J. Soc. Cosmet. Chem. **25** 381–395 (1974)

Sex hormones and skin

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The 1974 Medal Lecture by Professor F. J. Ebling, Department of Zoology, University of Sheffield, Sheffield S10 2TN, delivered before the Society of Cosmetic Chemists of Great Britain on the 7th March 1974 with G. A. C. Pitt Esq., President of the Society in the Chair.

Synopsis—As well as its more obvious ANATOMICAL and PHYSIOLOGICAL functions the SKIN plays an important part in social communication by vision, touch and smell. The epidermal surface, the activity of the glands and the distribution of the HAIR are particular features of skin which are concerned with sexual communication, and it is thus not surprising that they are profoundly influenced by HORMONES. STEROIDS have been widely used in efforts to improve skin texture; the effect of OESTROGENS is equivocal, but ANDROGENS certainly stimulate epidermal cell division. The SEBACEOUS GLANDS are unequivocally stimulated by androgens and inhibited both by oestrogens and anti-androgenic steroids, though their modes of action are not identical. PITUITARY factors appear to be necessary, at least in the rat, for the response of the sebaceous glands to TESTOSTERONE, and it seems possible they may act upon the conversion of the steroid to its active metabolites. Human body, AXILLARY and pubic hair is similarly androgen dependent. So sebum secretion, the growth of sexual hair, and hirsutism may be inter-related by their link with steroid metabolism within the skin. Is it possible that one function, or at least one by-product, of cutaneous androgen metabolism is the manufacture of pheromones or odours?

Introduction

When the human skin is viewed against its evolutionary inheritance, certain features are clear. We do not question its functions as a sensory structure or as a defensive barrier against both physical injury and chemical assault. Its role in preventing loss of precious water has been part of vertebrate history ever since some distant amphibious ancestor took the first steps to emerge from a primaeval swamp.

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The evolution of warm blood-bloodedness in the mammals was accompanied by the development of an insulating material known as hair. To adjust the pelt at intervals to seasonal changes in temperature, hair follicles undergo cycles of activity which appear to be linked to environmental changes through the endocrine system; even the human hair may retain a remnant of this moult cycle. But men were enabled to leave the forests and fan out through new fields by the development of superb mechanisms for keeping cool. Hair was lost, its insulating qualities being to some extent replaced by fat; the vascularity of skin became greatly increased, though heat loss could be reduced by shunting the blood through the deeper layers; and eccrine glands which could be brought into play for cooling developed over virtually the whole surface of the body.

The first men were almost certainly dark skinned; as the body hair became reduced, melanin pigmentation provided a protection against the damaging effects of ultraviolet radiation. But as man moved into areas where even the summer sun moved low in the sky the threat of radiation damage was replaced by another, namely the failure to synthesize vitamin D. So natural selection switched to favour pale skin. The evolutionary legacy is still reflected by the fact that Europeans tend to develop skin cancer in the tropics and West Indian immigrants to get rickets in Great Britain.

Our thinking about skin tends to be dominated by these evolutionary facts which concern our biological survival as individuals. But there is another level at which natural selection has operated, namely that of the social group. The survival of the group depends upon its coherence by communication, between the sexes, as Darwin himself realized, in the family, and throughout the troop. Although overshadowed by the sophisticated use of language, and sometimes suppressed because of its embarrassing inevitability, the role of skin remains important.

Much of the behaviour of our vertebrate ancestors was innate, that is to say it was programmed by heredity; patterns of courtship or aggression in one individual were automatically set in motion by so-called releasing mechanisms—physical structures, colours, movements, scents or sounds—in another. While mammalian and particularly human social interactions have become increasingly dependent on learned and thus much more rapidly modifiable patterns, the releasing features are still present, and more than a remnant of the innate responses still remains.

The buttocks provide a good fundamental example of a visual releaser. When a female ape is sexually receptive, they become red and swollen and she displays them to attract the male. In man they become permanently

inflated, especially in the female, to reach their greatest natural development in the steatopygia of the African Bushwoman, and their ultimate cultural exaggeration in the bustle. Desmond Morris has made the further interesting suggestion that since all the remaining sexual signals are in front of the body, the breasts have developed as a buttock mimic, thus making the human female equally attractive from either aspect.

