Steroid Metabolism and Genetics

Kenneth Savard

The inclusion of the broad subject of steroid hormones in a symposium of inborn errors of metabolism is perhaps at this time somewhat premature. However, if one considers the influence of heritable enzymatic traits in the broad scheme of mammalian metabolism as it is emerging in present research, there can be no doubt of the role that genetics play in influencing the pattern of human steroid metabolism.

Steroids are peculiar compounds related in structure to cholesterol, and quite closely related chemically to each other. The profound differences in their pharmacologic properties reveal a subtlety of structure-function relationship which has not yet been entirely explored. The androgens, estrogens, progesterone, cortisol and aldosterone, all are synthesized in highly specialized endocrine tissues that, in contrast to the other tissues of the body, not only synthesize cholesterol but transform it further, by a rather well-delineated series of transformations into one or the other of these steroid hormones.

Studies in human endocrinology have revealed that certain critical quantities of each hormone are required by the body for the regulation and maintenance of its vital functions: androgen for development and maintenance of male characteristics, estrogen and progesterone in the menstrual cycle and in pregnancy, hydrocortisone for general metabolism and for meeting the demands of stress, aldosterone for salt and water balance. The actual amounts of hormones required daily for these individual processes must vary only within rather narrow limits.

From the Endocrine Laboratory, University of Miami School of Medicine, Miami, Fla. Presented at the Symposium on Inborn Errors of Metabolism, Aug. 28, 1960, Montreal, Canada.

*Investigator of the Howard Hughes Medical Institute.
Genetic Influences

Anatomical Development

Among the various genetic influences that affect the actual level of hormone production are those which determine the actual anatomical development and/or the presence of steroid-producing tissues—the testis and the ovary. The associated deficiencies or disturbances in the production of male and female sex hormones are found in the fascinating, and hitherto baffling, intersexes—the hermaphrodite and pseudohermaphrodite. In fetal sexual differentiation the steroids themselves play a relatively secondary and dependent role, serving only in later life to develop and maintain the already established sex structures. However, the presence and development of the gonads themselves are directly associated with the genes and the chromosomes.

In the normal human, 22 pairs of autosomes and 2 sex chromosomes make up the accepted chromosomal picture. The female has two X chromosomes and is usually referred to as having the XX chromosomal pattern. Occasionally, abnormalities occur in which one of the X chromosomes is absent. Individuals with this XO chromosomal pattern are characterized by gonadal agenesis and possess little if any gonadal tissue. Clinically they have been described as having a male or a female appearance. In these individuals with Turner's syndrome (1), there is no definitive steroid defect, only a deficiency of gonadal tissue.

In the male there are 44 autosomes, paired, and 2 sex chromosomes, X and Y. The male determinants on the Y chromosome apparently outweigh the excess of female determinants on the autosomes and the X chromosome. Abnormalities occur in which an additional X chromosome is present, which once more is associated with a failure in the normal development of gonadal tissue, but in this instance the failure involves mainly the development of germ cells. The result is sterile male individuals or pseudo-males with female habitus and incomplete testis tissue (Klinefelter's syndrome) or seminiferous-tubule dysgenesis (1).

In the course of the normal process of sexual differentiation it may be recalled that in early fetal life the gonad passes through a stage where it is sexually undifferentiated and bipotential. Hereditary factors, as set by the gene-chromosome complex, provide the environment or the stimulus for the direction in which the sexual differentiation will go. Although there are indications that the fetal
testis is directly involved in this differentiation process (2), no specific steroid compound is implicated in the process yet. The chromosomal anomalies just described, with their associated syndromes of gonadal agenesis and dysgenesis, have no direct effect upon steroid metabolism, but only an anatomical one upon the specific tissues in which the steroids are elaborated. The steroid hormones ultimately produced by the anatomically defective gonad apparently are consistent with the specific tissue resulting from the defective embryological growth (3).

**Biosynthesis**

Our second consideration is of those situations of apparently normal development of the endocrine tissue in which a genetic influence manifests itself by impairment or derangement in the biosynthesis of steroid hormones. The best recognized and studied is the adrenogenital syndrome, involving the biosynthesis of adrenal-cortical hormones.

