Journal of Steroid Biochemistry, 1975, Vol. 6, pp. 695–702. Pergamon Press. Printed in Great Britain

STUDIES OF THE RELATION OF PLASMA ANDROGEN LEVELS TO ANDROGEN ACTION IN WOMEN

ROBERT L. ROSENFIELD

Biomedical Center for Population Research and Department of Pediatrics, University of Chicago, Pritzker School of Medicine, 950 East 59th Street, Chicago, Illinois 60637, U.S.A.

SUMMARY

Testosterone-estradiol-binding-globulin (TEBG) is a major determinant of androgen disposition and action. TEBG levels, but not free testosterone levels, correlate with the metabolic clearance rate (MCR) of testosterone in normal women. This suggests that the testosterone MCR reflects androgen removal by the liver, an organ which removes a large fraction of steroid on a single passage, rather than the concentration of unbound androgen. Consequently, testosterone production seems more closely related to androgen catabolism than to androgen action. In support of this concept, we have studied a hirsute woman in whom testosterone clearance and production were elevated in the presence of a normal free testosterone level; her hirsutism seems related to androgens other than testosterone. Although testosterone is of major importance, androgen action seems to result from the net effect of several free plasma 17β-hydroxysteroids, including particularly androstenediol and dihydrotestosterone. About 25% of women with moderate male-pattern hirsutism have normal total and free plasma testosterone levels. In most such cases total 17β-hydroxysteroids are also normal. However, an abnormally low fraction of all these 17β-hydroxysteroids is bound to TEBG. As a result, an increase in the plasma "total androgenicity index" is present in this group of patients. Such women do not necessarily evidence increased testosterone production. Obesity appears to be another important determinant of androgen disposition and action. The testosterone MCR correlates well with adiposity independently of the TEBG levels in normal women. In addition, hyperandrogenism is frequently present with minimal or no hirsutism in obese women. This finding suggests that obesity increases the apparent "threshold" at which hirsutism appears in response to androgen or that obesity is a result of slight hyperandrogenism.

INTRODUCTION

Male-pattern hirsutism in women has appeared to be a model hyperandrogenic state in which to conduct clinical studies of the discrepancies between plasma androgen levels and androgen action. Androgen action has not proven to be strictly proportional to the plasma testosterone concentration. The major reasons for disparities seem to be related to androgen binding to testosterone-estradiol-binding-globulin (TEBG) and the existence of several androgens in plasma, the most potent of which are 17β-hydroxysteroids. Obesity seems to be importantly related to androgen metabolism and action, as well. Significant previous research and current studies in our laboratory which bear on these concepts are reviewed below.

Relation of TEBG-Binding of Androgens to Androgen Disposition and Action

TEBG: identification and importance

About 99·1% of plasma testosterone is protein-bound in normal women. Several methods indicate that TEBG is the major determinant of testosterone binding to plasma protein [1–3]. Testosterone is but one of several androgenic and/or estrogenic hormones bound to TEBG, hence the term, sex hormone binding globulin. TEBG ligands have the common feature of being planar 17β-hydroxysteroids (Table 1). The presence in plasma of this high affinity-low capacity, beta globulin capable of binding testosterone was first reported in 1966 [4]. This binding has been studied by equilibrium dialysis, ultrafiltration, gel filtration, electrophoresis, steady state gel filtration and charcoal adsorption [2, 3, 5–9]. Evidence that differences

Table 1. Competition of selected steroids with testosterone for binding sites on TEBG (testosterone = 100%)

C_{19},17β-hydroxysteroids	(%)	C_{19},17α-hydroxysteroids	
Dihydrotestosterone	250·0	Epitestosterone	1·4
Androstane-3β,17β-diol	121·0	C_{19},17-ketosteroids	
Androstane-3α,17β-diol	108·0	Dehydroepiandrosterone	3·7
Testosterone	100·0	Androsterone	1·6
Androstenediol	90·0	Androstenedione	0·3
5β-Dihydrotestosterone	8·2	C_{18},17β-hydroxysteroids	
		Estradiol	10·0

in testosterone binding assessed by these methods are of physiologic significance is that each of these methods gives similar relative results, and the dialyzable fraction of plasma testosterone has been shown to be linearly related to plasma dilution and temperature [7]. The properties of TEBG have been recently reviewed by Anderson[10].

