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PROCEEDINGS

DEFECTIVE STEROIDAL BIOGENESIS IN CONGENITAL ADRENAL HYPERPLASIA

E. Mead Johnson Award Addresses

By Alfred M. Bongiovanni, M.D., and Walter R. Eberlein, M.D.
Children's Hospital of Philadelphia, and Department of Pediatrics, University of Pennsylvania

ADRENOGENITAL SYNDROME: UNCOMPLICATED AND HYPERTENSIVE FORMS

(Alfred M. Bongiovanni, M.D.)

Dr. Alfred M. Bongiovanni is a young man who started research work as an investigator at the Marine Biological Laboratory, Woods Hole, Massachusetts, even before he received his B.S. degree from Villanova College in 1940. While at Villanova, Dr. Bongiovanni received the Kolmer Medal for Excellence in Science. In 1943 he received his M.D. from the University of Pennsylvania, following which he immediately served a 2-year tour of duty in the United States Navy.

After discharge from the Navy, he filled residencies at the Children's Hospital of Philadelphia from 1947 to 1949. During the years 1949 and 1950, Dr. Bongiovanni served as Assistant Physician at the Rockefeller Institute in New York and in 1950-51 returned to the Children's Hospital of Philadelphia as Assistant Director of Clinics. In 1951 he was appointed the National Foundation of Infantile Paralysis Fellow to the Research Division of the Children's Hospital of Philadelphia. New opportunities and promotions quickly followed with an appointment as Assistant Professor of Pediatrics at Johns Hopkins in 1952; Senior Research Associate in the Pediatric Endocrine Division and Assistant Professor of Pediatrics at the University of Pennsylvania in 1954; and in 1955 Associate Professor of Pediatrics at the same university.

Dr. Bongiovanni is a Diplomate of the American Board of Pediatrics and a member of the Editorial Board of the American Journal of Medical Sciences and of numerous professional societies. In 1956 Dr. Bongiovanni received the Ciba Award.

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ADDRESS: (A.M.B.) 1740 Bainbridge Street, Philadelphia 46, Pennsylvania.
Dr. Bongiovanni has been author of about 50 articles, the great majority of which are on endocrinology and at least 23 of them with Dr. Eberlein, who is the co-recipient with Dr. Bongiovanni of this Award, as a co-author.

We are keenly aware of the honor bestowed upon us as the recipients of a Mead Johnson Award of this distinguished Academy. We accept it with humility and the resolve to apply ourselves more diligently to the problems of disease in children. We are grateful to the Committee on Awards, the members of the Academy and to the Mead Johnson Company. This recognition, accorded by our confreres, is deeply satisfying.

Our expression of gratitude would be woefully negligent without implicating the contributions of certain other people. We have both been happy victims of the “friendly persuasion” of one Joseph Stokes, Jr.—even when this becomes a more resolute “friendly pervasion,” it is always friendly and the experience is a gratifying one. One of us (A.M.B.) has for many years enjoyed the comfort of sound medical training and personal warmth under Dr. Stokes. The other (W.R.E.) is pleased to acknowledge his more recent but equal respect and affection for the guiding influence of a man well versed in the medical sciences and in the art of living, and working harmoniously and complacently in a world of many peoples. We are also indebted to Dr. Lawson Wilkins and Dr. Nathan Talbot, in whose departments we learned many things and initiated certain of our studies.

In 1657 William Harvey propheticallly stated: “Nature is nowhere accustomed more openly to display her secret mysteries than in cases where she shows traces of her workings apart from the beaten path; nor is there any better way to advance the proper practice of medicine than to give our minds to the discovery of the normal laws of nature by careful investigation of cases of rarer forms of disease. For it has been found in almost all things, that what they contain of useful or applicable nature is hardly perceived unless we are deprived of them or they become deranged in some way.” Archibald Garrod, while studying the disease known as alkaptonuria, enunciated certain principles bearing on the “inborn errors of metabolism.” Our own esteemed Irvine McQuarrie tells us that “in the course of investigations on the pathogenesis of strange clinical disorders occurring spontaneously in the human subject, enterprising clinicians have at times discovered previously unrecognized organ functions and interrelationships of functions which are of great importance.” McQuarrie stresses the importance “of the clinic in providing opportunity” for such studies.

