derives primarily or entirely from peripheral factors? The presence of a group of hirsute women with normal circulating androgens and numerous cases where androgens are increased without hirsutism, strongly supports this concept. Authors of these chapters suggest that the difference in response of hair follicles between individuals and in different sites may explain the dilemma posed by those with PCO syndrome, increased androgens, but without hirsutism, as well as true idiopathic hirsutism. Considerable data are now available that 5α-reductase activity is increased in idiopathic hirsutism based on studies of skin homogenates and cultured fibroblasts. Another interesting suggestion is that non-steroidal growth factors may play an important role in pilosebaceous regulation.

The measurement of circulating androgens has always been an important subject in the clinical and research approach to hirsutism. Controversy exists as to whether it is the unbound fraction or the total hormone which reaches target tissue. However, most investigators and clinicians find the best correlation between steroid action and blood levels involves measurement of free and albumin (unbound) testosterone. Unbound testosterone provides the best assessment of the androgen signal reaching the skin. Measurement of androstenedione is of interest, but secondary in value to measures of testosterone. DHEA sulphate levels can help in the evaluation of the adrenal contribution. Considerable interest has focused on measures of peripherally formed androgens, such as DHT. A number of the authors of this volume conclude that DHT blood levels do not provide insight into these events. We believe that this is because peripheral DHT is efficiently further metabolized to other end-products. The 3α-reduction product of DHT, androstanediol (3α,17β-diol), is usually increased in hirsute states. Although well-documented, the increase is rather small and requires very sensitive assays. Another end-stage peripheral metabolite is androstanediol glucuronide. In vivo studies by the editors strongly suggest that androstanediol and its glucuronide arise from different pools chemically, and perhaps anatomically. The latter pathway appears to be DHT → DHT glucuronide → androstanediol glucuronide. A combination of unbound testosterone and androstanediol glucuronide should allow assessment of hormone production in blood and peripheral formation of androgens.

Chapters 10 and 11 deal with the effective antiandrogens, cyproterone and spironolactone. These synthetic steroids act to reduce androgen production, and are peripheral antiandrogens. Treatment using either agent is highly effective over time (months). Finally, we conclude with a prospective chapter on new agents, such as the use of specific 5α-reductase inhibitors which act by reducing DHT formation in peripheral sexual tissues. These agents, if non-toxic chronically in humans, could be useful in androgen excess states of women (hirsutism) and prostate hyperplasia in men.

We believe that the basic and applied information on this topic is between the covers of this volume. We have not provided a flow sheet to aid in the clinical, laboratory, and therapeutic decisions; however, the information contained herein provides the state of the subject for both investigator and clinician.

RICHARD HORTON
ROGER LOBO

1

Adrenal and Gonadal Androgen Secretion in Normal Females

CHRISTOPHER LONGCOPE

Prior to the description of hormone receptor binding and interactions, androgens were described as substances 'capable of stimulating male secondary sex characteristics' (Dorfman and Shipley, 1956). Several steroids classified previously as androgens are now known to have no specific androgenic action of their own but act only as precursors to active hormones (Baird et al, 1968). Nevertheless, in this chapter we shall consider all pertinent C_{19} steroids as androgens for the sake of simplicity.

ADRENAL ANDROGEN SECRETION

Steroid biosynthesis

Initial studies indicated that androgens were present in the adrenal glands (Reichstein and Shoppee, 1943), but this was not definitive proof of synthesis in that gland. That the adrenal contained the necessary enzymes to convert acetate and cholesterol to glucocorticoids and androgens was shown using radiolabelled (Hechter et al, 1953; Bloch et al, 1957) steroids. The generally accepted scheme for androgen synthesis in the adrenal gland is given in Figure 1. The major pathway to Δ^4-androstenedione (Δ^4-A) is from cholesterol through dehydroepiandrosterone (DHA) to Δ^4-A. Although there is conversion of progesterone to Δ^4-A (Rao and Heard, 1957), this pathway is relatively minimal (Ward and Grant, 1963). Δ^4-A can also be reduced at C-17 to produce testosterone (T) (Ward and Grant, 1963), but T is not a major end-product of the androgen biosynthetic pathway in the adrenal. Δ^4-A can be hydroxylated at C-11 to form 11β-hydroxyandrostenedione (Jeanloz et al, 1953). However, Deshpande et al (1970) reported that cortisol was the major source of 11β-hydroxyandrostenedione rather than androstenedione.