**Adrenogenital Syndrome**

The adrenogenital syndrome, or congenital virilizing adreno-cortical hyperplasia, has provided some of the most inspired and ingenious studies in steroid biosynthesis in recent years. The recognition of the biochemical defect in this disease was the result of the brilliant application to the clinical aspects of this syndrome (8-10) of the basic discoveries of the enzymatic steps in the biosynthesis of the adrenal corticosteroids (11) and of their peripheral metabolism (12). In hydrocortisone synthesis, starting with progesterone, a series of hydroxylating enzymes occur, which introduce step-wise an atom of oxygen at three specific carbon positions on the steroid nucleus. For simplicity, we assume these steps to consist of: 1) 17-hydroxylation; 2) 11β-hydroxylation; 3) 21-hydroxylation, resulting in the formation of 11β,17α,21-trihydroxy-progesterone or hydrocortisone. Its circulating blood levels regulate the release of the regulating hormone ACTH: low plasma levels permit a release of ACTH from the anterior pituitary, high levels stop the release. The delicate balance between too much and too little hydrocortisone is maintained by the body in this way.

In the broad sense, in the adrenogenital syndrome the biochemical defect is that the adrenal cortex produces insufficient amounts of hydrocortisone to inhibit ACTH release by the anterior pituitary. This defect has been found to consist of a lack, or relative lack, of the...
21-hydroxylating enzyme or of the 11β-hydroxylating enzyme or in some instances of both enzymes. In all instances, insufficient hydrocortisone is produced to maintain normal pituitary ACTH-adrenal balance. The resultant ACTH-release increases total adrenal stimulation, causing bilateral hyperplasia and increased secretion of 11- or 21-desoxysteroids, the metabolites of which appear in abnormally high amounts in the urine. As secondary, but by no means clinically unimportant, consequences of this high but abnormal steroid biosynthesis, the adrenals secrete, (1) excessive amounts of androgen when the 21-hydroxylating enzyme is deficient; and (2) inordinate amounts of a salt-retaining steroid, 11-desoxycorticosterone (DOC) when the 11β-hydroxylating enzyme is deficient. In situation (1) a syndrome of congenital virilism results; in situation (2) hypertension results. A third form of this syndrome, the salt-losing variant, due to unknown biochemical causes, is characterized by the loss of electrolytes in the urine. As is well known, all three situations may be clinically reversed simply by the administration of the missing factor, hydrocortisone, or one of its current modifications (13).

To the author’s knowledge no chromosomal studies have been carried out on patients with this syndrome of adrenal virilism. However, the familial aspects of the disease has been studied and apparently associated with an autosomal recessive gene. While the clinical form of the disease varies among families, within a family with more than one affected sibling, only one of the forms of the disorder mentioned above will be found (14).

**Testicular Feminization Syndrome**

One less recognized syndrome, in which there is almost invariably a definite familial trait, is the testicular feminization syndrome, i.e., the syndrome of feminizing testes. In this particular form of the intersex problem, there may well be a distinct steroid hormone overtone. Individuals with this syndrome are characterized by their strikingly female appearance, with full breast development and generally distinct female habitus and comportment, but an absence of female genitalia. The testes are located in the pelvic region. The chromatin pattern is negative (male). Steroid production in these individuals is normal, the gonads respond to gonadotropins, and on their removal, symptoms of estrogen withdrawal appear. The biochemical basis of this syndrome is unknown as is also the chromosomal mosaic (1). The enzymatic defect of the gonads, if one exists,
may be in an excess of the enzymatic systems involved in the transformation of androgen to estrogen (6), a transformation which normal testis effects to a very small degree in vivo, but readily in vitro (6). Since this same transformation occurs peripherally (7), the biochemical defect may possibly lie in the "nonsteroidogenic" tissues. The disorder is transmitted through the maternal line and affects only males [i.e., male, according to chromatin pattern, (4,5)].

In the problem of the intersexes, the clinician was enormously aided by the discovery in 1949 of the chromatin blob (absent in males) on the nuclear border of cells of females (15). In consequence of the recent application of this discovery to humans (16), the current literature is replete with new solutions to problems of pseudohermaphroditism, gonadal dysgenesis, and aegnosis. It is not likely, however, that human chromosomal counts will supplant the now routine chromatin methods, at least not until less involved technics are developed. The importance of the fact that chromatin patterns must not be equated with chromosomal patterns is only too clearly emphasized by the current literature.

