Urinary 17-Ketosteroids in Various Endocrine Disorders

A. A. Zakharycheva

The purpose of the present review of the literature is an examination of the contemporary data on the clinical diagnostic value of the determination of the 17-ketosteroid content in the urine in various disorders of the endocrine glands.

The basis of the chemical structure of the 17-ketosteroids is the perhydrocyclopentanophenanthrene ring. The 17-ketosteroids can be looked upon as derivatives of two hydrocarbons: androstane and etiocholane, which are distinguished from each other by the steric configuration around the fifth carbon atom. The 17-ketosteroids have a keto group at carbon atom number 17 of the given hydrocarbons. This makes possible their colorimetric determination by means of the Zimmerman color reaction (1951).

At the present time, more than 48 isomers of the 17-ketosteroids are known. The most important of these, which are present in the
urine of healthy persons, are: (1) androsterone, (2) etiocholanolone, (3) dehydroisoandrosterone (dehydroepiandrosterone), (4) 11-β-hydroxyandrostenedione, (5) 11-ketoandrostenedione or 11-β-hydroxyandrosterone, and (6) 11-ketoetiocholanolone or 11-β-hydroxyetiocholanolone.

FORMATION OF HORMONES

According to the data of Aberhalden (1952), Mason and Engstrom (1950), and Kandrac (1955), one third the amount of androgenic metabolites in men comes from testosterone, formed in the interstitial cells of the testes, while two thirds is formed in the zona reticularis of the adrenal cortex; in women, they are formed predominantly in the zona reticularis of the adrenal cortex and to a small extent in the ovaries. The same authors point out that, alongside the androgens, which are formed in the reticular zone, the adrenal cortex also synthesizes the corticosteroids, including both mineralocorticoids and glucocorticoids, the first being formed in the zona glomerulosa and the second in the zona fasciculata. The presence of this double function in the adrenal cortex has also been recognized by many other authors, for example: Deane and Greep (1946), Dalton, Mitchell, Jones, and Peters (1944), Swann (1940), Sarason (1943), and others. However, there are objections to this position in the literature. Thus, for example, Sonnenberg (1951), working with radioactive adrenocorticotropic hormone, came to the conclusion that the hormones which are necessary for metabolism (the glucocorticoids and mineralocorticoids) are formed in the interior part of the adrenal cortex (X zone), which appears to be the functional stratum in which, depending on the requirements of the organism, various hormones are also formed. The external part of the zona fasciculata and the neighboring zona glomerulosa seem to be a reserve stratum which only begins to produce the indicated hormones when the body’s requirements for them are increased.

Tarakanov believes that any of the cells of the adrenal cortex can produce any of the hormones. As proof of this, he points out that in tumors of the adrenal cortex (androsteromas), composed of dark cells, the formation of hormones goes primarily along the path of formation of androgenic substances. This idea is supported by the abrupt increase in the urinary excretion of 17-ketosteroids and by their high content in tumor tissue. In Tarakanov’s opinion, the cells of these tumors readily accomplish the biosynthesis of androsterone...
and dehydroisoandrosterone at the same time that small quantities of other steroid hormones are being formed in them.

In experiments on dogs, West, Hollander, Kritchevsky, and Dobriner (1952) showed that testosterone proceeds from the testes through the v. spermatica in the native state. Ultimately, the testosterone in the body is metabolized. Dauby (1940), Abderhalden, Frankson, Albaux-Fernet, Berton, and Robert (1953), Axelrod and Miller (1953), Charvat (1952), and many others have shown that the metabolism of testosterone takes place mainly in the liver and to a lesser degree in the kidneys, under the influence of enzymes which have still not been studied sufficiently (Samuels et al., 1950). In the liver, the testosterone, undergoing far-reaching chemical transformations, is inactivated and is excreted in the urine exclusively in the form of its metabolic products, the principal ones appearing to be androsterone and etiocholanolone. During this process, the free steroids are bound to proteins and to sulfuric and glucuronic acids.

The 17-ketosteroids are also formed in the adrenal cortex. Dehydroisoandrosterone, Δ^4-androstene-3, 17-dione, and 11β-hydroxy-Δ^4-androstene-3, 17-dione are reported from here.

