

- relationship to hair pigmentation in phenylketonuria. *Nature*, **179**:199, 1957.
56. Bickis, I. J., Kennedy, J. P., and Quastel, J. H.: Phenylalanine inhibition of tyrosine metabolism in the liver. *Nature*, **179**:1124, 1957.
 57. Weil-Malherbe, H.: Blood adrenaline and intelligence, in Proc. First Internat. Neurochemical Symposium, Oxford, 1955, p. 458.
 58. Munier, R., and Cohen, G. N.: Incorporation d'analogues structuraux d'aminoacides dans les protéines bactériennes. *Biochim. et biophys. acta*, **21**:592, 1956.
 59. Brawerman, G., and Yčas, M.: Incorporation of the amino acid analog tryptazan into the protein of *Escherichia coli*. *Arch. Biochem.*, **68**:112, 1957.
 60. Tarver, H., and Gross, D.: Incorporation of ethionine into the proteins of Tetrahymena. *Fed. Proc.*, **14**:291, 1955.
 61. Block, R. J., Jervis, G. A., Bolling, D., and Webb, M.: The amino acid content of tissue proteins of normal and phenylpyruvic oligophrenic individuals. *J. Biol. Chem.*, **134**:567, 1940.
 62. Schrappe, O.: Zur pathologischen Physiologie des Phenylbrenztraubensaure Schwachsinn. *Nervenarzt*, **23**:175, 1952.
 63. Brown, D. M., Armstrong, M. D., and Smith, E. L.: Studies on phenylketonuria IV. Serum proteins in phenylketonuria. *Proc. Soc. Exper. Biol. & Med.*, **89**:367, 1955.
 64. Hsia, D. Y., Driscoll, K. W., Troll, W., and Knox, W. E.: Detection by phenylalanine tolerance tests of heterozygous carriers of phenylketonuria. *Nature*, **178**:1239, 1956.
 65. Knox, W. E., and Hsia, D. Y.: Pathogenetic problems in phenylketonuria. *Am. J. Med.*, **22**:687, 1957.

CONGENITAL DEFECTS IN ADRENAL STEROID SYNTHESIS

By Alfred M. Bongiovanni, M.D.

Children's Hospital of Philadelphia, and Department of Pediatrics, University of Pennsylvania

SCRUTINY of the adrenocortical steroids excreted in the urine of patients with the adrenogenital syndrome (due to congenital adrenal hyperplasia) has afforded an opportunity to localize the biochemical defects attributable to an inborn error of metabolism and has elucidated the normal pathway for biosynthesis in the adrenal gland in man.¹⁻³ The studies of Hechter¹ on the biogenesis of hydrocortisone in the beef adrenal has indicated a stepwise oxidation of progesterone toward the fulfillment of the requirements for the final product, namely hydrocortisone. Hydrocortisone is indeed a "final product" in the economy of the pituitary adrenal axis: When its rate of secretion is low, larger amounts of adrenocorticotropin (ACTH) are released in an attempt to stimulate the adrenal cortex. If the target gland cannot properly synthesize hydrocortisone, the pituitary continues to stimulate the gland, which produces large

quantities of "abnormal" intermediary metabolites. Certain of these latter substances are androgenic and account for the clinical manifestations.

An oxygen function must be introduced into the progesterone molecule at carbons 17, 21 and 11 in order for the adrenal cortex to manufacture hydrocortisone. The oxygen is introduced at each position, presumably under the control of separate enzymes, tentatively termed "hydroxylases" and specified by the position they affect. If one or more of these enzymes is lacking, hydrocortisone is not produced, or is synthesized in limited quantities. Depending upon the particular enzymatic defect, the unusual metabolites measured in the blood and urine vary, as does the type of disease encountered.

In all forms of the adrenogenital syndrome, virilization is present. The disease is initiated *in utero* so that female infants

This work was supported by a grant (EDC-25-A) from the American Cancer Society and by a grant (A-619) from the National Institute of Arthritis and Metabolic Diseases, Public Health Service.

ADDRESS: 1740 Bainbridge Street, Philadelphia 46, Pennsylvania.

are generally born with ambiguous external genitalia, due to the influence of abundant androgens even before birth. In the male, the condition may not be recognized for some months or years, after the development of precocious puberty and extraordinarily rapid growth.

VARIETIES OF ADRENOGENITAL SYNDROME

Uncomplicated Form

In the commonest variety of the adrenogenital syndrome, in either sex, there appears to be little or no disturbance in the salt and water metabolism of the child. Under these circumstances, the major defect appears to lie in the 21-hydroxylase. Therefore hydrocortisone is not produced, since the oxygen function is not introduced into the molecule at C 21. The urine contains large amounts of 17-ketosteroids and pregnanetriol, both of which arise from precursors of hydrocortisone that are not efficiently converted into their usual end-product. Studies of the blood and urinary corticoids point to a lack of hydrocortisone.

It is important to indicate that in the uncomplicated form of the disease, small amounts of hydrocortisone are actually produced, but the efficiency of the mechanism is poor. Perhaps this means that the "defective gene" has carried a small but insufficient amount of the enzyme to the affected child's adrenal cortex. Treatment with small doses of hydrocortisone, or one of its many analogues, fulfills the requirements, and the disease abates chemically and clinically.

The chemical properties of the steroids isolated from the urine of untreated children (Table I) point to the absence of the oxygen function at C 21, although other species of compounds indicate that as a rule, no difficulty is encountered with the oxidation of C 11 and C 17.

