Invited Editorial

Hidradenitis suppurativa:
an androgen-dependent disorder

F.J.G. EBLING

Sub-Department of Dermatology, Academic Division of Medicine, Royal Hallamshire Hospital, Sheffield S10 2JF, U.K.

The demonstration by Mortimer et al. (1986a; this issue, p. 263) that hidradenitis suppurativa responded to treatment with the antiandrogen cyproterone acetate, in a meticulously assessed double-blind trial, substantiates the view that the condition is androgen-dependent. Such a hypothesis was first advanced in the anecdotal report (Ebling et al., 1979) referred to by Mortimer et al., and details of the original four cases are now also published (Sawers, Randall & Ebling, 1986).

Hidradenitis suppurativa is a disorder of the pubic and axillary regions where, in both sexes, the skin is characterized by the presence of terminal hair and functional tubular (so-called apocrine) glands. The pubic and axillary hair is dependent on low levels of androgen for its development. Since apocrine units, often in association with holocrine lipid secreting glands, form hormonally controlled scent organs in many mammals (Ebling, 1977), there are phylogenetic grounds for postulating similar endocrine control—and, indeed, similar odorous function—in man. It is likely that sebaceous as well as apocrine glands are involved in hidradenitis; indeed, Plewig has argued for the inclusion of the hair follicle to form a triad of affected organs (see discussion in Ebling et al., 1979).

Two important questions need to be discussed. The first is whether the disorder results from an abnormally high level of free androgen or whether an enhanced response of the target organs is the critical factor. The second is the extent to which the success of the hormonal therapy can be ascribed to the undoubted lowering of free androgen which it achieves, to blockage of the androgen receptors, or to modification of peripheral testosterone metabolism. Such questions are, of course, of equal moment in considering the causation and treatment of other androgen-dependent disorders.

That hirsutism, alopecia and acne in women can result from over-production of androgen in cases of overt endocrine disturbance is not in doubt. The issue is whether such conditions can be ascribed to abnormally high systemic androgen levels in the absence of obvious disease. Modern techniques for the assay of hormones in body fluids have now made it moderately easy to show that in some patients the level of free testosterone in the plasma is high, within or a little above the normal range. From published data on hirsutism, alopecia and acne, it is usually possible to deduce that the mean total testosterone is significantly higher, or the mean sex hormone binding globulin (SHBG) lower, in patients than in control subjects. If the differences appear undramatic, the calculation of the testosterone/SHBG quotient may sometimes produce a more convincing result. Such demonstrations, carefully analysed and presented, give joy to the investigators. The pattern has, for example been nicely elucidated for acne by Darley et al.
What is striking about all these analyses, however, is not the statistically significant difference between the means for patients and normal subjects, but the large proportion of patients falling within the normal range. Thus, Lucky et al. (1983) found that hormone levels were normal in about 40% of women with acne or hirsutism, and Darley et al. (1982), who measured prolactin as well as testosterone and SHBG, found 25% to have no abnormality. The outstanding question, therefore, is why such subjects are hirsute or spotty and why an almost infinitely larger number of women of similar hormonal constitution remain unblemished.

Data showing similar trends have recently been published for cases of hidradenitis suppurativa (Mortimer et al., 1986b). The results were perhaps out of tradition, in that no significant abnormality of SHBG was detected, but the median total plasma testosterone in 41 patients with hidradenitis was 1.7 nmol/l as against 1.1 nmol/l in 25 controls, and this difference was highly significant, as was that between the free androgen indices. Nevertheless, no fewer than 32 patients, i.e. 78%, had indices within the normal range, i.e. less than 0.05. Only two showed grossly elevated values, 0.15 and 0.33, respectively; the remaining seven were all between 0.05 and 0.08. The authors were probably right to conclude that the overall pattern of endocrine abnormalities was sufficient to suggest an androgenic basis for the disease. However, in nine patients at most, and perhaps in only two, could the disorder be fairly attributed to an excess of testosterone.

All of the above evidence suggests that the critical factors in most cases of the disorders under consideration must lie in the end organs, rather than in the hormone levels. This view is supported by the finding that in a group of 52 hirsute women neither the rate of sebum excretion on the forehead nor the rate of hair growth on the thigh showed any correlation with either testosterone or SHBG levels (Ebling, Randall & Sawers, 1984). At the same time, sebum excretion was significantly correlated with plasma 5α-dihydrotestosterone (5α-DHT), and hair growth was correlated both with 5α-DHT and with androstenedione.