Control of TEBG levels

The TEBG level in men is lower than that of normal women. The administration of virilizing doses of testosterone depresses, and the administration of oral estrogens in contraceptive doses increases the TEBG level of normal women. Hence, it was postulated that changes in androgen/estrogen ratios within the body control the TEBG level [9]. The finding of low TEBG in hirsute women with a very slight increase in testosterone production suggested that the TEBG level might be very sensitive to subtle increases in androgens. We have tested the above hypothesis that androgen/estrogen ratios determine the TEBG concentration. Agonadal individuals were given intramuscular injections of depot estradiol or testosterone. We found that midfollicular levels of estrogen led to a rise in TEBG capacity of about 25% at three weeks and five months [11, 12]. Testosterone levels comparable to those in hirsute women decreased TEBG capacity about 8·5% at six days. These data are compatible with the concept that both sex hormones are physiologic regulators of the TEBG level. However, these relatively short-term studies suggest that the amounts of testosterone produced by hirsute females may not be sufficient to explain the low TEBG in such cases. Furthermore, the concept that TEBG level

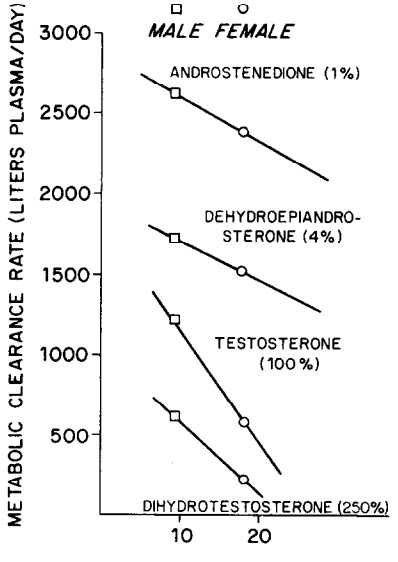

Fig. 1. The relationship between the metabolic clearance rate (MCR) and binding of C_{19} steroids to testosterone binding globulin (TEBG). The MCR of each steroid [35, 61, 62] has been related to the mean TEBG levels of men and women [2]. The affinity of each steroid for TEBG, relative to testosterone [41], is indicated in parentheses.

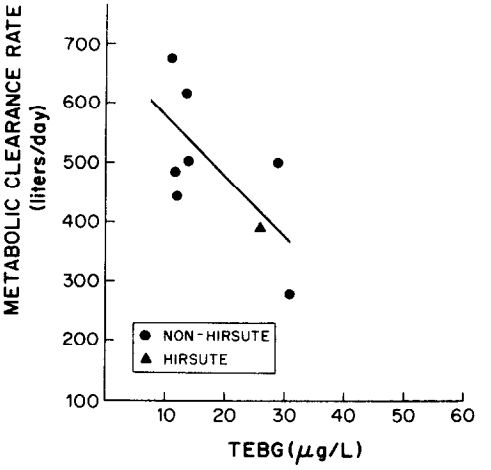

Fig. 2. Relation between testosterone MCR and the TEBG capacity of biochemically normal women. Slope −9·81, intercept 669.

is determined by sex hormone levels does not explain the fall in TEBG levels during the course of sexual maturation in man [2, 9]. Thyroid hormone in some situations would seem to be a determinant of the TEBG level, hyperthyroidism being associated with increased TEBG and *vice versa* [13]. Growth hormone has been reported to depress TEBG capacity, as well [14]. Low TEBG often occurs in obesity [9].

TEBG as a major determinant of androgen metabolism

Bardin and Lipsett were the first to suggest the relationship between plasma protein-binding and the metabolic clearance rate (MCR) of testosterone [35]. In their studies of hirsute women they almost always [16] noted an increase in testosterone MCR, even in the presence of a normal plasma testosterone level. Consequently they postulated a depression of testosterone-binding protein to be responsible for the increase in MCR. Several reports have confirmed their postulate that the mean percentage plasma testosterone binding of hirsute women was abnormally low, primarily because of the low TEBG levels [2, 9, 17].

Subsequent studies have supported the concept that differences in androgen binding to TEBG determine the rate of androgen egress from plasma. This is indicated by the inverse correlation between an androgen's MCR and the strength of its binding to TEBG. Figures 1 and 2 illustrate this relationship between the MCR and TEBG level. Note that those steroids with a high affinity for TEBG have relatively low MCR's, and differences between the sexes as regards TEBG levels correlate with inverse changes in androgen MCR. Kirschner *et al.*, also found in women that the MCR of androstenediol and testosterone were equal [18], expected since the affinity of TEBG for androstenediol is nearly equal to that for testosterone. Furthermore, changes in TEBG levels associated with hyperestrogenism, hyperandrogenism, or changes in thyroid function correlate inversely with the testosterone MCR [9, 13, 17]. The possibility that estrogen exerts its influence on testosterone MCR by

a mechanism other than through changes in TEBG has not been investigated with but a single exception. Bird *et al.*, suggested an increase in the overall rate of testosterone metabolism in the inner pool during estrogen administration [19].

The MCR of androstane-3α,17β-diol (androstanediol) is higher (1021 to 1371 liters/day) than would be expected on the basis of its binding to TEBG [20]. This may be explicable by the relatively high degree of binding of this steroid to albumin. Clark and Bird recently compared plasma protein-binding of androstanediol, dihydrotestosterone, and testosterone by electrophoresis and equilibrium dialysis [1]. They found human serum albumin to have a nearly 10-fold greater association constant for androstanediol than for testosterone. As a consequence of this, ten times more androstanediol than testosterone is bound to albumin in spite of 10% higher affinity and a lower dissociation constant of TEBG for androstanediol than testosterone [21]. Albumin-bound steroids seem to be more available than TEBG-bound steroid for hepatic degradation [22], perhaps because the hepatic sinusoidal system permits dissociation of albumin-steroid complexes due to close juxtaposition with hepatocytes.