The other C_{19} steroids in the adrenal are DHA and dehydroepiandrosterone sulphate (DHAS). As discussed later, they are major adrenal secretory products and, although in the periphery are readily interconvertible, may be formed, to some extent, along separate pathways in the

adrenal. The major pathway for DHA appears to be from 17-hydroxypregnenolone (Goldstein et al, 1960) and DHAS formation would then occur from the sulphurylation of DHA (Wallace and Lieberman, 1963). However, Calvin et al (1963) showed that pregnenolone sulphate could be converted to DHAS without the loss of the sulphate moiety. Roberts et al (1964) showed that cholesterol sulphate could be converted to DHAS also apparently without loss of the sulphate group. These studies suggested that DHAS might be formed in the adrenal primarily from cholesterol sulphate. Subsequent work by Lebeau et al (1964) and Killinger and Solomon (1965) indicates that the major pathway for DHAS is through DHA, and the pathway from cholesterol sulphate is probably a minor one.

Cholesterol, which is the precursor for adrenal steroid synthesis, is derived largely from the circulating low-density lipoprotein-bound

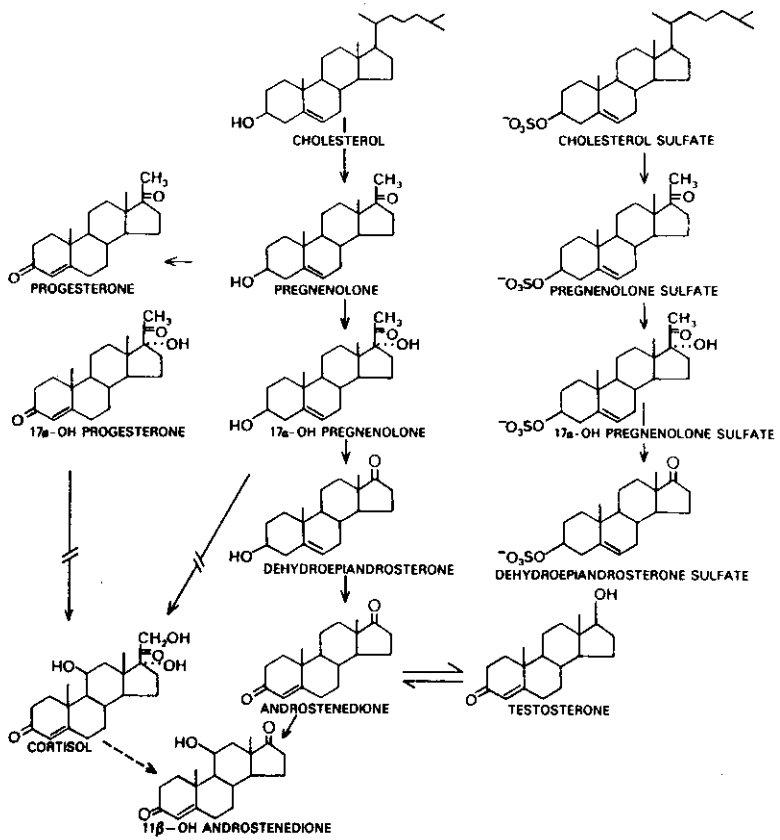

Figure 1. Pathways for androgen biosynthesis in the adrenal gland.

cholesterol entering the adrenal via the low-density lipoprotein receptor mechanism (Borkowski et al, 1972a,b; Brown et al, 1979). The cholesterol, on entering the resting gland, is esterified and stored primarily in the ester form.

Before entering the steroid biosynthetic pathway, cholesterol ester is hydrolysed and free cholesterol undergoes side-chain cleavage by 20,21-desmolase in the mitochondria. The 17α-hydroxylase, 17,21-desmolase and Δ^5-3β-ol-dehydrogenase are all located in the endoplasmic reticulum which may be absorbed on the mitochondrial surface (Hayano et al, 1956; Tamaoki, 1973).