I could discuss many more examples of structural releasers of sexual interest, such as lips, cheeks, eyes and hair, and it is hardly necessary for me to point out that all these are the targets of cosmetic chemistry in its efforts to improve on nature. I want, however, to confine myself to three features of the skin which are of sexual significance and which underlie the understanding of its hormonal connections, namely texture, smell and hair distribution.

At the beginning of this century, a work on pathology described skin as 'a tissue which is silk to the touch, the most exquisitely beautiful surface in the universe to the eye . . . more beautiful than velvet, softer and more pliable than silk, more impervious than rubber . . . '. The sensation of touch is one of the earliest of all pleasurable experiences and it becomes a powerful sexual stimulus; in the words of Havelock Ellis (1) 'Touch sensations constitute a vast gamut for the expression of affection, with at one end the note of minimum personal affection in the brief and limited touch involved by the conventional hand-shake and the conventional kiss, and at the other end the final and intimate contact in which passion finds the supreme satisfaction of its most profound desire . . . . Even the hand-shake of a sympathetic man is enough in some chaste and sensitive women to produce sexual excitement or sometimes even the orgasm'. (He was, I think, writing of an age when women's sexual feelings were severely repressed.) The erotic appeal of skin is visual as well as tactile. It looks and feels best when it is unwrinkled, smooth or even wet—facts exploited by photographers as well as by cosmeticians—and for some persons it seems that leather or even rubber works even better than the real thing.

Odour is a characteristic of the human body. In addition to the breath, Havelock Ellis (1) distinguished between the odours of the general skin, the hair and scalp, the armpit, the perineum, the mons veneris and the prepuce, and pointed out that the scents were detectable even in healthy and well-washed persons under normal conditions. Some of these regions of the body, for example the axilla and the genital areas, contain aggregations of tubular apocrine glands opening into the hair follicles and there is little doubt that these are responsible for the odorous secretion. But the general body skin

and the scalp have only holocrine sebaceous glands and the eccrine sweat glands; one cannot dismiss the thought that the former, if not the latter also, may contribute to the smell as well as to the texture of the skin.

Both the sebaceous and apocrine glands remain small during infancy and become active only after puberty. Body odours change at puberty, and characteristic odours are said to be emitted during sexual excitement by both men and women. Havelock Ellis (1) records the case of a woman who emitted a rose odour for 2 days after coitus, and mentions that in the seventeenth century there was a monk in Prague who was prepared to diagnose the chastity of women by their smell. Whatever is true of man, there is increasing recognition of the role of odours, or pheromones, as sexual or social signals in other mammals (2–4). They function not only as sex attractants, but also in the marking of territory and the establishment of social hierarchy, and they are produced by a wide variety of specialized skin glands, either apocrine, sebaceous, or mixed, which can occur in almost every region of the body. The rabbit, for example, has three pairs of apocrine glands (5), the chin and anal which are used for marking territory and appear to have similar secretions, and the inguinal which is concerned with sex attraction and produces a different chemical material (6).

The chemical structure of a few animal scents is known and some, indeed, form the classic materials of human perfumery. Such are civetone, from the civet cat, and muscone, from the male musk deer, which are macrocyclic ketones (7). The musk rat produces dihydrocivetol, a saturated ring alcohol, and the black tailed deer a lactone (8).

Facial and body hair are other features of the skin which develop at puberty, though follicles growing only a fine down have been present since birth. Whether male facial hair is sexually directed towards the female as well as serving for aggressive display to other males, I am unsure. Presumably it is commonly shaved off in many cultures, not to reduce sex appeal, but as a contribution to social harmony. And in spite of the exploitation of full frontal pubic hair to arouse sexual interest in the theatre, and a recent study in which 50% of women admitted to being excited by male body hair, I suspect that the main evolutionary significance of the pubic and axillary hairs is to act as wicks for the dissemination of odour produced by the apocrine and, probably, the sebaceous glands. Whatever the function of facial, pubic, axillary and other body hair, it is clear that it is, whether in male or female, an adult character manifested only during the reign of male type sex hormones.

It is reasonable to expect, therefore, that at least three features of the

skin—texture, glandular activity and body hair—should be profoundly susceptible to the influence of sex hormones. Steroid hormones have been widely used in cosmetics to improve skin texture for such circumstantial reasons. Is this justified? The question needs, perhaps, to be put precisely: 'Are there any effects which can be objectively measured, and can their value be discerned in a double blind trial against a placebo?' If, as only too commonly, the investigator has been asked 'What evidence is there to justify the marketing of this product?' the answer, if not invariably useless, must be somewhat less respectable!