Labbart (1952), L. Fizer and M. Fizer (1953), Dobriner and Lieberman (1950), and Fukushima, Dobriner, and Gallagher (1951) point out that the 17-hydroxycorticosteroids can be transformed into 17-ketosteroids by means of a chemical oxidation of the side chain, which, according to Axelrod and Miller, takes place in the liver. The authors suggest that this reaction is irreversible.

Fukushima et al. point out that from one third to one half of the androsterone and etiocholanolone excreted with the urine in men is the result of the endogenous production of testosterone, while from one half to two thirds comes from the adrenal cortex.

Consequently, 17-ketosteroids are formed in the body in three ways: (1) from testosterone, as the result of its metabolism, (2) from cholesterol-like substances in the adrenal cortex, and (3) from the 17-hydroxycorticosteroids by way of chemical oxidation of the side chain.

The 17-ketosteroids having a hydroxyl group at the third carbon atom are divided into the α and β forms, depending on the configuration of this group in relation to the plane of polarization of the molecule. The β-ketosteroids come exclusively from the adrenal cortex and normally constitute 5–15 per cent of the total amount of 17-ketosteroids; at the same time, the α-ketosteroids, which are found in
larger amounts, originate in both the adrenal cortex and the testes (Mason and Engstrom, 1950; Talbot, Butler, and Lacklon, 1940; Kandrac; and others).

EXCRETION

The daily excretion of 17-ketosteroids depends on the age and the sex.

Studies of the 17-ketosteroid content in the urine of healthy persons have shown that the largest quantity is observed between the ages of 18 and 40 years. The excretion of 17-ketosteroids is decreased in persons over 40 years of age.

According to the data of some authors, the daily excretion of 17-ketosteroids is almost identical in boys and girls up to 13 years of age. In the fifth year of life, it amounts to an average of 2.5 mg. in boys and 2 mg. in girls; in the tenth year of life, it is 8 and 7 mg., respectively; in the fifteenth year, it is 11 and 9 mg. In men between the ages of 20 and 40, the average excretion of 17-ketosteroids amounts to 16 mg./day, fluctuating between 10.5 and 22.4 mg., while in women the average is 10 mg./day with fluctuations between 7 and 17.5 mg.; from 50 to 60 years of age, the average is 8 to 10 mg./day in men and 6 to 8 mg./day in women. In the declining years (from 70 to 85) the daily excretion of 17-ketosteroids has fallen to 3 to 5 mg. in both men and women (cited by Abderhalden). Callow and Callow (1939), Hamburger (1948), Kirk (1949), Kenigsberg, Pearson, and McGavack (1949), and others report essentially the same normal values.

The data on the normal urinary content of 17-ketosteroids which have been reported by native authors also agree with the data of the foreign authors. According to the data of Shul'tsev (1951), the average daily excretion of 17-ketosteroids in man amounts to 15–16 mg. with fluctuations between 9.8 and 25 mg., while in women it is 10.5 mg. with fluctuations from 5–6 to 15.3 mg.; according to the data of Uvarovskaya (1951), the average is 14.2 mg. in man, with fluctuations between 8 and 17 mg., and 11.2 mg. in women with fluctuations from 7 to 14 mg.

Miloslavsky (1954), examining the urine of 68 healthy persons between 18 and 69 years of age, obtained an average 17-ketosteroid excretion in men of 15.32 mg./day with fluctuations between 10.52 and 27.15 mg., while in women the average was 12.55 mg./day with fluctuations between 9.72 and 23.2 mg.

Voigt, Schroder, Beckmann and Rosenkilde (1955), using the meth-
od of Zimmermann (modifications of which were also used by the preceding authors) for the determination of the urinary 17-ketosteroids, but with removal of chromogens from the final ether extracts by Girard’s Reagent T according to the method of Holtorff and Koch (1940), report a lower urinary 17-ketosteroid content in healthy persons of all ages than was previously reported in the literature.

For example, in men between 18 and 40 years of age, the values only fluctuated between 5 and 12.5 mg./day; in women of the same age, they were between 6 and 10.5 mg./day.