Site of androgen biosynthesis

The adrenal cortex consists of three zones: the glomerulosa, fasciculata and reticularis. While the glomerulosa synthesizes primarily C_{21} steroids with mineralocorticoid activity (Ayres et al, 1958), the exact relationship between the zonae fascicularis and reticularis and the androgens remains somewhat controversial. It has been postulated that the zona reticularis is the major source of the androgens (Jones, 1957). Ofstad et al (1961) reported a patient with a low urinary 17-ketosteroid excretion and amyloid degeneration of the zona reticularis, and in this patient, the zona fasciculata was intact and 17-hydroxycorticosteroid excretion was normal. The converse of this situation namely, hyperandrogenism associated with hyperplasia of the zona reticularis had previously been reported (Blackman, 1946). Jones and Griffiths (1968) reported that sulphurylation of DHA occurred only in the zona reticularis. Further supporting the concept that the reticularis is the source of adrenal androgens are the findings in the fetal adrenal and its prominent 'fetal zone'. In the fetal adrenal, which produces large quantities of DHAS, the 'fetal zone' is next to the reticularis, is made up of similar 'compact' cells, and disappears in the neonatal period at a time when adrenal DHAS secretion also declines. It has been reported that the fetal zone is deficient in Δ^5-3β-ol-dehydrogenase activity (Goldman et al, 1966), which could explain the large amounts of DHAS being secreted, but Winter et al (1980) were not able to confirm this in experiments carried out in vitro.

While these are strong arguments in favour of specific zona steroidogenic function, it has also been shown that both the fasciculata and the reticularis can synthesize glucocorticoids and androgens (Griffiths et al, 1963; Bell et al, 1980), and Maroulis and Abraham (1980) found both glucocorticoids and androgens in both these zones of the cortex. Interestingly, they found relatively high levels of dihydrotestosterone in the adrenal. They concluded that the difference in the secretion of steroids by the zones may be quantitative and not qualitative

Androgens in the adrenal vein

While the presence of enzymes necessary for the synthesis of specific steroids and the presence of those steroids in the adrenal are of

importance, the steroids actually secreted by the adrenal remain the critical point, namely the relative contribution of the adrenal to the overall amount of a steroid entering the blood each day. Because adrenal vein catheterizations are not done routinely in normal, healthy women, there are relatively few measurements on adrenal vein androgen concentrations. The paucity of these measurements, coupled with problems caused by episodic secretion and in measuring adrenal blood flow, mean that calculations of the actual adrenal secretion rate are, at best, rough estimates of the normal situation.

Early attempts to measure androgens in adrenal vein blood were not conclusive, but Wieland et al (1965) reported that in five women, including one with hirsutism, there were significant arteriovenous (A–V) gradients for DHAS, DHA and Δ^4-A across the adrenal, indicating adrenal secretion of these compounds. A small gradient for androst-5-ene-3β,17β-diol was also found but they were not able to show a gradient for T. No measurements or assumptions concerning adrenal blood flow were made, so actual secretion rates could not be calculated. Baird et al (1969) in one hirsute and one post-menopausal woman noted gradients across the adrenal for both Δ^4-A and T. The gradients for Δ^4-A were 20–100 as opposed to 2–6 for T. Kirschner and Jacobs (1971) reported a significant adrenal gradient for testosterone in 13 of 19 non-hirsute women with lymphoma, breast cancer or heart disease. Δ^4-A gradients were noted in only 5 of 12 of these same women and the gradients did not appear greater than those of T. Positive gradients for T were noted in 3 of 3 hypertensive women, but concentrations of DHA and Δ^4-A were not measured (Oake et al, 1974).

Initial studies (Lombardo et al, 1959) failed to show DHAS 'normal' in adrenal vein blood. However, Baulieu et al (1965) in two 'normal' men and a 70-year-old woman showed a significant gradient for DHAS across the adrenal, and concluded that DHAS secretion was always greater than that of DHA. Nieschlag et al (1973) reported a significant adrenal gradient for DHA in all 10 hirsute women but for DHAS in only 4 of 10. This study draws attention to the fact that with the relatively high concentrations of DHAS in plasma, its long half-life and the low adrenal blood flow, A–V gradients for DHAS may be very difficult to demonstrate.

Therefore, it would seem that in women the adrenal gland secretes primarily DHA, DHAS and Δ^4-A as androgen precursors, and secretes smaller amounts of the potent androgen T. The adrenal secretion of androstenediol is insignificant. 11β-Hydroxyandrostenedione is secreted but contributes nothing, either directly or as a precursor, to androgenic activity. The secretion rates of these compounds will be discussed later in conjunction with those of the ovary.

