperplasia ($\times 400$). In all four panels, the reactions were visualized with 3-amino-ethylcarbazole and hematoxylin (reddish-brown). M denotes medulla, ZR zona reticularis, ZF zona fasciculata, ZG zona glomerulosa, CAP capsule, CV central vein, and C cortex.

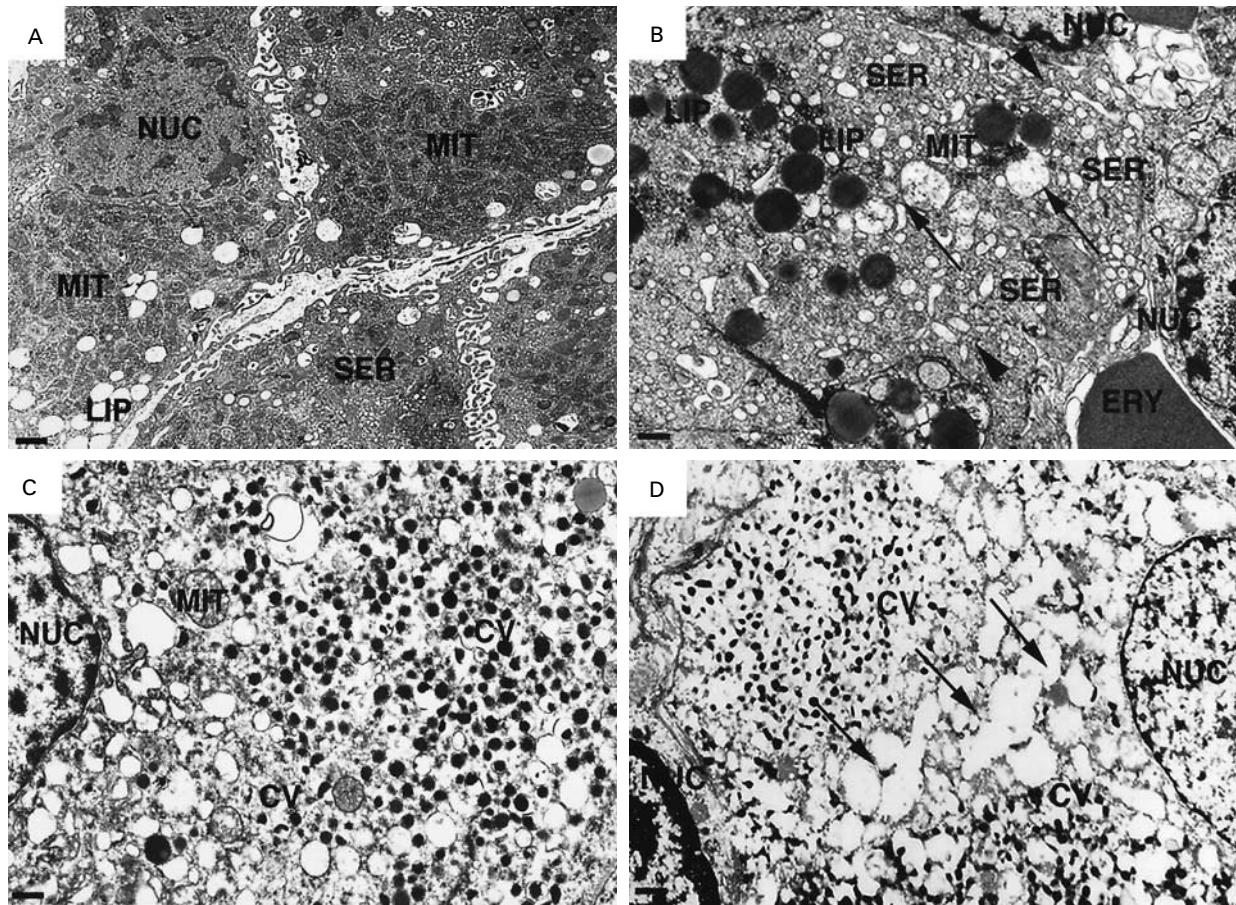


Figure 2. Electron Micrographs of a Normal Adrenal Gland (Panels A and C) and an Adrenal Gland from a Patient with 21-Hydroxylase Deficiency (Panels B and D), with Uranyl Acetate and Lead Citrate Staining.