Due to the relative complexity of freeing the ether extracts from chromogens, this method of determining urinary 17-ketosteroids has not yet received wide distribution. It is necessary to take into consideration the fact that, in the present stage of the study of the hormones, the normal values reported in the work of Voigt, Schroder, Beckmann and Rosenkilde cannot be compared with the normal values of all the previously mentioned authors, the more so since Schere (1953) has reported that the daily quantity of 17-ketosteroids determined in the urine is decreased by 5–60 per cent after the removal of chromogens from the ether extracts by the Girard reagent.

The urinary 17-ketosteroid content in persons of the same age is different on various days and at various times of the day.

In healthy persons between 18 and 35 years of age, the average variation among daily determinations is 1.5–2 mg. (Reiss, Hemphilli, Gordon, and Cook, 1949; Voigt, Schroder, Beckmann, and Rosenkilde, 1955; and others). At night time (from 11 o’clock in the evening to 7 o’clock in the morning), the 17-ketosteroid excretion is less; in the morning (between 7 and 11 o’clock), the excretion is the greatest; during the day (from 11 o’clock in the morning to 11 o’clock at night), the excretion is somewhat decreased but does not reach the low values of the nighttime excretion. For example, 2 mg. are excreted at night, 4 mg. in the morning, and 3 mg. during the day, or it might be 9, 13, and 11 mg., respectively (Pincus, 1943; Pincus, Romanoff, and Carlo, 1948).

During physical and emotional stress, the excretion of 17-ketosteroids is significantly increased. For example, the 17-ketosteroid excretion is increased in sportsmen during a race or other physical exertion. It has been noted that the amount of 17-ketosteroids is significantly higher in patients when they are admitted to a clinic than on the following days during their hospital stay (Pincus, 1943; D ingemanse and Huis in’t Veld, 1950; Baylis is, 1955; and others).
Meteorologic factors such as rain and snow decrease the excretion of 17-ketosteroids; their excretion is increased on a sunny day (Zimmerman and Hofschlaeger, 1953).

The excretion of 17-ketosteroids does not depend on the urinary volume or on the intake of fluids (Pincus, 1943; Appel, 1952; Zimmerman and Hofschlaeger, 1953).

The urinary excretion of 17-ketosteroids can be decreased in connection with many types of effect on the organism. During the first 24 hours after acute trauma, chills, burns, fractures, operations, and other factors, an increase in the urinary 17-ketosteroids is noted which exceeds the upper limit of normal and sometimes reaches 25–30 mg./day. One to three days later, the excretion of 17-ketosteroids falls to extremely low values (2–3 mg. per day), but rises to normal again with the approach of recovery. In weakened patients, this reaction is either not observed or is usually very weak (Mason and Engstrom, 1950; Abderhalden, 1952). Correspondingly, hyperplasia and sometimes also atrophy of the cells are found during histologic studies of the adrenal cortex in experimental animals (Rokhлина, 1941; Yusfina, 1949; Dingemanse et al., 1950). In this case, the hyperfunction of the adrenal cortex should not be considered pathologic but as a secondary protective reaction to the irritation, i.e., as a physiologic measure against the disease.

**CONTENT IN URINE**

Notwithstanding the fact that a decrease or lapse in function occurs during a primary disorder of the sex glands (eunuchoidism, hypogenitalism, castration, and so forth), the urinary 17-ketosteroid content can be either decreased, normal, or even increased in these cases.

According to Abderhalden, the average daily excretion of 17-ketosteroids in castrated men is 3.5 mg., with fluctuations between 0.3 and 7 mg./day. At the same time, the content of gonadotrophic hormones in the blood and their excretion in the urine are sharply increased in these patients. However, Voigt, Schroder, Beckmann, and Rosenkilde point out that, alongside a normal excretion of 17-ketosteroids, a moderate increase in their excretion can also be observed in castrated individuals. They explain this increase as a compensatory increase in the function of the adrenal cortex.

Kandrac showed that the normal or increased excretion of 17-keto-
steroids in castrated individuals is brought about by an increased formation of dehydroisoandrosterone (the adrenal fraction). At the same time, the excretion of adrosterone and etiocholanolone was significantly decreased.

According to the data of Werner (1943), the quantity of 17-ketosteroids was significantly decreased in only one third of 16 patients with eunuchoidism, while in the remaining patients it fluctuated within normal limits (from 7 to 17 mg./day). Other foreign authors have reported a significantly decreased excretion of 17-ketosteroids in eunuchoidism, amounting on the average to 5 mg./day (with fluctuations between 2 and 8.25 mg.).