Although TEBG clearly is a major determinant of the testosterone MCR, the nature of the relationship is unclear. Vermeulen's and Southren's groups demonstrated that infusions of testosterone increased the testosterone MCR in parallel with increasing free testosterone [9, 17]. However, the MCR in women was not as great as that of men in whom testosterone levels and binding were comparable unless chronic virilizing doses of testosterone were first administered to the women. Therefore, these workers concluded that testosterone influences its own MCR by induction of testosterone-catabolic enzymes. However, virilization reduces TEBG, and the possibility that TEBG plays a role in testosterone transfer to organs involved in testosterone clearance must be considered. The data of Vermeulen suggest that the free testosterone concentration itself was a less important determinant of the testosterone MCR than the percentage testosterone binding and/or TEBG capacity. Animal studies have not shown a relation between testosterone MCR and TEBG in females, possibly due to species differences in TEBG affinity [23].

In an effort to determine whether the plasma free testosterone concentration or the TEBG level itself was the major determinant of testosterone MCR, we undertook the following studies recently. MCR was performed by a modification of the method of Olivo *et al.*[24] and plasma testosterone was measured in 3–5 samples during the study by radioimmunoassay [25]. The correlations between total and free plasma testosterone and testosterone MCR and production rate were determined in 8 hormonally normal women. The testosterone MCR correlated significantly with percentage plasma free testosterone ($r = 0{\cdot}715$, one-tailed $P < 0{\cdot}025$) and TEBG level ($r = 0{\cdot}688$, $P < 0{\cdot}05$) (Figure 2). The testosterone MCR did not correlate with either the concentration of plasma free or total testosterone (Fig. 3). These results suggest that the testosterone MCR reflects androgen removal by such organs as the liver, which has a high blood flow and removes a large fraction (*c.* 50%) of testosterone on a single passage [26]. Since production rate equals the MCR × plasma concentration of testosterone, the testosterone production rate can be calculated to be more closely related to androgen catabolism than to the free androgen concentration.

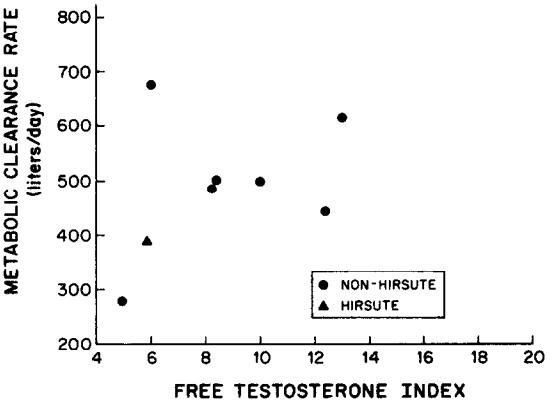

Fig. 3. Lack of relation between testosterone MCR and the free testosterone level of normal women.

Free testosterone concentration as a major determinant of androgen action

As a consequence of the above data on the relationship between TEBG and androgen clearance, it has seemed reasonable to assume that TEBG also plays an important role in the disposition of androgens to target organs. Therefore, our current concept is that the initial step in androgen action seems to be the passive diffusion of the unbound fraction from the vascular into the interstitial compartment. Consequently, though it constitutes a very small fraction of the total plasma androgen, the free plasma androgen concentration appears to exert biological activity. This concept is supported by the *in vitro* evidence that TEBG inhibits testosterone metabolism by placental microsomes [27] and ventral prostate [28] and inhibits the effectiveness of testosterone in maintaining prostate organ culture.

The concentration of free testosterone is too low to measure directly, so indirect methods have been developed. The free testosterone level is the product of [1] the total plasma testosterone concentration and [2] the percentage of testosterone free in plasma. We measure testosterone binding to TEBG in 1:20 diluted plasma at 4°C by charcoal adsorption, a technique that gives results proportional to equilibrium dialysis under these conditions [2]. Our results are expressed as a "free testosterone index". Vermeulen and coworkers measure the dialyzable fraction of testosterone in 1:5 diluted plasma at 37°C [29]. They express results as the "apparent free testosterone concentration"; this ranges from 2 to 7·5 pg/ml in normal women.

Table 2. Androgen production in hirsute women with normal free testosterone levels

Subject	Weight (kg)	Total testosterone (ng%)	Free testosterone index	Free 17β-OH steroid index	TEBG capacity (μg/L)	Testosterone MCR (L/day)	Testosterone BPR* (μg/day)
A	49·0	25·2	5·9	73	26	388	98
B	75·0	27·4	11·1	112	10	423	11·
C	79·5	22·5	10·5	115	8	609	137
D	142·4	40·7	19·3	137	7	1206	491
Normal		14–66	3–22	28–110	11–38	278–677	67–248

* Blood production rate.