Unlike normal adrenocortical cells (Panel A), those in a patient with 21-hydroxylase deficiency (Panel B) contain dilated smooth endoplasmic reticulum (SER) and large, round mitochondria (MIT), with sparse tubulovesicular internal membranes (arrows). Chromaffin cells with normal cytoplasm (Panel C) are filled with densely grouped catecholamine-containing secretory vesicles (CV), 50 to 450 nm in the greatest diameter. The majority of cells contain secretory vesicles with round or elongated, medium-density granules and a granular substructure of epinephrine-containing vesicles. In the adrenal gland from the patient with 21-hydroxylase deficiency, there is a conspicuous depletion of secretory vesicles, and the remaining vesicles are predominantly norepinephrine-containing, electron-dense vesicles lying in large lucent vacuoles (Panel D). The empty vacuoles are not secretory vesicles but vesiculated, rough endoplasmic reticulum (arrows). In all four panels, the bar represents 0.5 μ m. LIP denotes liposomes, NUC nucleus, and ERY erythrocyte.

up to 40 percent of circulating normetanephrine are produced from epinephrine and norepinephrine that have leaked from storage vesicles into the cytoplasm of chromaffin cells.^{17,18} This process is independent of exocytotic catecholamine release. Thus, unlike the low plasma and urinary epinephrine values, which reflect decreased adrenomedullary secretion of epinephrine, the low plasma concentrations of metanephrine and normetanephrine in patients with congenital adrenal hyperplasia reflect decreased adrenomedullary stores of both epinephrine and norepinephrine. This finding is consistent with the observation that adrenal epinephrine and norepinephrine are reduced in mice

with 21-hydroxylase deficiency,¹⁰ but it contrasts with the observation that adrenal epinephrine is decreased and adrenal norepinephrine increased in animals with reduced glucocorticoid synthesis.²⁴ Thus, decreased adrenomedullary secretion of epinephrine in patients with 21-hydroxylase deficiency may result not only from reduced phenylethanolamine *N*-methyltransferase activity but also from an overall decrease in catecholamine synthesis, which in turn may be related to the general changes we observed in the structural development of the adrenal medulla.

In our study, the group of patients with the salt-wasting form of adrenal hyperplasia had a larger mean

number of hospitalizations due to adrenal crises than the group with the simple virilizing form. Adequate glucocorticoid and mineralocorticoid replacement did not prevent hospitalization, suggesting that epinephrine deficiency may have had a role. However, non-compliance with treatment, inadequate doses of glucocorticoids when there was an intercurrent illness, or the physician's unease with outpatient treatment may have contributed to the decision to hospitalize a child.

Our findings have important clinical implications with regard to bilateral adrenalectomy as a treatment option for patients with congenital adrenal hyperplasia. Adrenalectomy has been proposed for selected patients in whom the disorder is difficult to control with conventional medical treatment.^{25,26} Opponents of this proposal argue that surgery may result in loss of the protective function of the adrenal medulla in times of stress. Our findings indicate that this protective function may already be absent in the most severe cases; thus, bilateral adrenalectomy may not pose this risk.

We conclude that congenital adrenal hyperplasia due to 21-hydroxylase deficiency not only affects the hypothalamic-pituitary-adrenal axis and the renin-angiotensin-aldosterone system but also severely compromises adrenomedullary secretion. The reduction in epinephrine secretion is probably due to a combination of the lack of intra-adrenal cortisol secretion and abnormal adrenomedullary formation.

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