Hypertensive Form

In rare instances, the adrenogenital syndrome is accompanied by high blood pres-

sure. Early studies of this condition revealed what appeared at first to be a paradoxical situation (Table I). The quantities of corticosteroids excreted ordinarily considered to represent hydrocortisone or its products, are quite large. However, isolation of the compounds reacting with the reagents ordinarily used, showed that the substance present in large quantity was not really hydrocortisone, but a molecule very close to it and devoid of an oxygen at C 11 (compound S). One of the intermediary metabolites which forms in this type of the disease is desoxycorticosterone. Ordinarily this latter substance (present in the adrenal cortex but in normal persons immediately oxygenated at C 11 and therefore transformed into corticosterone) remains unchanged in the disease, due to a deficiency of the enzyme responsible for oxidation at this position.

It appears that the hypertension is due to the production of desoxycorticosterone. Since the defect in this disorder does not involve a failure of hydroxylation at C 21, pregnanetriol excretion is not so high as in other forms of the condition. The pregnanetriol is somewhat above normal limits, probably due to a "backing up" one step behind the actual block.

Salt-Losing Form

In certain patients with the adrenogenital syndrome, there is rapid loss of salt and water beginning shortly after birth, and the general clinical and chemical characteristics of Addisonian crisis are present. Death may occur within the first few days of life unless treatment is instituted quickly.

Intensive studies directed at a differentiation of the enzymatic defect in this form of the disorder has failed to uncover any radically different picture than that present in the uncomplicated form of the disease. However those chemical findings described in the uncomplicated form (Table I) appear to be much more intense in the salt-losing variety of the adrenogenital syndrome. The excretion of pregnanetriol is greatest in this form of the disease and, while small

TABLE I
FORMS OF THE ADRENOGENITAL SYNDROME

	<i>Uncomplicated</i>	<i>Hypertensive</i>	<i>Salt-losing</i>
Virilization	Present	Present	Present
Blood pressure	Normal	High	Normal or low
Urine:			
17-ketosteroids	Elevated	Elevated	Elevated
pregnanetriol	4+	2+	6+
corticosteroids*	Low or normal	Elevated†	Decreased or absent
11-oxygenated steroids	Present	Absent	Present
Blood:			
corticosteroids*	Low or normal	Elevated†	Decreased

* Porter-Silber chromogens (17-, α 21-dihydroxy, α 20-keto).

† Not hydrocortisone.

amounts of hydrocortisone may be excreted in the uncomplicated type, there is virtually none in children with the addisonian picture.

For several years, numerous investigators have sought a salt-losing hormone as the cause of the form under discussion. We have been unable to discover any such substance in our laboratories. At the present time, we believe this particular type to be a variant of the uncomplicated form, in which the enzymatic defect is most severe. This does not preclude the role of a theoretic salt-losing hormone, but as of this presentation such a substance has not been described in the urine of these patients.

Nonetheless it is intriguing to consider that such a substance may exist for several reasons. Some weeks or months after the adrenal cortex of patients with the salt-losing form of the syndrome has been suppressed by treatment with cortisone (as indicated by lower excretion of 17-ketosteroids and pregnanetriol in the urine) the salt and water losses cease without any specific steroid therapy, such as desoxycorticosterone, directed at the control of salt and water metabolism. In addition, it has been known that under stress or upon the administration of ACTH, these patients may resume their loss of salt and water.

For the present, we suggest that the manifestations in children with this type of the adrenogenital syndrome are simply the result of extreme enzymatic defects which

are not truly different from those noted in the uncomplicated form.

GENETIC ASPECTS

Childs has presented evidence for a single, autosomal, recessive gene as the basis of the heredity of the disorder.⁴ He has estimated the gene frequency to result in an incidence of heterozygotes of 1 per 128 individuals in the general population. There was suggestive evidence for effects of the postulated gene in parents presumed to be heterozygotes. Clinical experience with families of children having this disorder, reveal an incidence in accordance with Childs' results. This knowledge is of value to the pediatrician called upon to advise the parents of an affected child with respect to future pregnancies.

REFERENCES

1. Hechter, O., *et al.*: The nature and biogenesis of the adrenal secretory product, in *Recent Progress in Hormone Research*, 6:515, 1951.
2. Bongiovanni, A. M., and Eberlein, W. R.: Clinical and metabolic variations in the adrenogenital syndrome. *PEDIATRICS*, 16: 628, 1955.
3. Bongiovanni, A. M., and Eberlein, W. R.: Defective steroidal biogenesis in congenital adrenal hyperplasia. *PEDIATRICS*, 21: 661, 1958.
4. Childs, B., Grumbach, M. M., and Van Wyk, J. J.: Virilizing adrenal hyperplasia: A genetic study. *J. Clin. Invest.*, 35:213, 1956.

CONGENITAL DEFECTS IN ADRENAL STEROID SYNTHESIS

Alfred M. Bongiovanni
Pediatrics 1958;21;1031

Updated Information & Services

including high resolution figures, can be found at:
<http://pediatrics.aappublications.org/content/21/6/1031>

Permissions & Licensing

Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
<http://www.aappublications.org/site/misc/Permissions.xhtml>

Reprints

Information about ordering reprints can be found online:
<http://www.aappublications.org/site/misc/reprints.xhtml>

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™



PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

CONGENITAL DEFECTS IN ADRENAL STEROID SYNTHESIS

Alfred M. Bongiovanni
Pediatrics 1958;21;1031

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://pediatrics.aappublications.org/content/21/6/1031>

Pediatrics is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. Pediatrics is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 1958 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 1073-0397.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