A general formulation expressing the mechanisms at play in the “inborn errors of metabolism” (modified after Dent) is

\[ A \rightarrow B \rightarrow C \rightarrow D \]

**NORMAL**

- **DEFICIENT ENZYME**

  \[ A \rightarrow B \rightarrow C \rightarrow D \]

  (1) LACK OF D
  (2) EXCESS OF C

**Fig. 1.** Representation of biosynthetic pathway of substance D via various precursors, A to C. The specific enzymes are presented as solid dots. At the top of the figure, the normal course provides an adequate production of D, and either D or D' may be detected in body fluids. When an enzyme is absent, depending upon its specific function, one of the precursors may accumulate and be detected either in its original form (C) or as a slightly altered substance (C').
depicted in Figure 1. Consideration of those defects which reside largely in the kidney, and termed “deviations of metabolism” by Dent, has been omitted. In the normal course of events, substance D (which may represent hemoglobin, gamma-globulin, hydrocortisone or a number of other end-products in the biosynthetic pathways of man) is produced through a series of reactions involving several precursors (A, B and C) and the specific enzymes for each transformation. Normally, D is produced, serves its purpose, and may be excreted in the urine as a slightly altered substance, D'. Traces of the precursors or their urinary products may normally be present. Such traces of precursors are not generally to be regarded as evidence of derangement; it is doubtful, even in frank metabolic disease, that substances wholly alien to the organism will make their appearance. If one of the enzymes is lacking, wholly or in part, one of the precursors "piles up" and a substance regarded as abnormal may be detected in large amount in the biologic fluids.

If the abundant precursor is toxic, or if the normal end-product is essential to proper function, clinical expression of disease will ensue.

A number of diseases have been shown to arise from such defects and others are presumed to belong to this category of "inborn errors," pending further study (Table I). The adrenogenital syndrome due to congenital adrenocortical hyperplasia merits assignment to this group of disorders for reasons to be presented.

Much work by others, preceding and concomitant with our own, deserves mention, but time does not permit due recognition of all the investigators. Wilkins\(^5\) has worked long and diligently on this problem with many fruitful results. Several pieces of the puzzle, with specific reference to steroid metabolism, have been supplied by Barter, Miller, Dorfman, Kepler, Mason, Marrian, Butler, Kelley \textit{et al.}, Sydnor, Jailer, and many others cited previously.\(^6\) The work of Hechter\(^6\) on the biogenesis of adrenal steroids has been invaluable in the

<table>
<thead>
<tr>
<th>System (Disease)</th>
<th>Defective Enzyme</th>
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<tr>
<td>Carbohydrate Metabolism</td>
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<tr>
<td>Glycogen storage disease</td>
<td>glucose-6-phosphatase (1 type)</td>
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<tr>
<td>Galactosemia</td>
<td>P-gal-uridyl transferase</td>
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<td>Oxalosis</td>
<td>?</td>
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<tr>
<td>Endocrine System</td>
<td></td>
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<tr>
<td>Congenital adrenal hyperplasia</td>
<td>11-hydroxylase</td>
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<td>Goitrous cretinism</td>
<td>21-hydroxylase</td>
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<tr>
<td></td>
<td>de-iodinase</td>
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<td></td>
<td>coupling enzyme</td>
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<tr>
<td></td>
<td>oxidase</td>
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<tr>
<td>Proteins and Amino acids</td>
<td></td>
</tr>
<tr>
<td>Agammaglobulinemia, hemophilia, etc.</td>
<td></td>
</tr>
<tr>
<td>Porphyria</td>
<td></td>
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<td>Cystinosis</td>
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<td>Tyrosinosis, phenylpyruvic oligophrenia</td>
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<tr>
<td>alkaptonuria</td>
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<td>Connective Tissue and Misc.</td>
<td></td>
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<tr>
<td>Hypophosphatasa</td>
<td>alkaline phosphatase (? precursor)</td>
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<td>Hemolytic spherocytic anemia</td>
<td>&quot;enolase&quot;</td>
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<tr>
<td>Hereditary jaundice</td>
<td>&quot;glucuronic transferase&quot;</td>
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<tr>
<td>Wilson's disease</td>
<td>(ceruloplasmin)</td>
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<td>Sickle-cell disease</td>
<td>&quot;freak&quot; enzyme</td>
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<tr>
<td>Methemoglobinemia</td>
<td>&quot;reductase&quot;</td>
</tr>
<tr>
<td>Niemann-Pick, Gaucher's, Hurler's and Hand-Christian-Schuller diseases</td>
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elucidation of the adrenogenital syndrome in man.

