ANDROGEN AND THE XANTHOMATOSES

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Hamblen, Arena and Cuyler [1] studied the output of urinary steroids which they classified as androgen in a case of Hand-Schüller-Christian disease. They found values ten times as large as the normal ones and felt that this increase was related to the general disturbance of lipoid metabolism rather than to an excessive activity of the gonads or of the adrenal cortex. Their patient, a male infant, did not excrete any sodium pregnandiol glucuronidate, a metabolite of secretion from the corpus luteum. After reading this report, we decided to assay the urine of a number of subjects with diseases of the skin classed as lipoidoses. This decision was based on the hypothesis that a relation exists between Hand-Schüller-Christian disease and at least some of the lipoidoses. This, however, is still a debatable subject, although cases of mixed varieties and transition states between have been reported and presented before various dermatologic groups.

METHOD OF STUDY

Subjects with various types of diseases of the skin, such as cutaneous xanthomatoses, were selected. Twenty-four hour urinary samples were extracted by a method which is a modification of that described by Dingemanse.[2]

The specimen of urine was acidified with 150 cc. of concentrated hydrochloric acid. The mixture was extracted with three separate samples of carbon tetrachloride (125 cc. each), a reflux condenser being used for two hours each time. The carbon tetrachloride fractions were united and evaporated to dryness under reduced pressure, and the residue was taken up in 100 cc. of ether. The ether was extracted in a separatory funnel three times with a saturated sodium bicarbonate aqueous solution and five times with 10 per cent sodium hydroxide. The

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1. Hamblen, E. C.; Arena, J. M., and Cuyler, W. K.: Hand-Schüller-Christian Disease: Report of Case in Which Urinary Androgens Were Titrated, Am. J. Dis. Child. **60**:352 (Aug.) 1940.

2. Dingemanse, E.; Borchardt, H., and Laqueur, E.: Capon Comb Growth-Promoting Substances ("Male Hormones") in Human Urine of Males and Females of Varying Ages, Biochem. J. **31**:500 (April) 1937.

ether was then washed with 10 per cent sulfuric acid and three times with distilled water. An aliquot part of the ether solution was decolorized with activated charcoal and evaporated to dryness under reduced pressure. The residue was taken up in 10 cc. of 60 per cent ethyl alcohol. Two cubic centimeters of a solution of metadinitrobenzene (2 Gm. in 100 cc. of 95 per cent alcohol) and 2 cc. of a 15 per cent aqueous solution of potassium hydroxide were added. Colorimetric estimation was made after ninety minutes with a spectrophotometer (technic of Neustadt [3]).

A sample of crystalline androsterone was dissolved in 60 per cent alcohol and treated with metadinitrobenzene and potassium hydroxide as previously described and used as a control. A blank solution was prepared by adding activated charcoal to ether and treated as described.

Relation of Excretion of 17-Keto Steroids to That of Total Cholesterol in Patients with Lipoidoses*

Patient	Disease	17-Keto Steroids, Mg. per 100 Cc. Blood	Total Cholesterol, Mg. per 100 Cc. Blood
L. P.	Xanthoma tuberosum and diabetes	17	410
P. G.	Xanthelasma	6	224
C. N.	Xanthoma tuberosum	19.3	363
J. N.	Necrobiosis lipoidica	19.5	195
M. K.	Xanthoma tuberosum	19.5	878
K. B.	Xanthoma disseminatum	6.0	205
E. G.	Necrobiosis lipoidica	8.0	157

* 17-keto steroids are a group of compounds which include the androgens. Some of them have biologic activity similar to the testis secretion, while others are inert. They originate in the gonads, in the adrenal cortex and possibly from other sources.

COMMENT

All investigators agree that at present the colorimetric procedure measures 17-keto steroids and not the true androgen. The term androgen usually refers to the comb growth–stimulating material, which is present in the urine in a lower concentration than that of 17-keto steroids. Assays were not made of the comb growth–stimulating material in our patients' urines, since the 17-keto steroids were within the normal range. Our method of assay differs from that of Hamblen and his co-workers only in minor details, and in our opinion their values should properly be called 17-keto steroids and not androgen. In their report and the photographs submitted, we have been unable to find evidence of increased production of androgen. In the cases of disturbance of lipoid metabolism we have studied, we have failed to find an elevation in the 17-keto steroids similar to that reported by Hamblen, Arena and Cuyler. We are unable to give any explanation for this discrepancy in results other than that the kinds of metabolic disturbance in the patients we studied

3. Neustadt, R.: Photo-Colorimetric Method for Determination of Androsterones in Urine, Endocrinology **23**:711 (Dec.) 1938.

are different in some essential from those in patients with Hand-Schüller-Christian disease. Are findings, such as those reported by Hamblen, Arena and Cuyler, of increased steroids a regular occurrence in Hand-Schüller-Disease? It appears from our results that an increase of the 17-keto steroids is not characteristic of the cutaneous xanthomatoses. The question arises then whether Hand-Schüller-Christian disease and the xanthomatoses familiar to the dermatologist belong to the same group of metabolic disease.

SUMMARY

A report is cited from the literature in which an increased quantity of androgen is stated to have been found in the urine of an infant with Hand-Schüller-Christian disease. Reasons are given for our belief that the material assayed was probably not androgen but should have been more properly labeled 17-keto steroids.

The urine of 7 subjects with varieties of lipoidoses contained normal quantities of 17-keto steroids. Androgen was not increased in amount. Our patients did not show clinical evidence such as is commonly present with increased quantities of androgen.

Since the results reported by Hamblen, Arena and Cuyler for Hand-Schüller-Christian disease and ours for the cutaneous xanthomatoses differ, the question arises whether the former disease belongs metabolically to the group of diseases which includes lipoidoses of the skin.