Small cyclic, diurnal, and episodic changes occur in the plasma free testosterone level of normal women [25, 30]. Nevertheless, the free testosterone level has been demonstrated to fluctuate within a fairly narrow range in normal women.

Measurement of the free testosterone level has provided empiric validation of the concept that the concentration of free testosterone, rather than the total concentration, is responsible for androgen action. For example, women with male pattern hirsutism often have normal total plasma testosterone levels with elevation of the free testosterone concentration [2, 29, 31]. This is because fractional testosterone binding to TEBG is diminished, a phenomenon related in 90% of cases to diminished TEBG levels rather than to displacement of testosterone from TEBG by competing 17β-hydroxysteroids [2]. Pregnant and hyperthyroid subjects have high TEBG levels and total plasma testosterone levels; however, they have normal free testosterone levels and are not virilized [29, 32]. In addition, the high level of protein-bound testosterone in hyperthyroidism is not associated with depressed LH [33].

On the basis of the data reported in this and the preceding section, we suspect that the elevated plasma free testosterone level [2, 29, 31] and testosterone blood production rate [35, 36] reported in those hirsute women in whom the plasma total testosterone level is normal are not necessarily associated. Both phenomena are related independently to the low TEBG capacity. The high free plasma testosterone level is the factor responsible for the excess androgen effect, whereas the elevated testosterone production reflects primarily the high rate of irreversible testosterone metabolism. In four studies of the testosterone MCR of hirsute women selected on the basis of a normal free testosterone level, we have found evidence in support of the concept that an elevated testosterone production rate is not directly related to hirsutism. One obese subject (Table 2, D) with a normal free testosterone index was found to have marked elevation of the testosterone metabolic clearance rate and blood production rate. This woman's high index of plasma free 17β-hydroxysteroid levels in the presence of normal free testosterone levels suggests that her hirsutism is explicable by elevation of plasma free androgens other than testosterone.

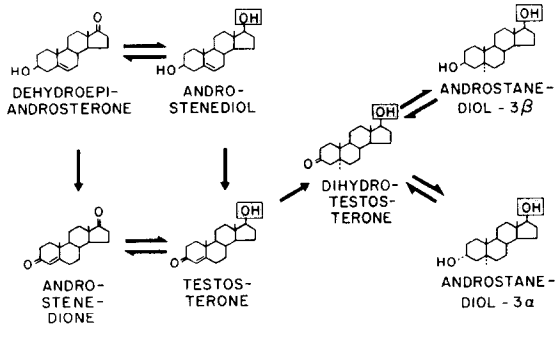

Fig. 4. 17β-hydroxyl pathway of androgen metabolism [52, 63–66, 47, 61]. The 17β-hydroxyl group is indicated by a box.

Relation of plasma androgens other than testosterone to androgen action

Normal women. The most potent androgens are the unconjugated 17β-hydroxysteroids shown in Fig. 4. The approximate relative potencies of the 17β-hydroxysteroids (as compared to testosterone) are dihydrotestosterone (125%), testosterone (100%), androstanediol (50%), androstenediol (33%) and androstane-3β,17β-diol (<10%) [37]: Estimates of the androgenicity of the latter two compounds are based on bioassay and/or analogue data, definitive studies not having been undertaken in man. These studies differed with regard to route, vehicle, and chemical form of administered steroid and type of study subjects, all of which determine the effectiveness of administered androgen [37–40].

The first indication that 17β-hydroxysteroids other than testosterone circulated was when plasma was found to contain ether-extractable material other than testosterone which was capable of displacing ^{3}H-testosterone from TEBG [15, 41]. Most of the androgenic 17β-hydroxysteroids have subsequently been identified in plasma. The average plasma levels of these steroids in normal women, as measured in our laboratory are: dihydrotestosterone 20 ± 8 (S.D.) ng% (modification of method of Chen *et al.*[42]), testosterone 36 ± 17 ng% [2, 41] and androstenediol 68 ± 24 ng% [43]. Controversy exists as to the normal plasma concentration of androstanediol-3α. Strickland and coworkers have reported androstanediol to average 17 ng% in women [44]. Because specificity of the method was merely inferred and not tested, these results are questionable. Kinouchi and Horton recently reported a RIA for the measurement of plasma androstanediol [45] in which specificity was tested and appeared to be good. They reported average normal female plasma values to be 2 ng%.

Hirsute women. Murphy was the first to report frequent elevation of total plasma 17β-hydroxysteroids in hirsute women [15]; she felt this indicated high levels of testosterone and other androgens. We subse-

Table 3. Total plasma androgen levels, free plasma androgen indexes, and TEBG capacity of normal and hirsute women (mean ± S.D.)