Control of adrenal androgen secretion

The major stimulus to glucocorticoid secretion by the adrenal is adrenocorticotropic hormone (ACTH) and the administration of ACTH is followed by a rapid rise in glucocorticoid levels in the blood and urine. The

administration of ACTH is also followed by a rise in urinary 17-ketosteroids (Kappas and Gallagher, 1955; Hamman and Martin, 1964) and in plasma 17-ketosteroids (Migeon, 1955). The rise in urinary 17-ketosteroids in response to ACTH is less than the rise of urinary 17-hydroxycorticosteroids in both actual numbers and as percentages of basal values.

ACTH can stimulate adrenal androgen secretion, as shown by Vaitukaitis et al (1969), who reported that adrenal vein levels of DHA, but not of DHAS, rose significantly after synthetic ACTH 1–24. Nieschlag et al (1973) showed that DHA levels rose in all nine normal women within 2 hours following the start of an 8-hour infusion of 40 IU of ACTH. However, this rise was not sustained in all women throughout the infusion. In some, but not all, subjects the concentrations of DHAS rose significantly, and this rise was sustained for the duration of the infusion. Vermeulen and Ando (1978) also reported that the administration of synthetic ACTH, 0.25 mg, resulted in a prompt rise in DHA levels in peripheral blood from a basal level of 4 ng/ml to a peak of 12 ng/ml, a three-fold increase in 60 min. Cortisol levels also showed a three-fold rise with a peak at 90 min, but DHAS levels remained unchanged throughout the 120-min experiment.

Weil et al (1979) noted an increase in circulating Δ^4-A levels 60 min after ACTH 0.25 mg intravenous, from a basal level of 0.97 ng/ml to 1.99 ng/ml. At the same time there was little or no change in testosterone levels, from 0.24 ng/ml to 0.29 ng/ml. Following a five-hour infusion of ACTH, Anderson and Yen (1976) noted that the circulating levels of Δ^4-A rose almost three-fold, and testosterone rose two-fold. It is possible that the rise in testosterone resulted from the peripheral conversion of the increased Δ^4-A, a major source of testosterone in women (Horton and Tait, 1966). Givens et al (1975) also noted a slight rise in T after ACTH in normal women previously given dexamethasone, but the rise in Δ^4-A was far greater than the rise in T. These authors also felt the rise in T could be explained by peripheral conversion of Δ^4-A. They also noted diurnal variations in the levels of Δ^4-A and T which were temporally related to the diurnal variation in cortisol secretion. Δ^4-A levels varied about 40% from peak to nadir, but the variation in T was only 20% and not significant. The levels of DHA have been noted to vary episodically and synchronously throughout the day with those of cortisol (Rosenfeld et al, 1975) while the levels of DHAS did not fluctuate either to the same degree or synchronously with those of DHA and cortisol. Thus the secretion of certain adrenal androgens occurs synchronously with cortisol and can be stimulated by ACTH. The major site for ACTH stimulation is on the conversion of cholesterol to pregnenolone. Whether there are other hormones which also control adrenal androgen secretion has long been a source of discussion.

Albright et al (1942) postulated that luteinizing hormone (LH) may have a controlling influence on adrenal androgen secretion. However, while human chorionic gonadotropin (hCG) may play a role in androgen secretion by the fetal adrenal cortex, there is little evidence that

gonadotropins have a direct influence on adrenal androgen secretion (Grumbach et al, 1978; Parker and Odell, 1980) in the adult. The marked increase in adrenal androgen secretion which occurs at puberty without a commensurate increase in the levels or secretion of either ACTH or cortisol (Kenny et al, 1966; Apter et al, 1979; DePeretti and Forest, 1976) was interpreted as due to stimulation by a non-ACTH-like hormone (Grumbach et al, 1978). Parker et al (1983) reported on the isolation of a 60 000 molecular weight glycopeptide from human pituitaries which stimulated the production of DHA but not cortisol by suspensions of dog adrenal cells.

Subjects with prolactinomas have been noted to have elevated levels of DHA and/or DHAS (Murru et al, 1977; Carter et al, 1977; Vermeulen and Ando, 1978), but in other studies DHA and/or DHAS were within the normal range (Parker et al, 1978; Drucher and David, 1980). It would appear, therefore, that prolactin, at the physiological level, does not stimulate adrenal androgen secretion.

The adrenal secretion of androgens appears to be controlled by ACTH and an adrenal androgen secretory hormone as postulated by Grumbach et al (1978) and Parker and Odell (1980). The relative importance of each in the normal control of adrenal androgen secretion remains uncertain.