The prime clinical manifestation of the adrenogenital syndrome due to congenital adrenal hyperplasia is early virilization in either sex, with pseudohermaphroditism in the female. The large excretion of 17-ketosteroids in the urine in this condition, representing excessive androgens, has been well known for some years. Our studies have also indicated that the urinary excretion of pregnanetriol (3α, 17α, 20α-pregnanetriol, No. 12 in Fig. 2) is uniformly increased in patients with this syndrome. The increased urinary excretion of this substance has proved to be of greater value in the diagnosis and treatment of this disorder than the 17-ketosteroids—particularly during the first year of life and in certain male children in whom the distinction from constitutional precocity cannot be made with certainty on the basis of the 17-ketosteroids alone. Pregnanetriol is the urinary product of an unduly abundant precursor of hydrocortisone (17-hydroxyprogesterone, No. 4 in Fig. 2).

Investigation of concentrations of hydrocortisone (Fig. 3) before and after stimulation with adrenocorticotropic hormone (ACTH), revealed a relatively poor synthesis of this essential substance by patients with the disease. This is further evidence for the aforementioned defect in steroidal metabolism. But it is to be noted that the defect varies in degree, is often not complete and that traces of the precursor or its product (pregnanetriol) are to be found normally.

The pathway of hydrocortisone synthesis is shown in Figure 2 (No. 1-6). Figure 2 indicates also the relative inability of the

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**Fig. 2. Schema of the normal biosynthesis of hydrocortisone (according to Hechter) with enzymatic blocks indicated for the uncomplicated form of congenital adrenal hyperplasia (A) and the variant associated with hypertension (B and B').**
affected adrenal gland to hydroxylate at carbon-21, for which reason an absence of the enzyme "21-hydroxylase" in the adrenal cortex is presumed. Due to the enzyme deficiency, hydrocortisone is not produced in normal quantities, and its precursor (17-hydroxyprogesterone) accumulates and is excreted in the urine as pregnanetriol.

A particularly interesting form of the syndrome is accompanied by hypertension. A female pseudohermaphrodite (Fig. 4), 9 years of age, reared as a male, presented the clinical features of the disease and an elevated blood pressure, 180/120. Although the amount of pregnanetriol excreted was greater than normal (6.6 mg/day), it was not so high as in other children this age, with the disorder. Furthermore, the concentration of corticoids in the serum was abnormally high without stimulation (24.7 to 26.2 \( \mu \)g/100 ml, normal 8.0 ± 1.0). The corticoid measured proved not to be hydrocortisone but another precursor, compound S (\( \Delta 4 \)-pregnene-17\( \alpha \), 21-diol-3, 20-dione, No. 5 in Fig. 2). The urine of this patient contained large amounts of the reduced metabolite of compound S (pregnane-3\( \alpha \), 17\( \alpha \), 21-triol-20-one, No. 9 in Fig. 2), and in addition, the reduced metabolite of desoxycorticosterone (pregnane-3\( \alpha \), 21-diol-20-one, No. 14 in Fig. 2).