**Urinary Steroid Metabolites**

A further manifestation of familial or genetic factors in the overall steroid metabolism, only now beginning to emerge, is the 24-hour urinary levels of the metabolites of various specific hormones: aldosterone, corticosteroids, estrogens, 17-ketosteroids (androgens), pregnanediol (progesterone), etc. To those familiar with the clinical determination of these compounds, one impression is dominant—that there is no readily fixed value for any one of these steroid levels for healthy and apparently normal individuals. One is always struck by the fact that normal excretion levels are always expressed as a range for a particular age group, or sex. Deviation from this range of normal values, be it high or low, is considered pathological. Most always, these so-called normal values (or ranges) have been derived from a large number of individuals assessed once or, at the most, twice. The range of values of one steroid category or another, when graphed, would display the typical bell-shaped Gaussian distribution curve. Individuals whose urinary steroid values have been found to fall in a particular range in the above distribution, will, on re-study at later intervals, persistently show the same value, be it high, normal, or low. This has been observed by many analyzers of urinary steroids and the impression appears to be true for such categories of
urinary steroids as 17-ketosteroids, corticosteroids, estrogens, as well as specific steroids like dehydroepiandrosterone, aldosterone, estriol, etc. Thus, it would seem that the urinary level of steroids normally excreted by a particular person, will persist through that person’s healthy life, whether that level be at the high, low, or average range of normal. An individual’s urinary steroid pattern or profile thus will be somewhat characteristic of his total steroid metabolism and (like his amino acid, protein, carbohydrate metabolism) it will reflect his “biochemical individuality” (17).

It must be recalled that urinary steroid metabolite levels are the consequence of two metabolic factors: the total production of a specific hormone by the glandular source and the peripheral catabolism of the steroid so produced. Very few steroids have single urinary metabolites; all have alternate pathways of metabolism (12). The various enzymes responsible for these different pathways can vary according to the biochemical make-up of the individual.

Two important papers have recently appeared illustrating these points. The first is the observation of Bush and Mahesh (18), who studied the urinary 17-ketosteroids of a young woman with mild virilism. Her values were in the upper normal range, being made up of an abnormally high proportion of 11-oxygenated 17-ketosteroids (presumably derived from hydrocortisone). The twin sister, who had no clinical complaints, was examined and found to have the same unusually high proportion of 11-oxygenated 17-ketosteroids. The deviation from the normal level in these twins revealed a distinct familial determinant of the enzymatic factors controlling this aberrant, but clinically unimportant, steroid secretion pattern. A further and more striking relationship in urinary steroid levels is reported by Kappas and Gallagher in a set of male monozygotic dichorionic triplets (19). Two of the brothers possessed almost identical urinary 17-ketosteroid levels in the high normal range. On analysis, the urines showed impressively high levels of androsterone and etiocholanolone as well as the 11-oxygenated derivatives. These high values persisted during and following stimulation with ACTH. The data presented in this study of two of the triplets revealed a clear genetic determinant of the individual’s characteristic pattern of steroid hormone production and metabolism. It should be pointed out that the third brother possessed a characteristic steroid pattern, which, though different from and lower than his brothers,’ due to his imbalanced fetal blood supply, did show the reproducibility (at a 4-year
interval) of his characteristic urinary pattern and ACTH response. These two studies clearly demonstrate the determination by genetic factors of the individual profile of hormone elaboration and the pathway of metabolism to urinary products.

A reported manifestation of genetic influence in a secondary phase of steroid catabolism is the association of familial nonhemolitic jaundice with a partial deficiency in glucuronic acid conjugation of corticosteroids (20). This integrates the final biochemical step in steroid metabolism into the picture of inherited influences.

Conclusion

Although a clear distinction between anabolic and catabolic processes of steroid metabolism was not made in any of the above studies, the influence of genetic background upon the picture of over-all steroid metabolism can no longer be in doubt. It remains now for future studies to be carried out on normal people, not in their usual role as controls for their less lucky, diseased fellows, but rather as subjects of studies to establish the inherited capacity to elaborate and metabolize characteristic amounts of specific steroid hormones. At the present time, there is no evidence of any pathological significance to such correlations; perhaps all of them will be at a subclinical level. On the other hand, such mild conditions as irregular menses, idopathic hirsutism, premenstrual tension, all of whose hormonal causes have so far eluded investigators, may well be a reflection of genetic influence causing a slight derangement in the quantitative character of steroid metabolism.

References

4. Patterson, G., and Bonnier, G., Hereditas 23, 49 (1937).