What are the qualities of 'skin texture'? Obviously, certain features can be loosely assessed by eye or touch, but do these reflect any anatomical changes which remain measurable after the skin has been assaulted by biopsy and histology? Are there differences in dermal constitution or in epidermal cell replacement, or are there more subtle changes in the keratinized surface or its lipid mantle?

Attempts to answer these questions have yielded confusing and equivocal results. In 1949, Eller and Eller (9) reported that topical application of oestrogenic ointments to the backs of senile female subjects locally increased the size of the epidermal cells, as well as accentuating the waviness of the basal layer, which in senile skin normally lacks rete-pegs. Their results might appear reasonably informative were it not for the facts that inunction of oestrogen free ointment by itself had a similar—if less marked—effect, that the ointments were applied under occlusion, and that the effective concentrations of oestrogen must have been at least 100 times greater than any amounts normally used in hormonal cosmetics.

The conclusions can, moreover, be contrasted with those reported in 1962 by Montagna, Formisano and Kligman (10). Three groups, each of 10 men and 10 women, aged 65 or more, were anointed daily for 6 weeks on one side of the face and on the back of one hand, with 1% testosterone propionate, 1% progesterone, or 0.5% ethynyl oestradiol, respectively. The opposite side of the face and the other hand were treated with ointment base alone. In untreated senile skin the Malpighian cells were shrivelled and vacuolated, with irregular nuclei, but testosterone or progesterone regularly restored the properties of younger skin, as well as giving it increased fullness and producing some alleviation of wrinkles. Only a few of those treated with oestrogen or the ointment base alone showed any amelioration. This effect of testosterone is not perhaps surprising, since there is general agreement that given systemically, it stimulates epidermal cell division in

experimental animals, in spite of the disputed contention that oestrogens do so (for review see 11).

Clinical trials of hormonal creams have produced equally inconclusive results. Behrman (12) put an oestrogen on one side of the face in some 30 women, using an oestrogen free cream on the other. Neither the observers nor the women themselves noticed any differences. Similarly, in a double blind trial carried out by the British Consumers' Association (13), a face cream containing oestrogen scored no better than one without hormone.

Steroids used in face creams have not been confined to oestrogens. It has, for example, been claimed that pregnenolone (14), a common precursor of progestogens, androgens and oestrogens, will produce a degree of oedema in senile skin, though it must be admitted that the cosmetic results are not dramatic (15).

When we turn to the skin glands, the experimental results are much easier to interpret. In experimental animals or in man, and whether measured histologically or by changes in sebum secretion, it is generally agreed that male hormones increase, and oestrogenic female hormones decrease the activity of the sebaceous glands (6, 16, 17). The effect of injecting testosterone propionate or oestradiol benzoate on the sebaceous glands of immature female rats was described by me in 1948 (18). Similarly, it can be shown in the rabbit that specialized glands of apocrine type are enlarged by testosterone and diminished by oestradiol (19).

Using a simple technique in which the sebum is collected from the forehead on pads of cigarette papers, Strauss and Pochi (20, 21) have clearly shown that sebaceous secretion is influenced by similar factors in man. They have established that secretion is very low until puberty, when it rises in both males and females, that oral treatment with methyl testosterone prior to puberty, though not afterwards, will greatly increase it, and that oral oestrogens will markedly suppress it in adult males.

We have studied sebum production in rats by measuring the changes in the level of hair fat (22). The animals are washed in detergent and warm water to reduce the base level, and dried with a hair dryer. A sample of hair is then clipped from one flank, and the level of fat determined gravimetrically after successive extraction with di-ethyl ether. After an interval of days, a sample from the other flank is similarly treated. That testosterone increases and oestradiol decreases secretion has been clearly demonstrated in castrated male and in spayed female rats.

The sebaceous glands are holocrine, that is to say that their secretion is formed by complete disintegration of the cells, which are replaced from

the periphery. Clearly there are two main components of secretion: the formation of new cells and the synthesis of sebum within them. It was therefore of great interest to discover whether steroid hormones act at one or both of these points. The rate of cell division was determined by mitotic counts in histological sections, the rats being injected with colchicine 5 h before they were killed, a procedure which arrests dividing cells in the metaphase. The somewhat unpredictable conclusion, confirmed a number of times, was that whereas testosterone does indeed greatly increase cell division, oestradiol has little or no effect on it, even though in low doses it markedly depresses secretion (23). By administering both steroids simultaneously, it is thus possible to produce a high rate of mitosis coupled with a low rate of secretion (24). It must, therefore, be concluded that oestradiol reduces secretion not by inhibiting cell replacement but by interfering with sebum synthesis within the cells themselves.