The production of desoxycorticosterone, an intermediary metabolite, appeared to be responsible for the hypertension in this patient. The defect is somewhat different from that already described, and results from the lack of a second enzyme, 11-hydroxylase, in the abnormal adrenal cortex. No 11-

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**Table:**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Serum Corticoids (0.5 mg/kg)</th>
<th>ACTH Response (4 HR)</th>
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<td>Normal</td>
<td><img src="Graph.png" alt="Graph" /></td>
<td><img src="Graph.png" alt="Graph" /></td>
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<tr>
<td>Adrenogenital</td>
<td><img src="Graph.png" alt="Graph" /></td>
<td><img src="Graph.png" alt="Graph" /></td>
</tr>
<tr>
<td>Addison's disease</td>
<td><img src="Graph.png" alt="Graph" /></td>
<td><img src="Graph.png" alt="Graph" /></td>
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**Figure 3:** Concentration of hydrocortisone in the blood of 18 normal individuals and 16 with congenital adrenal hyperplasia, before and 4 hours after stimulation with ACTH, 0.5 mg/kg. The short horizontal bar denotes the value following stimulation. In general, the concentrations are lower and the response to stimulation poorer in the adrenogenital syndrome, but the exceptions bear testimony to the variability of the defect.
Figure 4. Patient D.V., female pseudohermaphrodite with congenital adrenal hyperplasia and hypertension.

Hydroxylated steroids (normally present) were found in the urine. In this instance, 21-hydroxylase is present, but the clinical manifestations of the disturbance are related both to an insufficiency of hydrocortisone and an overproduction of deoxycorticosterone.

This is the first time that endogenous deoxycorticosterone has been incriminated as a cause of hypertension in man. In all forms of the disease (Fig. 5) due to insufficiency of hydrocortisone, the anterior pituitary secretes large amounts of ACTH, which stimulates the defective adrenal cortex—however, the adrenal produces little or no hydrocortisone, but large amounts of androgens and certain intermediary metabolites as described.

The efficacy of replacement doses of hydrocortisone or its analogues in suppressing the clinical and chemical manifestations has been thoroughly studied by Wilkins. Suffice it to say that treatment...
with appropriate steroids is a specific remedy for the adrenogenital syndrome due to adrenocortical hyperplasia.

Aside from the elucidation of the causes of some clinical manifestations of the adrenogenital syndrome, these studies reveal the nature of steroidal biosynthesis in man. The deprivation of certain critical transformations in the production of hydrocortisone has uncovered many of the normal intermediary metabolites and suggests that the biogenesis of adrenal corticosteroids in man is similar to that described by Hechter in the bovine gland.

THE SALT-LOSING FORM OF CONGENITAL ADRENAL HYPERPLASIA

(Walter R. Eberlein, M.D.)

Dr. Walter R. Eberlein, the other co-recipient of this E. Mead Johnson Award, graduated from Harvard College in 1942 and Harvard Medical School in 1945. Following an internship at the San Francisco Hospital and a tour of duty in the Army of the United States, Dr. Eberlein served a year as a Graduate Assistant in Pediatrics at the Massachusetts General Hospital. From 1949 to 1954 several training and research experiences followed, including a Fellowship in Pediatrics at the Mayo Foundation, an Assistantship at the Kinder- spital in Zurich, Switzerland, a Fellowship in Pediatric Endocrinology at Johns Hopkins, and a Clinical and Research Fellowship at Massachusetts General Hospital. In 1954, Dr. Eberlein became an Instructor in Pediatrics at the University of Pennsylvania and in 1956 an Assistant Professor of Pediatrics.

Dr. Eberlein is a Diplomate of the American Board of Pediatrics and is a member of many professional societies. Dr. Eberlein has published 29 scientific papers, 23 of them with Dr. Bongiovanni.

Various laboratory studies have made it possible to define two abnormal forms of adrenal steroid synthesis in patients with congenital adrenal hyperplasia, and to explain biochemically why some patients with this disease develop systemic hypertension and others do not. However, the same studies have failed to uncover any difference in steroid synthesis in patients with the uncomplicated form of the disease and those who also develop a disturbance of electrolyte regulation, the so-called "salt-losers."