Group	No.	Testosterone (ng%)	Androstenediol (ng%)	Dihydrotestosterone (ng%)	Androstenedione (ng%)	Dehydroepiandrosterone (ng%)	17β-OH steroids (ng%)	TEBG capacity (μg/L)	% free testosterone	Free testosterone index	Free 17β-OH steroid index
A. Hirsute: High free testosterone index + normal free 17β-hydroxysteroid index											
	5	91 ± 26	64 ± 36	16 ± 4·6	328 ± 102	546 ± 383	269 ± 108	11·9 ± 6·4	37·1 ± 9·6	32 ± 4·6	93 ± 16
B. Hirsute: Normal free testosterone index + high free 17β-hydroxysteroid index											
	11	36 ± 10	76 ± 33	15 ± 9·3	294 ± 194	1095 ± 377	340 ± 85	8·0 ± 1·6	44·5 ± 5·0	15·8 ± 4·5	150 ± 43
C. Hirsute: Normal free androgen indexes + low TEBG											
	4	40·2 ± 4·5	43·2 ± 25·6	9·9 ± 1·5	152 ± 49·2	468 ± 125	190 ± 41	9·5 ± 0·5	38·3 ± 1·9	15·5 ± 1·7	73 ± 19
D. Normal female range											
		14–66	30–100	8–28	55–200	137–1261	106–392	11·3–37·0	17·9–39·3	3·1–22·1	28–110

quently explored the possibility that plasma free androgen levels in hirsute women might sometimes be increased by elevated concentrations of 17β-hydroxysteroids other than testosterone or by low TEBG [2]. We found the free testosterone level to be elevated in 60% of moderately hirsute women. 25% of the patients in this series had normal free testosterone levels but an elevation of an index of the free fraction of the total plasma 17β-hydroxysteroids ("free 17β-hydroxysteroid index"). On the basis of the elevated free 17β-hydroxysteroid index in the presence of normal free testosterone levels, we hypothesized that in about 25% of hirsute women elevated unbound plasma levels of androgens other than testosterone contribute importantly to the hirsutism. This concept was subsequently supported by the reports that total plasma levels of dihydrotestosterone [46], androstenediol [43], or androstanediol [45] were elevated in some hirsute women.

In order to improve our perspective of the relation of androgens other than testosterone to hirsutism, we have fractionated plasma androgens in groups of hirsute women which we felt would be instructive. The results are summarized in Table 3. These data show that the total plasma levels of 17β-hydroxysteroids other than testosterone are usually normal in hirsute women. Furthermore, those measured contribute only about 50% to the total "17β-hydroxysteroid" level in testosterone equivalents. Dihydrotestosterone was elevated in only one of 20, androstenediol in only 4 of 20. These results are not surprising in view of the usually normal total level of plasma 17β-hydroxysteroids in such women. Androstenedione was elevated in all of group A; this would seem to reflect its importance as a precursor of plasma testosterone [35, 47]. Dehydroepiandrosterone was elevated in 3 of group B to levels of 1332–1677 ng%; this steroid spuriously contributes about 60 ng% to the apparent total 17β-

Table 4. Plasma androgenicity index in selected groups of hirsute women

	Average plasma conc (ng%)*	Androgenicity† (relative to testosterone = 1·0)	% Free in‡ plasma		Plasma androgenicity index§
A. High free testosterone index + normal free 17β-hydroxysteroid index					
Androstenediol	64	0·33	1·36	=	28·8
Testosterone	91	1·00	1·24	=	113·0
Dihydrotestosterone	16	1·25	0·56	=	11·1
				TOTAL:	152·9
B. High free 17β-hydroxysteroid index + normal free testosterone index					
Androstenediol	76	0·33	1·64	=	41·0
Testosterone	36	1·00	1·49	=	43·6
Dihydrotestosterone	15	1·25	0·67	=	12·2
				TOTAL:	106·8
C. Low TEBG, free androgen indexes normal					
Androstenediol	43	0·33	1·39	=	19·7
Testosterone	40	1·00	1·26	=	50·4
Dihydrotestosterone	10	1·25	0·57	=	7·1
				TOTAL:	77·2
D. Normal women					
Androstenediol	68	0·33	1·00	=	22·4
Testosterone	36	1·00	0·90	=	32·4
Dihydrotestosterone	20	1·25	0·45	=	11·2
Androstanediol	2	0·50	0·70	=	0·7
				TOTAL:	66·7

* See Table 3 and text.

† See preceding page.

‡ Based on the assumption that 0·9% testosterone is dialyzable in whole plasma of normal women, that the affinity of 17β-hydroxysteroids for TEBG is the major determinant of this binding, and that adsorption and dialysis technique results are proportional.

§ Product of the preceding columns.

hydroxysteroid level, on the basis of its cross-reactivity in the assay (Table 1), in such cases.