OVARY

It had long been considered that any circulating androgens present in women arose solely from the adrenal gland, and that there was 'no reason to believe this organ [ovary] is an important source of androgens in normal women' (Dorfman and Shipley, 1956). Subsequently, studies have shown that the ovary secretes androgens in greater quantity than oestrogens (Baird et al, 1968).

Biosynthesis

The overall pathway for androgen biosynthesis in the ovary (Figure 2) is generally similar to that described for the adrenal gland. The enzymes involved and their intracellular location are similar. The Δ^5-pathway is favoured in the follicle and stroma, but in the corpus luteum the Δ^4-pathway appears to be favoured (Marsh et al, 1976).

Location of ovarian androgen biosynthesis

Androgen biosynthesis has been noted to occur in each of the various specialized areas of the ovary: The graafian follicle (Ryan and Petro, 1966), corpus luteum (Hammerstein et al, 1964) and stroma (Savard et al, 1965). In the thecal cells of the follicle the major androgen synthesized is Δ^4-A (Ryan and Petro, 1966), but small amounts of DHA (Savard et al, 1965), T and dihydrotestosterone (DHT) (McNatty et al, 1979) have been recovered after in vitro incubations of human thecal cells. The original

report that granulosa cells of the follicle secrete little, if any, androgens (Ryan and Petro, 1966) was confirmed in later studies (McNatty et al, 1979). While Δ^4-A, T and DHT were released into the medium after incubations of granulosa cells, the amounts per cell were several orders of magnitude less than for thecal cells. The corpus luteum produces Δ^4-A but little T (Savard et al, 1965) and these androgens are thought to originate from the theca lutein cells of the corpus luteum.

The stroma, or interstitial tissue, was shown capable of synthesizing DHA (Savard et al, 1965), Δ^4-A, T and DHT (Savard et al, 1965; Rice et al, 1964b; McNatty et al, 1979). While Δ^4-A was the major androgen identified, the amounts of T formed were greater than from other tissues (Savard et al, 1965).

While these studies suggest that A would be the androgen secreted in greatest amounts by the ovary, the exact contribution from each compartment is not readily measurable. Perhaps the best approximation in this regard is measurements in ovarian vein blood at different times of the cycle as noted below.

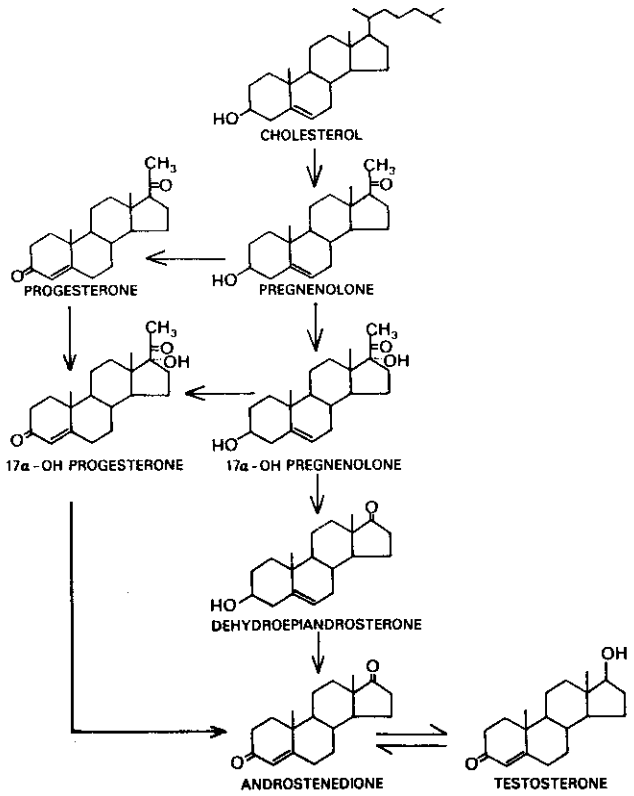

Figure 2. Pathways for androgen biosynthesis in the ovary.