The latter form of the disease is common. It has come to be known since 1939 (when the first two cases were reported in detail by Butler, Ross, and Talbot and by Wilkins, Fleischmann, and Howard) that approximately one-third of all infants with congenital adrenal hyperplasia develop hyponatremia, hyperkalemia and dehydration during the first few weeks of life. This clinical picture closely resembles that seen in Addison's disease; by analogy, early investigators concluded that the salt-losing state was due to deficient production of an adrenal salt-retaining hormone, now known to be aldosterone. Three observations later suggested a different explanation. First, infants with this disorder often require administration of larger amounts of salt-retaining hormone, desoxycorticosterone acetate (DOCA), to correct the electrolyte disorder than do adults with Addison's disease. Second, the administration of ACTH causes some of these infants to lose even more salt. Finally and most recently, it has been shown that such infants excrete normal, or above normal, amounts of aldosterone in the urine. These facts have led some observers to conclude that in this form of the disease the hyperplastic adrenals secrete a salt-losing hormone, which either prevents the normal action of aldosterone or causes sodium diuresis in some other way. In the past, we have been unable to detect such a steroid in the urine, nor have we found any steroid metabolite in the urine of salt-losers which was not also present in the urine of patients who did not lose salt.

Recently we investigated this problem again. We chose for study 9 control subjects...
ranging in age from 6 days to 18 years, an adolescent boy with Addison's disease, and 12 untreated infants and children with congenital adrenal hyperplasia. A 24-hour specimen of urine was collected from each subject and analyzed for three groups of steroids, each of which served to measure the type and amount of adrenocortical secretion: 17-ketosteroids were assayed colorimetrically; pregnanetriol, the metabolite of 17-hydroxyprogesterone, by means of column chromatography; and tetrahydrocortisone, the metabolite of hydrocortisone, by means of paper chromatography.19 Figure 6 reveals that the excretion of 17-ketosteroids by 12 subjects with congenital adrenal hyperplasia greatly exceeded the normal and increased with advancing age. It is therefore obvious that the adrenals of these patients were not only structurally large (hyperplastic) but functionally active. It may also be seen that the adrenals of the salt-losers were particularly active.

Figure 7 shows the amount of pregnanetriol excreted by the various subjects. The normal adrenal cortex secretes only a small amount of 17-hydroxyprogesterone into the blood stream, as measured by the urinary excretion of the metabolite pregnanetriol. All 12 patients were found to excrete large amounts of the metabolite, indicating that their adrenals secreted large amounts of the

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**Fig. 6.** The shaded section of the graph indicates the amount of 17-ketosteroids excreted in the urine by normal children. Each circle in the figure represents the excretion of 17-ketosteroids by 1 of the 12 patients with congenital adrenal hyperplasia; the average excretion of the group is indicated by a line.
precursor. The amount increased with advancing age. Again there is a suggestion that the adrenals of the salt-losers were especially active.

Figure 7 depicts the excretion of pregnanetriol by subjects with congenital adrenal hyperplasia. The amount increased with advancing age. Again there is a suggestion that the adrenals of the salt-losers were especially active.

Figure 8 depicts the normal range (column 1) of excretion of tetrahydrocortisone in the urine; this product directly reflects the amount of hydrocortisone produced by the adrenal cortex. When the gland is atrophic, as in Addison’s disease (column 2), little hydrocortisone is secreted by the adrenal and hence little or no tetrahydrocortisone is excreted. Compare now the findings in the 12 patients with adrenal hyperplasia (columns 3, 4, 5). In five no tetrahydrocortisone was found in the urine; in two, only small amounts were detected. But note that five patients excreted normal quantities of tetrahydrocortisone.