How should these findings be interpreted? It is known that the urinary excretion of 5α-androstanediol, end product of 5α-reduction of testosterone in target tissues, is abnormally high in both acne and hirsutism (Mauvais-Jarvis, Charranson & Bobas-Masson, 1973). It may be, therefore, that the level of 5α-DHT in the plasma also, to some extent, reflects peripheral metabolism. In respect of androstenedione, however, in spite of the demonstration that it is the major metabolite of testosterone by plucked hairs in vitro (Schweikert & Wilson, 1974), it is very unlikely (though perhaps not impossible) that its plasma level reflects the peripheral oxidation of testosterone. More probably, high levels are the basic abnormality, as certainly in gross hormonal disturbances of the adrenal cortex or ovary. This interpretation, however, implies that androgen-sensitive hair follicles respond directly to androstenedione as well as to testosterone.

These thoughts need to be borne in mind in interpreting the therapeutic findings of Mortimer et al. (1986a; this issue, p. 263). These authors obtained a clear improvement in five out of 10 patients (Group A) given reverse sequential therapy with 50 mg of cyproterone acetate and 50 μg of ethinyloestradiol for 6 months. In four of these the improvement was maintained when the treatment was changed to Eugynon 50® (E50), containing 500 μg of norgestrel and 50 μg of ethinyloestradiol. Of the remaining five who did not initially respond to CPA, four improved subsequently on E50. Of eight patients treated initially with E50, three improved, and in two of these the improvement was maintained when they were switched to CPA. Of the five who did not respond to E50 initially, two subsequently responded to CPA.
Hidradenitis suppurativa

One must sympathize with the dismay of the investigators to discover that both cyproterone acetate and the chosen control regimen of E50 had similar consequences. Nevertheless, in view of the fact that the average duration of the hidradenitis had been 7-6 years, the effectiveness of one or other of the treatments in all but four of 18 cases can hardly be denied.

The authors do not appear to be single-minded in their beliefs about the possible modes of action of the two therapies. On the one hand, in their discussion, they appear to opt for peripheral actions on the grounds that the severity of the hidradenitis did not correlate with the abnormalities of circulating androgens and neither did the response to treatment relate to any reduction in the levels of male hormone. On the other hand, in their summary, they imply that the similar efficacies of CPA and E50 are related to the similar reductions in free androgen index which are induced by the two treatments.

In general, the evidence from all sources supports the view that a peripheral action is the critical factor in the effect of CPA. Firstly, it must be made clear that, while CPA is known to induce modest reductions in both testosterone and androstenedione (Sawers, Randall & Iqbal, 1982), this effect is not unique to the antiandrogen; oestrogens can also produce it. Moreover, CPA does not, when given alone, increase SHBG; the effect of the combined therapy appears to be due entirely to the ethinyloestradiol (Sawers et al., 1982). The evidence that CPA by itself can reduce sebum excretion by about 40% within a few days (Ebling et al., 1979) thus negates the view that its major action is by increasing SHBG concentration and decreasing the free androgen level. In the sebaceous glands at least, the critical action is much more likely to be blockage of the intracellular androgen receptors.

The mode of action of E50 is perhaps more problematical. In the hidradenitis study, the effect on SHBG was not identical with that produced by the reverse sequential therapy with CPA; but the regimens were not identical either, even though they each included ethinyloestradiol. It seems likely that the major action was again peripheral, probably by inhibition of 5α-reductase by the norgestrel.

In summary, reverse sequential therapy with cyproterone acetate and ethinyloestradiol appears to be beneficial in most—though not all—cases of female hidradenitis suppurativa. On these grounds, hidradenitis may be designated as an androgen-dependent disorder and placed alongside acne vulgaris, hirsutism and androgenic alopecia. The finding that, although the mean free androgen index in hidradenitis was greater than normal, most patients had indices within the normal range, does not detract from this conclusion, since such a pattern is characteristic also for the other androgen-dependent conditions. Evidence of several kinds points to the conclusion that, notwithstanding the fact that the level of circulating androgens is reduced by it, antiandrogenic therapy acts principally and critically by blocking the androgen receptors at the target site. It is likely that norgestrel also has a peripheral action, namely inhibition of the metabolism of testosterone to 5α-dihydrotestosterone.

REFERENCES


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