In women after ovariectomy and during the climacteric, the quantity of 17-ketosteroids excreted can be as low as in the normal but can also be moderately increased. According to Abderhalden, in the first case, the 17-ketosteroid content of the urine varies from 0.5 to 6 mg., averaging 3 mg./day, while in the second case it varies from 0.5 to 10 mg., averaging 6–7 mg./day. Uvarovskaya detected a normal 17-ketosteroid content—from 7 to 16 mg., averaging 13 mg./day—in women during the climacteric.

Voigt and his coworkers point out that the 17-ketosteroid content is usually increased in most women during the climacteric.

The presence of an increased 17-ketosteroid excretion at the climacteric should be explained by a compensatory increase in the function of the adrenal cortex.

**DISEASE DISTURBANCES**

As is well known, in Itsenko-Cushing’s disease, there is an initial disturbance of the diencephalohypophyseal system which is accompanied by an increase in the function of the anterior lobe of the pituitary and an increased production of tropic hormones (N. M. Itsenko, 1946; E. A. Vasyukova, 1952). Under the influence of the increased production of ACTH, hyperfunction of the adrenal cortex develops. Therefore, one can expect an increased urinary excretion of 17-ketosteroids in this disease.

According to data obtained on adult patients with Itsenko-Cushing’s disease at the clinic of the All-Union Institute for Experimental Endocrinology (O. M. Uvarovskaya), the 17-ketosteroid content in a 24-hour urine averaged 11–12 mg. in 44 cases (with fluctuations between 5 and 29 mg.).

Out of 16 patients with Itsenko-Cushing’s disease examined by
Miloslavsky (1954), 4 had a normal content but in the remainder it was increased; the average 17-ketosteroid content in men was 23 mg./day with fluctuations between 12 and 29, while in women it was 20 mg./day with fluctuations between 8 and 30.

Benard, Rambert, and Horn (1952), investigating the 17-ketosteroid excretion in 13 patients with Itsenko-Cushing's disease, found an average daily urinary 17-ketosteroid excretion of 13 mg. with fluctuations between 7 and 26; according to their data, the 17-ketosteroid excretion does not go in parallel with the degree of virilization and is sometimes changed by jumps, independently of the therapeutic effects. In 5 of the 13 patients with an increased 17-ketosteroid content in the urine, this value was decreased to normal in the stage of remission and during recuperation.

According to the data of other foreign authors (Fraser, 1941; Engstrom and Mason, 1950; Braunsteiner and Enzinger, 1952), the excretion of 17-ketosteroids in Itsenko-Cushing's disease varies from the normal values to 25–40 mg./day, no parallelism being observed between the severity of the disease and the excretion of 17-ketosteroids.

However, the 17-ketosteroid excretion can also be low in the presence of a clinically expressed picture of hypercorticalism. Therefore, one cannot be guided solely by a 17-ketosteroid determination as a means of evaluating the functional state of the adrenal cortex; it is necessary to have recourse to the determination of other products of the metabolism of the adrenocortical hormones, e.g., the total corticoids, glucocorticoids, and pregnanediol in the urine, high values for which will also indicate increased adrenocortical activity. Albright (1942-43) connects a combination of an increased excretion of corticosteroids and a normal excretion of 17-ketosteroids with a selective disease in the individual zones of the adrenal cortex producing the steroid compounds from which the 17-ketosteroids and corticosteroids are ultimately formed.

Cope, Nathanson, Rourke, and Wilson (1943) explain a normal or decreased excretion of 17-ketosteroids by a destructive inactivation of the 17-ketosteroid precursors produced in the liver.

Shul'tsev, Frankson, Albaux-Fernet, Berton and Robert, Lloyd and Williams (1948), Gilder and Hoagland (1946), and many others have found the 17-ketosteroid excretion in acute hepatitis and cirrhosis of the liver to be decreased 30–40 per cent in comparison with the normal. Apparently, the presence of a fatty infiltration of the liver,
which can occur in Itsenko-Cushing's disease, brings about a decreased urinary excretion of 17-ketosteroids.