Concentration of androgens in ovarian vein blood

In a report of androgen concentrations in ovarian vein blood, Lloyd et al (1971) found gradients across the ovary for A and T in both the follicular and the luteal phases of the cycle. The ovarian/peripheral vein ratios were generally greater for A than for T, and the gradients did not appear to vary in any specific fashion throughout the cycle. Gradients for DHA were not specifically measured, but there were differences in the concentrations of DHA between the left and right ovarian veins in those individuals in whom such measurements were made. These findings for DHA would indicate ovarian secretion of this steroid but without peripheral measurements further conjectures on the magnitude of its secretion would be meaningless. The results of Lloyd et al (1971) are in general agreement with a smaller study in normal women in which Rivarola et al (1967) also noted gradients for T, Δ^4-A and DHA. The latter workers were unable to detect any gradient for DHAS. McNatty et al (1976) noted a significant gradient across the ovarian vein for Δ^4-A and T but did not measure DHA or DHAS. However, these investigators, sampling both ovarian veins and at different times of the cycle, noted similar concentrations in both ovarian veins early in the cycle, but a marked difference in the concentrations in the ovarian veins was noted in the mid-follicular phase. The concentrations then became relatively equal in the luteal phase. These data indicate that the dominant follicle (Hodgen, 1982) was the source of most of the androgen. The higher concentrations of both A and T were noted in the vein of the ovary with the large (>8 mm) follicle or with the corpus luteum. It was also noted that the follicular fluid contained concentrations of androgens that were far greater than those in peripheral plasma, and that the concentrations in fluid from large and small follicles were generally similar except in the late follicular phase.

Although 5α-reductase activity has been noted in ovarian tissue (Smith et al, 1974), the concentration of DHT in the ovarian vein was not higher than in peripheral blood (Calabresi et al, 1976).

In post-menopausal women, measurements of androgens in ovarian vein blood indicate that there is still some ovarian secretion of Δ^4-A and T (primarily the latter), but no evidence for DHA, DHAS or DHT secretion (Judd et al, 1974; Longcope et al, 1980).

Control of ovarian androgen secretion

Although both LH and follicle-stimulating hormone (FSH) stimulate the ovary, only LH is involved directly in controlling androgen synthesis and release. The cells in the compartments of the ovary that are specifically involved in androgen synthesis and production (i.e. the theca and stroma) have LH receptors (Dorrington and Armstrong, 1979; Richards, 1980), and both types of cells have been shown to respond to LH or hCG in vitro (Savard et al, 1965). While prolactin is required for corpus luteum development in some species, this does not appear to be the case for the human (Birnbaumer and Kirchick, 1983), and there is little evidence that

prolactin plays a role in ovarian androgen secretion. Therefore, androgen production by the corpus luteum would also appear to be under the control of LH (Rice et al, 1964a) which is required for the further development and function of the corpus luteum after ovulation (Fritz and Speroff, 1982). LH stimulates androgen synthesis by stimulating the conversion of cholesterol to pregnenolone.

Ovarian androgen secretion during the menstrual cycle

Since LH levels change dramatically through the cycle, and since androgen secretion from the ovary is under LH control, at least in part, it is not unexpected that ovarian androgen secretion varies through the cycle. Sequential measurements of ovarian vein androgen levels have not been made in any one individual through the cycle but peripheral blood levels are available. The levels of A and T are lowest in the early follicular phase and then rise to their highest levels just prior to, or at the time of, ovulation and then gradually fall during the luteal phase (Judd and Yen, 1973; Abraham, 1974). However, Aedo et al (1980a,b) noted that the peak of Δ^4-A and T occurred early in the luteal phase. They also noted that the secretion of Δ^4-A and T was similar in ovarian vein blood from both ovaries, indicating that the developing follicle and corpus luteum were not major sources of these steroids but that the stroma, under LH influence, was. DHT levels do not vary during the cycle (Abraham, 1974; Aedo et al, 1980b), indicating that the normal ovary is not secreting significant quantities of that androgen. DHA and DHAS levels also remain relatively stable through the cycle (Abraham, 1974; Frölich et al, 1976; Vermeulen and Verdonck, 1976).

Post-menopausal ovary

In many post-menopausal women the levels of androgens in the ovarian venous blood are higher than in arterial blood, indicating that secretion of androgens continues (Judd et al, 1974; Longcope et al, 1980). Secretion of T appears to be favoured in those women with positive gradients and probably represents the continued stimulation of stromal tissue by the elevated levels of LH.