Since we conceptualize androgen action as resulting from the net effect of several *free* plasma androgens, we have begun to examine the relation of free plasma 17β-hydroxysteroid levels to hirsutism. To do so we have formulated the plasma "total androgenicity index". This index is the sum of the products of (a) plasma level, (b) androgenic potency, and (c) percentage plasma binding of each androgenic 17β-hydroxysteroid.

Results of preliminary calculation of the androgenicity index in hirsute women are shown in Table 4. These data indicate that the total plasma androgenicity is increased in each of the above groups of hirsute women in which there is an elevation of either index of free plasma androgen levels. This elevated androgenicity in the presence of normal total 17β-hydroxysteroid levels is related to the low TEBG level of these patients. A low TEBG level does not seem to necessarily be associated with high free androgens as indicated by the findings in group C; however, the measurement of androstanediol might change this conclusion.

These studies support our concept that androgens other than testosterone contribute importantly to androgen effects. However, it must be kept in mind that the "androgenicity index" as presently formulated is based on certain assumptions that must be refined. 17-ketosteroids are presumed to be virtually devoid of androgenicity except to the extent that they are converted to circulating 17β-hydroxysteroids; although conversion occurs in target-organs [48, 49], the extent remains to be clarified. 17β-hydroxysteroids, particularly androstenediol, are presumed to be androgenic *per se*; however, the inherent androgenic potency of the 17β-hydroxysteroids is not known with accuracy, and it is possible that their androgenic effects and mode of action may differ in a qualitative sense [48, 50, 51, 52]. TEBG-binding of each 17β-hydroxysteroid is assumed to be the major determinant of plasma binding; this assumption has not been thoroughly tested for non-testosterone androgens. Though Kirschner's data suggest that this assumption is true for androstenediol [18], TEBG-binding is known to influence plasma binding of androstanediol less than expected [1]. In addition, these are cross-sectional studies and the extent to which a single androstenediol level, for example, is representative has not been established.

Recent data further support the concept that non-testosterone 17β-hydroxysteroids may be important mediators of androgen action. Two hirsute women (Table 2) have been found who have an abnormal free 17β-hydroxysteroid index and TEBG capacity in the presence of normal free testosterone levels and testosterone production rate.

Adiposity as a determinant of testosterone metabolism and action

The possibility that obesity influences androgen metabolism has received relatively little attention in spite of its known influences on progesterone [53, 54] and cortisol [55, 56] metabolism. Two recent studies indicate that adipose tissue may be an important site of androgen metabolism. Schindler *et al.*, demonstrated *in vitro* that adipose tissue contains the enzymatic activity necessary to convert androstenedione to estradiol [34]. Edman and MacDonald studied the entry into plasma of ^{14}C-estrone following ^{14}C-androstenedione infusion into obese women [57]. They found that the rate of estrone entry into plasma after androstenedione infusion was inversely related to body weight. These findings suggested that adipose tissue was an important site of sex hormone metabolism and storage.

Two sets of observations have led us to suspect that obesity is importantly related to androgen disposition and action. First, in the above studies of testosterone MCR, we found that this was related to body weight independently of TEBG capacity. Seven normal women and one otherwise normal hirsute woman (in whom free plasma androgens and TEBG were clearly normal) have been studied. The testosterone MCR correlated as well with weight ($r = 0{\cdot}699$; $P < 0{\cdot}05$, one-tailed) (Fig. 5) as with the TEBG level, although there was not significant correlation between weight and TEBG. Furthermore, the relationship between testosterone metabolic clearance rate and weight/height^2, a better index of obesity [58], was slightly closer ($r = 0{\cdot}737$, $P < 0{\cdot}025$). The findings suggest that obesity is an important determinant of testosterone MCR. However, judgement must be reserved because a correlation between these functions was not observed in a previous, smaller series [35].

Secondly, in oligomenorrheic women we have found a correlation between obesity and hyperandrogenism which is independent of hirsutism [59]. These conclusions were reached in collaboration with members of our Department of Obstetrics and Gynecology after the study of the relationship between hirsutism, obesity,

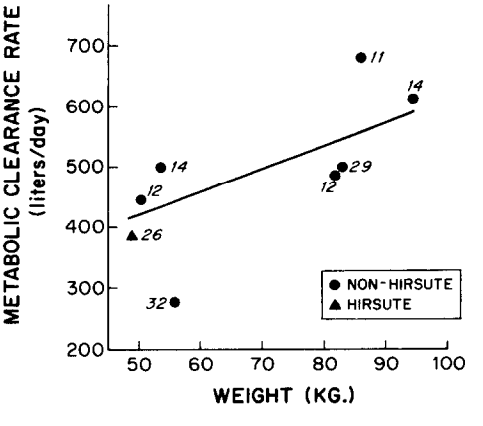

Fig. 5. Relation between testosterone MCR and body weight of normal women. Slope 4·84, intercept 152. Numbers indicate the TEBG capacity of each subject.

oligomenorrhea, and hyperandrogenism in 64 women. With the exception of severe hirsutism, none of these parameters alone were found to be associated with elevated plasma free testosterone or free 17β-hydroxysteroid levels. However, significant hyperandrogenism was present with minimal or no hirsutism in oligomenorrheic obese women. One possible explanation for these findings is that one major source of blood flow to the skin passes through the subcutaneous fat before reaching the hair follicle [60]; it seems possible that the plasma from these vessels is "siphoned off", stored, or metabolized before reaching the hair follicle, thus diminishing the amount of androgen that reaches this particular target organ. Another explanation might be that slight hyperandrogenism stimulates appetite.