The opportunity for further testing of this hypothesis arose by the discovery of steroids which were anti-androgenic but not oestrogenic. It was of obvious interest to see whether such compounds would, in common with oestrogens, reduce sebum secretion in animals stimulated by testosterone. But, if the compounds are anti-androgenic as distinct from oestrogenic, they ought, unlike oestrogens, also to reduce cell division. We were able to show that this was true for several anti-androgenic steroids. In an experiment on cyproterone acetate (25), six litter-mate groups of six castrated male rates were used (*Fig. 1*). A dose of 2 mg per day of the anti-androgen significantly reduced both sebum secretion and sebaceous mitoses in rats treated with testosterone implants giving an uptake of 0.2 mg per day. A dose of oestradiol of the order of only 2 μg per day, however, caused a much greater reduction in sebum secretion, without significantly affecting mitosis. If the two suppressing steroids are acting at different points, their effects when administered together should be greater than either by itself. This is so. When 2 μg of oestradiol was added to 2 mg of cyproterone acetate, the result was a further reduction in sebum secretion. If the steroids had acted at the same point, it is inconceivable that any effect would have been produced by increasing the dose by one-thousandth. These results ought to dispose of the view that oestrogen competes with androgens in any 'anti-androgenic' sense. They are also evidence against the view that oestrogens reduce sebaceous secretion by suppressing endogenous androgen production, for that would inevitably result in reduced sebaceous mitosis.

Sebaceous secretion is also influenced by the pituitary (*Fig. 2*). Removal of the pituitary reduces sebum production in castrated rats and treatment

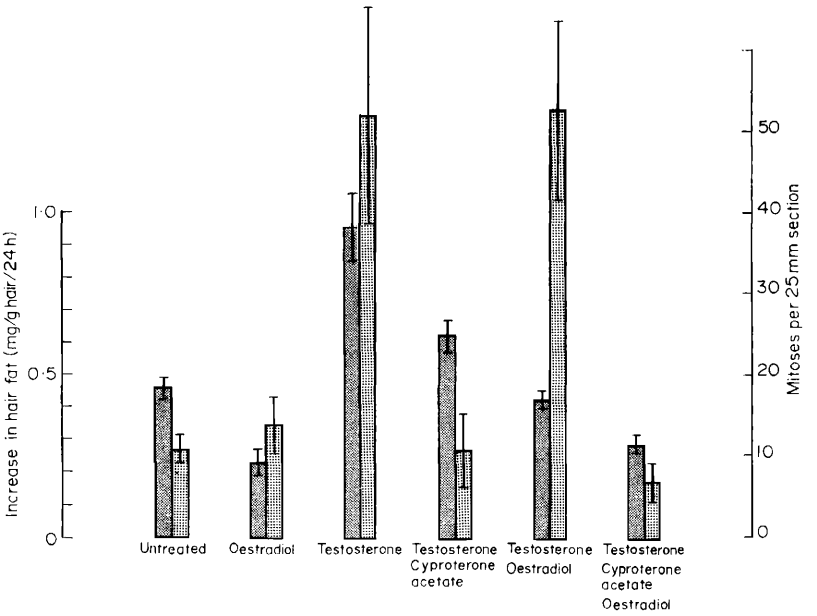

Figure 1. Independent and combined effects of oestradiol and cyproterone acetate in castrated rats treated with testosterone. Means ± SEM for six litters, each of six rats. The changes in hair fat were measured between 16 and 24 days after the start of treatment. Details of dosage are given in the text.