In patients with Itsenko-Cushing's disease, deep x-ray therapy in the diencephalohypophyseal region can be accompanied by a decrease in the excretion of 17-ketosteroids (Ioffe and Zakharycheva, 1946). According to the data of Forbes and Albright (1952), Sosman (1949), Skrimshir (1955), Luft (1946), Johnsen (1952), and others, single and especially repeated courses of x-ray therapy produce a decrease in the 17-ketosteroid excretion from 20–30 to 9–10 mg./day.

A normal or decreased 17-ketosteroid excretion in the late stages of Itsenko-Cushing's disease can be evidence of the appearance of degenerative changes in the adrenal cortex (Miloslavsky, 1954; Zakharycheva and Samokhvalova, 1956).

In the case of adrenocortical tumors, both benign and malignant, which manifest themselves clinically in the Itsenko-Cushing syndrome (fatty type) or in pronounced virilization, the urinary 17-ketosteroid excretion is sharply increased: up to 40 and even 1000 mg./day (Uvarovskaya, 1951; Miloslavsky, 1954; Benard, Rambert, and Horn, 1953; Voigt, Schroder, Beckmann, and Rosenkilde, 1955; and others).

However, now and then, a normal or subnormal urinary 17-ketosteroid content is seen in tumors of the adrenal cortex. Therefore, only high values for urinary 17-ketosteroids can have diagnostic significance for adrenocortical tumors, a normal value not being a valid indication of the absence of a tumor (Simpson, 1951; Dohau, Rose, Eiman et al., 1953).

After removal of a tumor of the adrenal cortex, it is necessary to carry out repeated determinations of the urinary 17-ketosteroids. A decrease in their excretion to normal values and lower attests to the radical removal of the tumor, in the opposite case, one might think that some metastases of the tumor remained.

In the adrenogenital syndrome caused by hyperplasia and hyperfunction of the adrenal cortex, which is often manifested in adult women by masculinization (virile hypertrichosis, a rough voice, amenorrhea, and hypoplasia of the uterus) and more rarely by the development of an Itsenko-Cushing syndrome, the urinary excretion of 17-ketosteroids is increased. According to the data of Mason and Engstrom, the urinary 17-ketosteroid content fluctuated between 35 and 123 mg./day in women with the above-mentioned symptoms between the ages of 20 and 30. Voigt et al. and Wintersteiner (1941)
reported a normal or moderately elevated 17-ketosteroid content (20-
30 mg./day) in this syndrome. Eberlein and Bongiovanni (1955),
studying the urinary 17-ketosteroids and corticosteroids (by the
method of paper chromatography) in women with virilism of adrenal
origin, reported that, alongside the increased excretion of urinary
17-ketosteroids (from 20 to 60 mg./day), no corticosteroids (fraction
E or cortisone, fraction F or hydrocortisone, and their tetrahydro
derivatives) could be detected (in contrast to the case in healthy per-
sons). On the basis of these facts, they came to the conclusion that,
due to the decreased synthesis of corticosteroids, the ACTH content
of the blood is increased in the adrenogenital syndrome. This in-
creased ACTH concentration in the blood produces, in its turn, hyper-
plasia of the adrenal cortex and an increase in its function with re-
spect to the production of androgens, which then brings about the
increased urinary excretion of 17-ketosteroids in the adrenogenital
syndrome. According to the results of their urinary studies, the de-
creased synthesis of corticosteroids and the increased production of
androgens by the adrenal cortex, as well as the high content of ACTH
in the blood in virilism of adrenal origin, have been confirmed by
Bierich, Bihland, and Voight (1955).

In women with virilism due to cystic degeneration of the ovaries,
there is a normal or insignificantly increased content of urinary 17-
ketosteroids (19–25 mg./day). According to the data of Simpson
(1951) and of Fellinger, Braunsteiner, and Enzinger (1952), the
urinary 17-ketosteroid excretion is increased to the level of excretion
in adults and even higher in children with early sexual maturation of
diencephalohypophyseal origin. In cases of early sexual develop-
ment caused by the presence of an adrenocortical tumor, the quantity of
17-ketosteroids excreted can be significantly above normal.

In order to confirm the diagnosis of adrenocortical tumor in chil-
dren, it is recommended that the individual fractions of the 17-keto-
steroids be determined (α and β) and that the corticosteroids and
urinary pregnanediol be examined.