Many of these studies were carried out in the Clinical Research Centers of the University of Chicago Hospitals under grants RR-305 and RR-55 from the General Clinical Research Centers Program of the Division of Research Resources, National Institutes of Health. This work was also supported in part by USPHS grants HD-06308, HD-70152, and HD-07110. Special studies were carried out by Patricia Otto.

REFERENCES

1. Clark A. F. and Bird C. E.: *J. Endocr.* **57** (1973) 289–298.
2. Rosenfield R. L.: *J. clin. Endocr. Metab.* **32** (1971) 717–728.
3. Rosner W. and Deakins S. M.: *J. clin. Invest.* **47** (1968) 2109–2116.
4. Mercier-Bodard C., Alfsen A. and Baulieu E. E.: *Acta endocr., Copenh.* Suppl. **147** (1970) 204–224.
5. Burke C. W. and Anderson D. C.: *Nature, Lond.* **240** (1972) 38–40.
6. Corval P. L., Chrambach A., Rodbard D. and Bardin C. W.: *J. biol. Chem.* **246** (1971) 3435–3443.
7. Forest M. G., Rivarols M. A. and Migeon C. J.: *Steroids* **12** (1968) 323–343.
8. Pearlman W. H., Crepy O. and Murphy M.: *J. clin. Endocr. Metab.* **27** (1967) 1012–1018.
9. Vermeulen A., Verdonck L., Van der Straeten M. and Orie N.: *J. clin. Endocr. Metab.* **29** (1969) 1470–1480.
10. Anderson D. C.: *Clin. Endocr.* **3** (1974) 69–96.
11. Rosenfield R. L. and Fang V. S.: *J. Pediat.* **85** (1974) 830–837.
12. Rosenfield R. L., Fang V. S., Dupon C., Kim M. H. and Refetoff S.: *J. clin. Endocr. Metab.* **37** (1973) 574–580.
13. Gordon C. G., Southren A. L., Tochimoto S., Rand J. J. and Olivo J.: *J. clin. Endocr. Metab.* **29** (1969) 164–170.
14. DeMoor P., Heynes W. and Bouillon R.: *J. steroid Biochem.* **3** (1972) 593–600.
15. Murphy B. E. P.: *Recent Prog. Horm. Res.* **25** (1969) 563–601.
16. Kirschner M. A. and Bardin C. W.: *Metabolism* **21** (1972) 667–689.
17. Southren A. L., Gordon G. G., Tochimoto S., Olivo J., Sherman D. H. and Pinzon G.: *J. clin. Endocr. Metab.* **29** (1969) 1356–1363.
18. Kirschner M. A., Sinhamahapatra S., Zucker I. R., Loriaux L. and Nieschlag E.: *J. clin Endocr. Metab.* **37** (1973) 183–189.
19. Bird C. E., Green R. N. and Clark A. F.: *J. clin Endocr. Metab.* **29** (1969) 123–126.
20. Bird C. E., Choong A., Knight L. and Clark A. F.: *J. clin. Endocr. Metab.* **38** (1974) 372–375.
21. Heynes W. and DeMoor P.: *J. clin. Endocr. Metab.* **32** (1971) 147–154.
22. Baird D. T., Horton R., Longcope C. and Tait J. F.: *Recent Prog. Horm. Res.* **25** (1969) 611–664.
23. Mahoudeau J. A., Corvol P. and Bricarie J.: *Endocrinology* **92** (1973) 1120–1125.
24. Olivo J., Vittek J., Southren A. L., Gordon G. G. and Rafii R.: *J. clin. Endocr. Metab.* **36** (1973) 153–159.
25. Rosenfield R. L. and Helke J. C.: *Am. J. Obstet. Gynaec.* **120** (1974) 461–465.
26. Rivarola M. A., Singleton R. T. and Migeon C. J.: *J. clin. Invest.* **46** (1967) 2095–2100.
27. Mowszowicz I., Kahn D. and Dray F.: *J. clin. Endocr. Metab.* **31** (1970) 584–586.
28. Lasnitski I. and Franklin H. R.: *J. Endocr.* **54** (1972) 333–342.
29. Vermeulen A., Stoica T. and Verdonck L.: *J. clin. Endocr. Metab.* **33** (1971) 759–767.
30. Dupon C., Rosenfield R. L. and Cleary R. E.: *Am. J. Obstet. Gynaec.* **115** (1973) 478–483.
31. Tulchinsky D. and Chopra I. J.: *J. clin. Endocr. Metab.* **39** (1974) 164–169.