This finding may seem surprising and even cast doubt upon the belief that in congenital adrenal hyperplasia the primary defect is an inability of the adrenal cortex to synthesize and secrete hydrocortisone normally, for here are five patients with the disease who appear able to do so. Closer examination of these five patients explains the discrepancy by defining what is meant by “normal synthesis of hydrocortisone.” The normality of this function of the adrenal cortex, in many ways its most important function, can be assessed by determining the efficiency with which the adrenal performs this task. The adrenal
must convert 17-hydroxyprogesterone into hydrocortisone efficiently to meet the changing needs of the body. The amount of 17-hydroxyprogesterone produced by the adrenal for this purpose can be estimated by measuring the amount of 17-hydroxyprogesterone which the adrenal cannot utilize, and which therefore escapes into the urine in the form of its metabolite (pregnanetriol). The amount of hydrocortisone synthesized from the precursor can be measured by the amount of tetrahydrocortisone excreted in the urine.

Figure 9 indicates that the normal adrenal cortex synthesizes hydrocortisone efficiently. Almost all the precursor (17-hydroxyprogesterone) is converted into hydrocortisone, and hence very little pregnanetriol is excreted. The opposite is true of the abnormal adrenal cortex of the five patients (col. 5, Fig. 8) who excreted normal amounts of tetrahydrocortisone. Large amounts of 17-hydroxyprogesterone were supplied for synthesis, but most of it could not be used; hence large amounts of the steroid were wasted and excreted into the urine in the form of pregnanetriol. One can calculate that the adrenals of these five subjects had to work 10, 50, even 100 times as hard as the adrenals of the control subjects to make the same amount of hydrocortisone from the precursor (17-hydroxyprogesterone). This was found to be true of all 12 patients with congenital adrenal hyperplasia. The normal subjects excreted 5 to 50 times as much tetrahydrocortisone as unutilized precursor. All 12 patients with the disease excreted very little tetrahydrocortisone compared to pregnanetriol. In none of the 12 patients, accordingly, were the adrenals able to synthesize hydrocortisone in a truly normal fashion.

The results of this study might seem to imply that the actual amount of hydrocortisone secreted by the adrenal in this disease is unimportant and should be ignored.
Quite the opposite is true. As far as normal metabolism is concerned, be it electrolyte regulation or carbohydrate and protein anabolism, the important consideration is certainly the amount of hydrocortisone being produced. The present study suggests that herein lies the basic difference between the salt-losing and the patient who retains salt but shows all the other features of the disease. In column 5 of Figure 8 are the five patients discussed at some length, in whom the adrenals were shown to secrete "normal" amounts of hydrocortisone. None of these five had a demonstrable salt-losing tendency. In column 3 are four patients who excreted no trace of tetrahydrocortisone. All four patients were active salt-losers. In between these two groups are three patients (Column 4) clinically suspected of being potential salt-losers. All three were found to have slightly low concentrations of sodium and some elevation of potassium in the serum, but none of the three was dehydrated. The serum electrolytes of all three returned to normal when hydrocortisone alone was administered. However, one of the three returned to the hospital several months later with an upper respiratory tract infection and by then had become an active salt-loser.

The present study has done more than merely substantiate the theory that hydrocortisone synthesis is impaired in all patients with congenital adrenal hyperplasia.
ADRENAL HYPERPLASIA

It has also shown that in spite of the impairment, in some patients, by virtue of tremendous adrenocortical overactivity, the adrenals manage to secrete enough hydrocortisone to maintain normal electrolyte balance, but obviously at the expense of normal growth and sexual maturation. These patients have the uncomplicated form of the disease. In other patients, the adrenal cortex is unable to synthesize an appreciable amount of hydrocortisone, no matter how hard it tries. These patients early in life develop a salt-losing tendency. Finally, this study suggests, there are patients whose adrenals can synthesize some, but by no means enough, hydrocortisone. These are the potential salt-losers; under conditions of stress their adrenals fail to make enough hydrocortisone to meet the increased needs of the body, and at such times they may become active salt-losers.

Judging from this study, the important difference between the salt-loser and the patient with this disease without a disturbed electrolyte regulation would seem to lie in the severity of the underlying enzymatic defect in hydrocortisone synthesis.

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