RELATIVE CONTRIBUTIONS OF THE ADRENAL AND OVARY TO OVERALL ANDROGEN PRODUCTION (Figures 3 and 4)

In considering the secretion of androgens by the adrenal and ovary, the major aspect is the relative contribution of each gland to the overall production rates of these steroids. As shown in Figure 3, DHAS is secreted from the adrenal gland but not the ovary, although a small amount is derived from the peripheral conversion of DHA. Using data from Sandberg et al (1964) and Gant et al (1971) on the metabolic clearance rate of DHAS (~8 l/day) and data from Abraham (1974), Zumoff et al (1980)

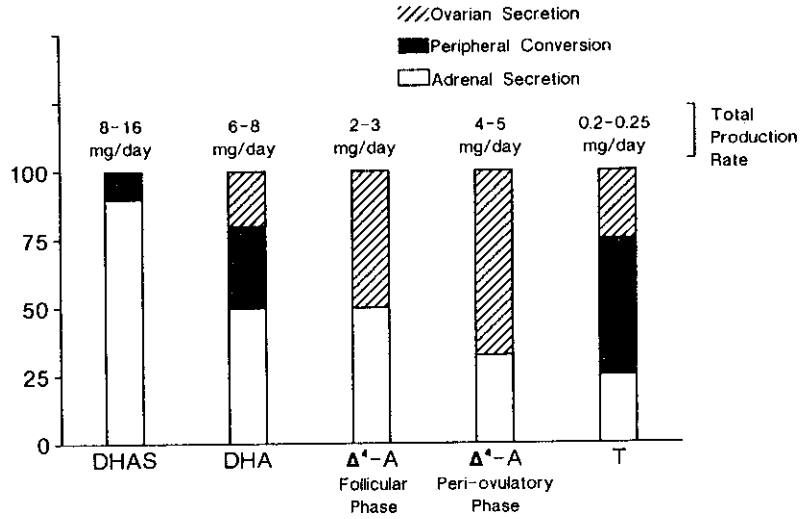

Figure 3. Percentage contributions of adrenal secretion, conversion in peripheral tissues and ovarian secretion to androgen production. For each steroid, total production is normalized to 100% but actual ranges of production for each steroid are noted above each bar.

and Cumming et al (1982) on the values for DHAS concentration (1–2 μg/ml) a production rate can be calculated of 8–16 mg/day. Of this, 7–14 mg/day, or 90%, will arise from the adrenal cortex and the rest by peripheral conversion of DHA.

For DHA with a metabolic clearance rate of 1600 l/day (Horton and Tait, 1966) and circulating levels of 4–5 ng/ml (Landgren et al, 1977; Zumoff et al, 1980) the production rate will be between 6 and 8 mg/day as reported by Kirschner et al (1973). The direct adrenal contribution will be about 50% (3–4 mg/day) while 20% (1–2 mg/day) will arise from the ovary and the other 30% will arise from peripheral conversion of DHAS (Abraham, 1974; Poortman et al, 1980). Thus the adrenal contributes 80%, directly and indirectly, to the production rate of DHA.

The production rate of Δ^4-A has been reported to be in the range of 2–3 mg/day (Baird et al, 1968) in the follicular phase of the cycle but it increases to 4–5 mg/day in the peri-ovulatory portion of the cycle; the latter figure being based on a plasma concentration of ~3 ng/ml (Baird et al, 1974; Ribeiro et al, 1974) and a metabolic clearance rate of ~2000 ml/day (Horton and Tait, 1966). The adrenal secretion will be relatively constant at 1.0–1.5 mg/day throughout the cycle, but ovarian secretion will fluctuate from ~1.0 mg/day to 3–3.5 mg/day depending on the stage of the cycle.

The production rate of T is in the range of 200–250 μg/day (Horton and Tait, 1966; Kirschner and Bardin, 1972; Saez et al, 1972) and does not appear to alter markedly during the cycle, even though the production rate of androstenedione, its major precursor, does vary. The adrenal secretes

about 50 μg/day and the ovary secretes an additional 50 μg/day, but the major source is the peripheral conversion of androstenedione, with some contribution from DHA.

Neither the adrenal nor the ovary contributes significant amounts to the production rates of androstenediol or dihydrotestosterone and only the adrenal secretes 11β-hydroxyandrostenedione which has no androgenic potential itself or as a pre-hormone.

SUMMARY

Both the adrenal and the ovary contain the biosynthetic pathways necessary for androgen synthesis and secretion. The fetal ovary is not very active but the fetal adrenal is an important source of DHAS. However the secretion of DHAS declines markedly after birth and until puberty there is little androgen secretion by either the adrenal or the ovary.