32. Rivarola M. A., Forest M. G. and Migeon C. J.: *J. clin. Endocr. Metab.* **28** (1968) 34–40.
33. Ruder H., Corvall P., Mahoudeau J. A., Ross G. T. and Lipsett M. B.: *J. clin. Endocr. Metab.* **33** (1971) 382–387.
34. Schindler A. E., Eberg A. and Friedrich E.: *J. clin. Endocr. Metab.* **35** (1972) 627–630.
35. Bardin C. E. and Lipsett M. B.: *J. clin. Invest.* **46** (1967) 891–902.
36. Kirschner M. A. and Jacobs J. B.: *J. clin. Endocr. Metab.* **33** (1971) 199–209.
37. Dorfman R. I. and Shipley R. A.: *Androgens.* John Wiley & Sons, New York (1956) 116–117.
38. Alibrandi A., Bruni G., Ercoli A., Gardi R. and Melli A.: *Endocrinology* **66** (1960) 13–18.
39. Dorfman R. I. and Dorfman A. S.: *Acta endocr., Copenh.* **41** (1962) 101–106.
40. Rosenfield R. L., Lawrence A. M., Liao S. and Landau R. L.: *J. clin. Endocr. Metab.* **32** (1971) 625–632.
41. Rosenfield R. L., Eberlein W. R. and Bongiovanni A. M.: *J. clin. Endocr. Metab.* **29** (1969) 854–859.
42. Chen J. C., Zorn E. M., Hallberg M. C. and Wieland R. G.: *Clin. Chem.* **17** (1971) 581–584.
43. Rosenfield R. L. and Otto P.: *J. clin. Endocr. Metab.* **35** (1972) 818–822.
44. Strickland A. L., Apland H. and Burton J.: *Steroids* **21** (1973) 27–46.
45. Kinouchi T. and Horton R.: *J. clin. Endocr. Metab.* **38** (1974) 262–268.
46. Ito T. and Horton R.: *J. clin. Endocr. Metab.* **31** (1970) 362–368.
47. Horton R. and Tait J. F.: *J. clin. Invest.* **45** (1966) 301–313.
48. Anderson K. M. and Liao S.: *Nature, Lond.* **219** (1968) 277–279.
49. Hodgins M. B.: *Steroids* **18** (1971) 11–23.
50. Baulieu E. E.: *Rev. Eur. Etud. Clin. Biol.* **15** (1970) 723–727.
51. Baulieu E. E., Lasnitzki I. and Robel P.: *Nature, Lond.* **219** (1968) 1155–1156.
52. Liao S., Liang T., Fang S., Castañeda E. and Shao T. C.: *J. biol. Chem.* **248** (1973) 6154–6162.
53. Davis M. E. and Plotz E. J.: *Am. J. Obstet. Gynaec.* **76** (1958) 939–954.
54. Davis M. E., Plotz E. J., Lupu C. I. and Ejarque P. M.: *Fertil. Steril.* **11** (1960) 18–48.
55. Schteingart D. E. and Conn J. W.: *Ann. N.Y. Acad. Sci.* **131** (1965) 388–403.
56. Streeten D. H. P., Stevenson C. T., Dalakos T. G., Nicholas J. J., Dennick L. G. and Fellerman H.: *J. clin. Endocr. Metab.* **29** (1969) 1191–1211.
57. Edman C. D. and MacDonald P. C.: Proceedings of the 21st Annual Meeting of the Society for Gynaecologic Investigation, March 27–29, 1974, Los Angeles, California, Abstract 46.

58. Mann G. V.: *New Engl. J. Med.* **291** (1974) 178–185.
59. Hosseinian A. J., Kim M. H. and Rosenfield R. L.: *Gynaec. Invest.* **5** (1974) 16.
60. Durward A. and Rudall K. M.: *The Biology of Hair Growth.* Academic Press, New York, (1958) pp. 189–218.
61. Horton R. and Tait J. F.: *J. clin. Endocr. Metab.* **27** (1967) 79–88.
62. Saez J. M., Forest M. G., Morera A. M. and Bertrand J.: *J. clin. Invest.* **51** (1972) 1226–1234.
63. Baulieu E. E. and Mauvais-Jarvis P.: *J. biol. Chem.* **239** (1964) 1578–1584.
64. Baulieu E. E. and Robel P.: *Steroids* **2** (1963) 111–118.
65. Chapdelaine A., MacDonald P. C., Gonzalez O., Gurpide E., VandeWiele R. C. and Lieberman S.: *J. clin. Endocr. Metab.* **25** (1965) 1569–1579.
66. Forleo R. and Ingiulla W.: *Steroids* **10** (1967) 347–358.