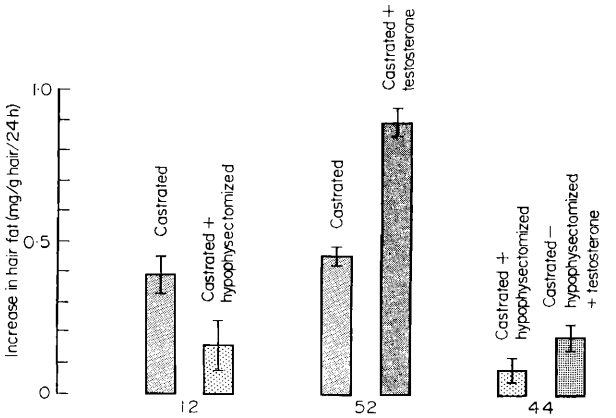

Figure 2. Effects on sebum secretion of hypophysectomy in castrated rats (left-hand group), and of testosterone in castrated rats (centre group) and in hypophysectomized-castrated rats (right-hand group). The numbers of litter-mate pairs used for the comparisons are shown below each set of histograms.

with testosterone then results in a much lower level of secretion than when the pituitary is present (26, 27). There is general agreement about this, but considerable dispute about how the facts should be explained (28). Shuster and Thody maintain that the increment actually due to testosterone is the same whether or not the pituitary is present, but that pituitary hormones have an independent effect on the skin, either directly or indirectly through other endocrine organs. They claim that MSH is the major, indeed the only, pituitary hormone acting directly on the skin (29), and they suggest that thyrotrophic hormone, acting through the thyroid gland, indirectly but independently affects the sebaceous glands (30). A full response to testosterone thus requires the additive effects of all these hormones.

I do not dispute that thyroid hormone or pituitary factors may have direct and independent effects on sebaceous secretion. The disagreement arises because I believe that irrespective of any such effects, the pituitary may actually potentiate the response to testosterone, producing a synergistic effect over and above any purely additive one. Moreover, I do not believe MSH has been established as the sole pituitary factor; growth hormone and prolactin are still candidates.

That pituitary factors play such a permissive role in the response to testosterone was indicated in experiments, performed about 20 years ago by Rothman and his co-workers (31) and by myself (32), using gland size as the criterion. The conclusion is amply borne out by hair fat measurements. During the last 7 years we have measured the effect of testosterone on sebum secretion in 52 castrated rats using matched litter mates as untreated controls, and in 44 hypophysectomized castrated rats similarly matched (*Figs 2 and 3*). The mean increment due to testosterone in the hypophysectomized animals was only 22% of that in those with intact pituitaries (27). Moreover, in somewhat smaller groups of rats, we have been able to restore the full response with preparations of growth hormone (*Fig. 3*) or prolactin (26).

The concept of a permissive role in the response to androgens for one or more pituitary factors may be important. Following the evidence that testosterone is metabolized in its target tissues to 5α-dihydrotestosterone, we tested the effect of this steroid on sebaceous secretion. In castrated rats the response was similar to that of testosterone, but in hypophysectomized rats it was relatively greater (33). We were similarly able to demonstrate significant responses to androstenedione (33) and to 5α-androstane-3β, 17β-diol (34), though a number of other metabolites, including 5α-androstanedione and androsterone, gave insignificant responses (*Fig. 3*). These

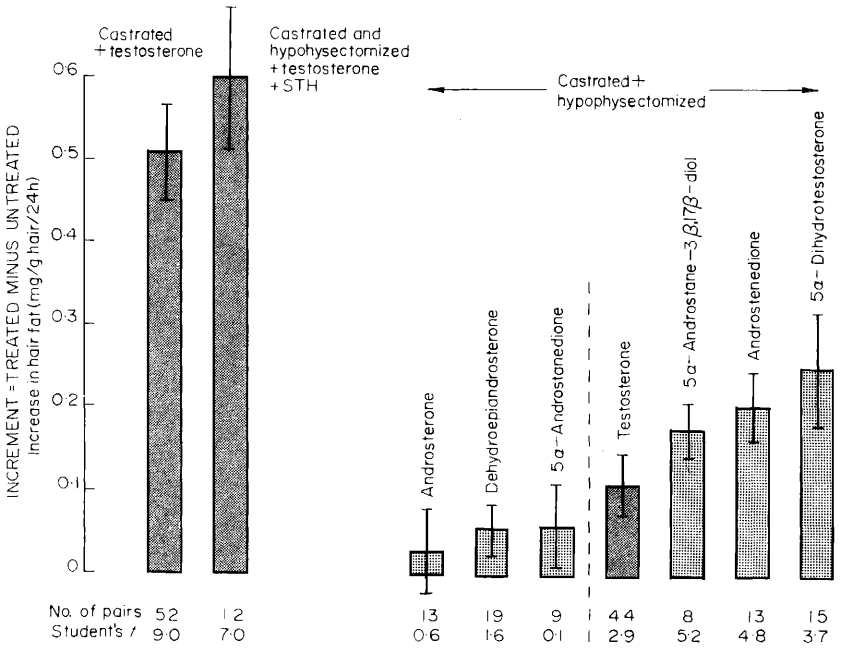

Figure 3. Increments in sebum production produced in rats by doses of 0.2 mg/24 h of steroid, calculated by subtracting the increase in hair fat (expressed as mg/g hair/24 h) in a litter mate control from the increase in each treated animal. STH = bovine growth hormone (Squibb).