According to the data of Mason and Engstrom, the 17-ketosteroid
excretion in children between the ages of 3 and 12 years with the
adrenogenital syndrome fluctuates between 6 and 69 mg./day, the
quantity of 17-ketosteroids increasing with age.

In boys with testicular tumors accompanied by the clinical picture
of early sexual development, an increased excretion of 17-keto-
steroids is also observed (Kandrac).
The presence of a tumor proceeding into the ovary from the ectotrophic tissue of the adrenal cortex, like arrhenoblastoma in women, is accompanied by a sharp increase in the urinary excretion of 17-ketosteroids (Novak, 1942).

In luteoma of the ovary, the 17-ketosteroid content can be within normal limits. However, Engel, Dorfman, and Abarbanel (1953) sometimes found an increased urinary secretion (up to 74–79 mg./day) in luteomas. This increase was due to androsterone and its isomers; the concentration of dehydroisoandrosterone (the adrenal fraction) was normal.

In patients with acromegaly, the quantity of 17-ketosteroids varies significantly—from subnormal values to those which significantly exceed the upper limit of normal. Mason and Sprague (1948), studying the 17-ketosteroid content in the urines of 64 patients with acromegaly, reported fluctuations in their excretion between 2.7 and 21 mg./day in women and between 0.7 and 28.4 mg./day in men. Working with a large amount of clinical material, Benard, Rambert, and Horn (1952) obtained predominantly increased values for the 17-ketosteroid excretion in patients with acromegaly.

In contrast to this, Uvarovskaya (1951) noted that the average 17-ketosteroid excretion in men with acromegaly was 10 mg./day with fluctuations between 3 and 18, while in women it was 6.7 mg./day with fluctuations between 4 and 13, i.e., it appeared to be subnormal or normal.

Decourt, Jayle, Michard, and Louchart (1933), having detected an increased content of 17-ketosteroids and follicle-stimulating hormone in the urine of 7 patients with acromegaly (2 men and 5 women), explain the increased excretion of androgens by an increased production of ACTH, on the one hand, and an increased production of gonadotrophins, on the other.

In Addison’s disease, according to the data of some authors (Voigt, Schroder, Beckmann, and Rosenkilde, 1955; and others), the excretion of 17-ketosteroids is significantly decreased: in men it is 3–7 mg./day while in women it is 1–2 mg./day; often, in severe cases, no 17-ketosteroids are detected at all. Uvarovskaya (1951) and Moloslavsky (1954) have also pointed out the sharply decreased excretion of 17-ketosteroids in Addison’s disease in both men and women.

In myxedema, a sharp decrease in the excretion of 17-ketosteroids is noted. According to the data of Mason and Engstrom (1944, 1950), the quantity of 17-ketosteroids excreted in myxedema varies from 0
to the lower limit of normal, but in the overwhelming majority of cases it is less than 2 mg./day.

By the studies of Beierwaltes and Bishop (1954) and of other foreign authors, it has been determined that the 17-ketosteroid content in the urine of female myxedema patients is less than 3 mg./day, while in men it is less than 7 mg./day. Patients with hypothyroidism but without the clinical symptoms of myxedema excrete the normal quantity of 17-ketosteroids in the urine.

According to the same authors, in thyrotoxicosis the quantity of 17-ketosteroids in the urine either is slightly decreased or fluctuates within the lower limits of normal. Forbes, Donaldson, Reifenstein, and Albright (1947) and Kenigsberg and McGavack (1952) also detected a decreased excretion of 17-ketosteroids in thyrotoxicosis (from 2.5 to 5-6 mg./day), but the authors were unable to find any relation between the severity of the clinical picture, the duration of the disease, and the quantity of 17-ketosteroids. The above-mentioned authors note that successful treatment leads to an increase in the 17-ketosteroids compared to the low initial level. These data agree with the data of Pemberton (1936), who found a decrease of the adrenal cortex and a degeneration of its cells in thyrotoxicosis. In contrast to these authors, Voigt, Schroder, Beckmann, and Rosenkilde have reported a normal or even increased 17-ketosteroid excretion in thyrotoxicosis.

In pituitary cachexia, pituitary nanism, and anorexia nervosa, the 17-ketosteroid excretion is sharply decreased (Fraser, 1941; Uvarovskaya, 1951; Voigt, Schroder, Beckmann, and Rosenkilde, 1955).