Post-pubertally, the adrenal secretes DHAS, DHA, Δ^4-A and T from the reticularis and probably the fasciculata. This secretion is under ACTH control, at least in part, but apparently also under control of another pituitary polypeptide tentatively called 'adrenal androgen secretory hormone'. The adrenal secretion rates are in the range of 7–14 mg/day for DHAS, 3–4 mg/day for DHA, 1–1.5 mg/day for Δ^4-A and 50 μg/day for T.

Androgen secretion from the ovary arises in part from the theca cells of the follicle, the corpus luteum and the stromal cells, under LH control, and will vary somewhat during the normal menstrual cycle. The ovarian secretion rate in the follicular phase is 1–2 mg/day for DHA, 1–1.5 mg/day for Δ^4-A and about 50 μg/day for T. In the peri-ovulatory period the

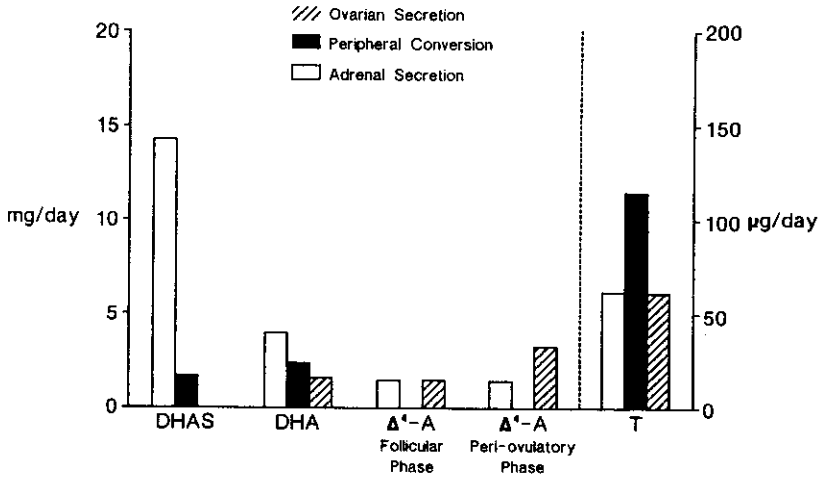

Figure 4. Secretion rates of androgens by the adrenal, by conversion in peripheral tissue and by the ovary. Scale for DHAS, DHA and Δ^4-A on the left, T on the right.

secretion rate of Δ^4-A can rise to 3–3.5 mg/day but there appears to be little change in the secretion of DHA and T. The normal ovary does not secrete significant amounts of DHAS.

In about 50% of post-menopausal women the ovaries continue to secrete some T but little Δ^4-A or DHA.

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2

Gonadal and Adrenal Androgen Secretion in Hirsute Females

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Hirsutism and related symptoms may be due to (1) glandular causes, i.e. non-tumorous and tumorous ovarian and/or adrenal hypersecretion of androgenic steroids (2) extraglandular causes, i.e. increased peripheral conversion of preandrogens, decreased specific plasma androgen binding, target organ hypersensitivity, or administration of androgenic drugs or (3) a combination of any of these factors.

Numerous methods have been used to verify the presence of excess androgens and to determine their origin (Maroulis, 1981). Depending on the number of steroids analysed, elevated peripheral levels of at least one androgen can be demonstrated in more than 90% of cases. However, the type, frequency, and extent of abnormalities vary considerably.

None of the circulating androgens has an exclusive gonadal or adrenal source. Plasma concentrations reflect the sum of entry into circulation from glandular secretion and extraglandular tissue production, as well as their hepatic and extrahepatic clearance. Thus, the measurement of peripheral steroids does not allow the determination of their site of origin. The estimation of secretion rates is complicated by the complexities of ovarian and adrenal steroidogenesis. Multiple variables have to be taken into account, e.g. episodic, diurnal, cyclic and age-related variations.

GENERAL METHODOLOGICAL CONSIDERATIONS

Various approaches have been utilized to study glandular secretion in hirsute females; however, all of these methods are associated with limited validity and provide only semiquantitative estimates of momentary secretory activity (Baird, 1976; James et al, 1976).

Isotope dilution techniques yield approximations of the total blood production rates from the measurement of plasma concentrations and metabolic clearance rates; they cannot identify the gonadal and adrenal contributions. This requires additional analysis of samples obtained