results suggest that the response to testosterone may be dependent on its conversion to 5α-dihydrotestosterone and perhaps to the 5α-androstanediols (*Fig. 4*) and that the conversion may, at least in the skin, be pituitary dependent. This hypothesis would be very tidy, were it not for the fact that androstenedione, also, appears fairly potent without further conversion.

The next stage in such an investigation is clearly to compare the metabolism of testosterone in the presence and absence of the pituitary. So we have attempted to identify the principal metabolites present in the skin and other target organs 1 h after injection of testosterone-4-^{14}C. In castrated rats, only about 5% of the total activity in the skin samples remained present as unchanged testosterone; about 35% was recovered as 5α-dihydrotestosterone and about 5% as androstenedione. In contrast, in two experiments each using pooled material from 25–30 hypophysectomized-castrated rats, 70 and 40% of the radioactivity, respectively, was recovered in unchanged testosterone. The evidence is consistent with the view that the

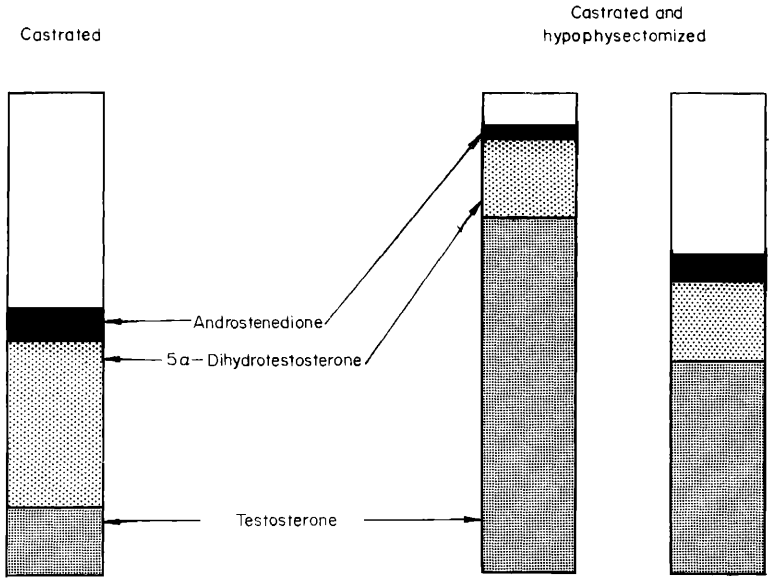

Figure 4. Recovery of identified metabolites, expressed as percentage of total recovered radioactivity in skin samples, 1 h after injection of testosterone-4-^{14}C into male rats. Each histogram represents results from a pool of 25–30 rats.

response of the skin to androgens involves their conversion to active metabolites which is pituitary mediated, though more results are needed to substantiate the hypothesis.

Finally, we come to body hair. The problem is usually not how to stimulate hair growth, but how to suppress it in women in which it occurs in culturally unacceptable amounts. While there is no doubt that the facial, axillary, pubic and body hair is all androgen dependent, growth of facial and body hair is often abnormal in women who show no apparent endocrine disturbance. Is it possible that this 'idiopathic' hirsutism is also related to peripheral androgen conversion? There is evidence that genital skin from both men and women is better able than general body skin to convert testosterone to 5α-dihydrotestosterone, and this is true for the foetus as well as the adult (35). But an even more interesting clue comes from a recent report that hirsute women excrete five times as much 5α-androstanediol as normal subjects (36). Does the growth of sexual hair perhaps depend on the conversion at site of endogenous androgens not only 5α-dihydrotestosterone but to the 5α-androstanediols?