FRACTIONS

Besides the determination of the total 17-ketosteroids in the urine, the determination of the separate \(\alpha\) and \(\beta\) fractions of the 17-ketosteroids seems to be valuable. Normally, the ratio between the \(\alpha\) and \(\beta\) fractions is 9:1 (Talbot, Butler, and MacLacklon, 1940; Frame, 1944; and others).

According to their data, the average content of the \(\alpha\) and \(\beta\) fractions in healthy persons is: \(\alpha\) fraction in men, 13 $\pm$ 2 mg.; \(\alpha\) fraction in women, 6.3 $\pm$ 2.5 mg.; \(\beta\) fraction in men, 1.3 $\pm$ 0.2 mg.; \(\beta\) fraction in women, 1.1 $\pm$ 0.1 mg.

These same authors point out that in tumors of the adrenal cortex, parallel with the increase in the total 17-ketosteroids, both the \(\alpha\) and \(\beta\) fractions are also increased. The relationship between them
changes in the direction of an increase in the adrenal fraction ($\beta$ fraction); an inverse relationship between them is frequently observed ($\alpha : \beta = 1:2-4$), or their quantities may become identical.

In virilism caused by hyperplasia of the adrenal cortex, and in Itsenko-Cushing's disease with an increased excretion of 17-ketosteroids, both fractions are sharply decreased; the ratio between them equalizes itself somewhat (3-4:1). In Itsenko-Cushing's disease with low values for urinary 17-ketosteroids, normal ratios between the $\alpha$ and $\beta$ fractions are observed. In eunuchoidism and hypogenitalism, the ratio between the $\alpha$ and $\beta$ fractions approaches 1:1 (the same authors).

Uvarovskaya, determining the $\alpha$ and $\beta$ fractions in 13 healthy subjects, obtained a ratio of 2.9:1 between them, while in tumors of the adrenal cortex (2 cases) the ratio was 1:2.7, in Itsenko-Cushing's disease (8 cases) it was 3.6:1, and in 5 cases of eunuchoidism the ratio averaged 1.6:1.

With the aid of chromatographic methods, the 17-ketosteroids can be divided into a series of constituent components (androsterone, etiocholanolone, isoandrosterone, dehydroisoandrosterone, 11-hydroxyandrosterone, and others) and one can determine more exactly how much of the total is related to androgenic substances of exclusively adrenal origin (Dingemanse, 1952; Kellie, 1953; Lakhsmann, 1954; and others).

Thus, N. Callow and R. Callow (1939-1940) detected 1.3 mg./liter of androsterone, 1.3 mg./liter of etiocholanolone and 0.2 mg./liter of dehydroisoandrosterone in the urine of healthy women. The same amounts of androsterone and dehydroisoandrosterone were detected by them in patients with hyperplasia of the adrenal cortex. In patients with malignant tumors of the adrenal cortex, the concentration of dehydroisoandrosterone was sharply increased at the same time that the concentration of androsterone either increased insignificantly or remained unchanged. The high values for the individual fractions of the 17-ketosteroids and the changing relationship between them in tumors of the adrenal cortex has been confirmed by a series of other foreign authors (Dohau, Rose, Eiman, Richardson, and Lintel, 1953, and others).

**ADMINISTRATION OF HORMONES**

The administration of certain hormone preparations has an effect on the 17-ketosteroid content of the urine. Thus, for example,
Deakins, Friedgood, and Ferrebee, as well as Frame, Fleischmann, and Wilkins (1944), showed that the injection of testosterone propionate increased the excretion of 17-ketosteroids, while the injection of 17-methyltestosterone and other 17-methylsteroids did not have this effect. When given in large doses or for a long period of time, any of the androgens will depress the excretion of 17-ketosteroids, which is explained by Reifenstein (1945) and also by Mason and Engstrom (1950) as the result of the suppression of the production by the anterior lobe of the pituitary of the tropic hormones which stimulate both the sex glands and the adrenal cortex.