I have travelled a fair distance in my discourse, and the time has come

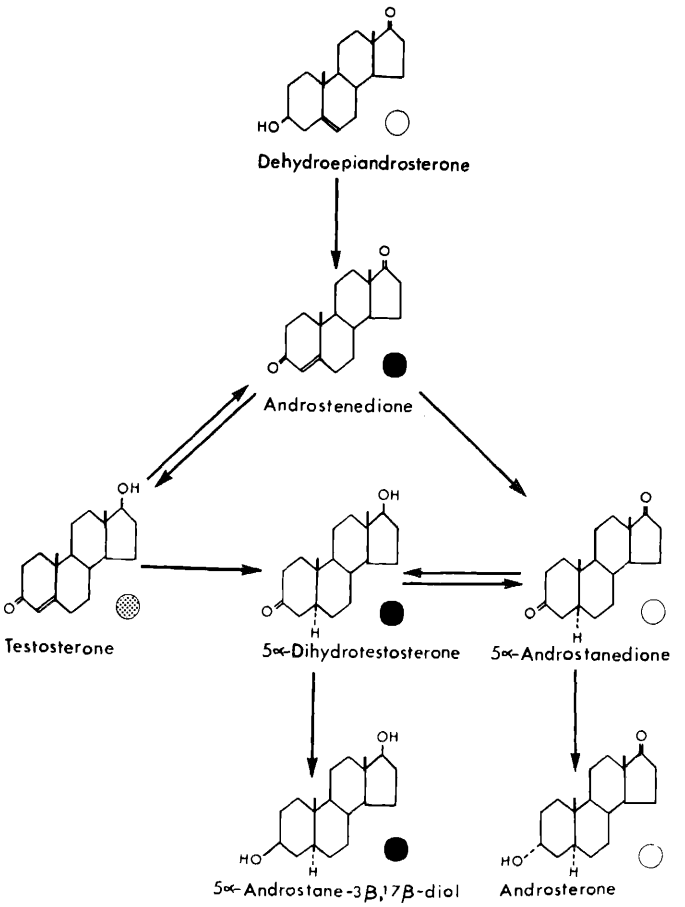

Figure 5. Possible pathways of androgen metabolism in rat skin. Solid circles indicate compounds which have been clearly shown to have significant effects on sebum production in hypophysectomized-castrated rats; open circles indicate compounds which have failed to do so; the stippled circle indicates a small effect significantly demonstrated only by the use of a large number of rats.

to summarize some of the details of the journey. I have drawn attention to those qualities of the skin, namely texture, appearance, feel and smell, which are concerned with sexual communication and discussed the underlying mechanisms especially in relation to the epidermis, the sebaceous and apocrine glands, and the body hair. In man, no less than in other animals, these structures change at puberty and are all profoundly influenced by both male and female hormones. Sebum secretion, the growth of sexual

hair and the problem of hirsutism may be interrelated by common involvement in the transformation of steroids in the skin, which is possibly, at least in relation to the sebaceous glands, mediated by pituitary hormones. Perhaps the epidermis, also, may be affected by steroids, and the application of non-active precursors was not a foolish idea, even if pregnenolone did not produce a striking effect. To add one more facet to the problem, is it possible that one function, or perhaps by-product, of cutaneous androgen metabolism could be the manufacture of pheromones? When we injected testosterone-4-^{14}C into rabbits, we were able to recover the label from the odoriferous part of the inguinal gland secretion (6). We do not know the chemical nature of the rabbit scent. But not all musk-like scents are macrocyclic ketones or lactones, some are 16-unsaturated steroids; for example, the compound 5α-androst-16-en-3β-ol has been identified in human urine as well as being responsible for the characteristic smell of the boar (37). Such a compound could, in theory, be formed from an endogenous androgen.

My story has included a modicum of firm evidence, a deal of speculation, and even a whiff of pure innuendo, for which I should need to ask no forgiveness here. Perhaps it was just a convenient way of linking the discovery, over 25 years ago, that rat sebaceous glands were influenced by hormones with our current study of steroid transformations in the skin, taking in the work on anti-androgens and the pituitary on the way. Or perhaps, at least, in hindsight, and admitting the gaps in logic, there is a connecting thread. In either case, Mr Chairman, I present it to you as the 1974 Medal Lecture. And may I add that I have been not only honoured, but more than a little overcome by your invitation to me to give it. I have been a member of the Society for 10 years, and although I cannot be described as a Cosmetic Chemist I have always felt, and feel now, that I am among friends.

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