Hamblen, Patte, and Guyler noted a 14–26 per cent decrease in 17-ketosteroid excretion after the administration of estrogens to 22 women with varying degrees of ovarian insufficiency who had excreted moderately increased amounts of 17-ketosteroids before the treatment. The authors believe that the estrogens exert exactly the same effect on the pituitary as testosterone, i.e., they also suppress the secretion of tropic hormones. The injection of desoxycorticosterone or 11-dehydrocorticosterone into the organism does not increase the excretion of 17-ketosteroids; the first is transformed into pregnanediol in the body, while the second yields an insignificant amount of 11-ketopregnanediol.

The injection of progesterone does not produce an increase in the urinary 17-ketosteroids (Pearlman, 1945-1948); 30–35 per cent of the injected progesterone is excreted in the urine in the form of pregnanediol.

Interesting information has been obtained from the injection of cortisone in healthy persons and in patients with endocrine disorders (Jailer, Louchard, Cold, and Knowlton, 1933). In healthy persons, the intramuscular injection of 200 mg. of cortisone produces a 40 per cent decrease in the urinary 17-ketosteroid excretion (on the very first day after injection). In patients with androgenital syndromes, daily intramuscular injections of 200 mg. of cortisone, continued for 4–5 days, produced a significant decrease in the urinary 17-ketosteroid excretion.

The injection of cortisone in patients with Itsenko-Cushing’s disease produced a less sharp decrease in urinary 17-ketosteroid excretion in these patients than in those with adrenogenital syndromes.

In patients with adrenocortical tumors, the injection of cortisone in the same doses produced no decrease in the urinary 17-ketosteroid content. The authors suggest that this cortisone test be used in the
differential diagnosis of adrenocortical tumors and virilism of adrenal origin. The authors explain the mechanism of the cortisone effect in the following way: the injected cortisone inhibits the production of ACTH in the pituitary, as a result of which the secretion of adrenal hormones is decreased. In the case of adrenocortical tumors, their production of hormones does not depend on a functioning pituitary.

A significant increase in the excretion of 17-ketosteroids is observed after the injection of ACTH, especially with its prolonged use (Conn, Louis, and Johnston, 1949; Forsham, Thorn, Prunty, and Hills, 1947-1948; Mason and Power; Rynearson, Ciaramelli, and Evans, 1948; and others).

ACTH has a dual effect on the adrenals. On the one hand, on the day of a single injection, a maximal stimulation is obtained which promotes the function of the adrenal cortex and increases the synthesis of steroids, while on the other hand, ACTH stimulates the cells of the cortex, especially the cells of the zona fasciculata, promoting proliferation and leading to hypertrophy of the organ, which also brings about a maximum production of hormones, this being observed in the course of a few days.

Labhart (1952), studying both aspects of the effect of ACTH on the adrenal cortex, used this to discover its actual and potential reserves. He believes that the functional capacity of the adrenal cortex, as the central organ of adaptation, should be evaluated not only by its activity at a given moment but also by its ability to meet increased demands. The relationships between these and other reserves of the adrenal cortex can serve as an aid in the diagnosis of its functional state.

The author found that the injection of 20 mg. of ACTH by means of a daily intravenous drip lasting 8 hours produced an increase in the urinary 17-ketosteroid excretion of 5-10 mg. during the first 24 hours. This reaction demonstrates the normal value for the actual functional reserves of the adrenal cortex. During the following days, the urinary 17-ketosteroid excretion increased further and reached a maximum of 40-50 mg./day on the third day. This value is characteristic for the normal potential reserves of the adrenal cortex. According to the author, the actual functional reserves are retained in Itsenko-Cushing’s disease, but the potential reserves are lacking, so that the later increase in the function of the adrenal cortex is impossible. In adrenal insufficiency, various relationships are found,
depending on whether it is a case of primary or secondary (pituitary) insufficiency. In Addison's disease, both the actual and the potential reserves are lacking. In patients with pituitary cachexia and anorexia nervosa, the actual reserves are lacking but good potential reserves are seen.

CONCLUSION

On the basis of all that has been said, it is possible to state that the clinical determination of the 17-ketosteroids and their fractions ($\alpha$ and $\beta$) is very valuable for the diagnosis of disorders of the endocrine glands. However, in evaluating the data from these analyses, it is necessary to take into consideration the clinical picture and the results of other studies: pneumoadenography, the peripheral blood picture, biochemical data, characteristic changes in metabolism, etc.

REFERENCES