For Debate . . .

Primary Cutaneous Virilism or Idiopathic Hirsuties?

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Ideas have a life-cycle: they stimulate understanding in their youth but become stale and inhibitory with age. The same is true of the names of diseases which spring from these ideas. Following on some of our own recent studies, and in particular in the course of presenting them at seminars and lectures, it became apparent that the term "idiopathic hirsuties" has now outlived its usefulness let alone its credibility. The purpose of this note is to propose the new and I believe more correct and stimulating term of "primary cutaneous virilism," of which the old idiopathic hirsuties is just one symptom.

Sex-dependent Functions in Skin

As a result of a clinical suspicion that the skin of hirsute women was thicker than normal we went on to show that skin collagen was increased in hirsute women.¹ Now we know that there is much more skin collagen in males than in females² and we have also shown that skin collagen can be increased by androgens.³ This suggested that more than just hair was virilized in the skin of women with idiopathic hirsuties, so we looked at some of the many other sex-dependent functions in the skin. The sweat gland response to cholinergic stimulation is greater in males than in females and the concentration of potassium in the sweat is lower.⁴ In females with idiopathic hirsuties we found that the sweat rate in response to cholinergic stimulation was nearer male than female levels, as was its potassium concentration.⁴ We also found in the same patients that the rate of sebum excretion was nearer that for males than for normal females.⁴

So the situation is that in women with idiopathic hirsuties not only is the hair more masculine but the independent sex-related criteria of skin collagen and thickness, sweat rate and constituents, and sebum excretion are all more male than female. This is not mere hirsutism, it is cutaneous virilism. The protruding hairs are but the phallic symbols of an underlying androgen volcano "male-storm."

But when we take a closer look at this androgen volcano we find that it rumbles mainly in the skin. There are lies, damned lies, and clinical impressions. It is my firm belief that in women with idiopathic hirsuties the virilism is mainly in the skin. In other words, the skin in idiopathic hirsutism is disproportionately virilized; there is far less evidence of systemic virilism—muscle build and subcutaneous fat, clitoral hypertrophy and the like—than in patients with, say, adrenal or ovarian virilism. The clinical observation of disproportionate cutaneous virilism makes it likely that the defect is in the skin itself, which is why I propose the term primary cutaneous virilism.

Testosterone Production

What can this defect be? While the plasma testosterone concentration is usually increased in idiopathic hirsutism there is a far more impressive increase in testosterone production.⁵ Moreover, and crucial to the argument, *extrahepatic* clearance of testosterone is increased in this condition.⁵ Now the evidence is hardening that testosterone is a transport androgen and that androgenicity at the target site is related to trapping and conversion of testosterone and other precursors into compounds such as 5 α -dihydrotestosterone, and this particular transformation appears to occur in the skin itself.⁶ So although it is not yet proved it seems probable that the defect in primary cutaneous virilism is an increase in the skin's own capacity to synthesize androgens from their circulating precursors.

It follows that the increased adrenal production of testosterone is a secondary consequence of the increased androgen sump in the skin itself. In other words the cutaneous virilism of idiopathic hirsuties is not caused by increased adrenal production of androgen: it is the cutaneous virilism which itself causes the adrenal overproduction of androgen—another nice example of my upside-down principle.⁷ We can take this still further because it is known that primary cutaneous virilism (idiopathic hirsuties) has a very strong familial predilection, and so it seems not improbable that the enhanced cutaneous metabolism of androgen is, in fact, genetically determined.

Conclusion

Although we are still close to the beginning of this essay we are closer still to the end, so let me summarize: my conclusion is that idiopathic hirsutism is just one symptom of primary cutaneous virilism, which is a genetically transmitted disorder of androgen metabolism in the skin. Other symptoms of the disease include seborrhoea, a not unimportant cosmetic problem on the scalp and a dermatological problem on the face, where it may cause acne. Surprisingly, sweating is not complained of, though the symptom can be elicited. As for thick skin, this does not seem to worry women.

How far should one stretch an idea? I would now like to take my hypothesis to a point which may well break it. Mediterranean women are more hirsute than their Northern European sisters. My own clinical guess is that their skin is thicker too. Is it more virilized? We have shown that there is less skin collagen in the female but that in both males and females skin collagen decreases with age;² furthermore, collagen is "aged" by exposure to ultraviolet radiation.^{8,9} Since ideally our skin should not fall to pieces before our innards it seems not unreasonable in an evolutionary sense (and reasonableness is one of the very best of reasons) that those habitually exposed to ultraviolet radiation should have more skin collagen to begin with—as does the Negro, for example.¹⁰

Evolutionary mechanisms are often adaptive, and what I am

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now proposing is that in order to compensate for skin ageing induced by ultraviolet radiation the Mediterraneanphilic Caucasian may have adapted and heightened the mechanism of androgen synthesis in the skin, since androgen increases skin collagen. On this hypothesis we should find that the hirsute female of Mediterranean stock forms more testosterone metabolites in her skin than does her more northern sister. The alternative of a direct effect of ultraviolet radiation on testosterone metabolism in the skin certainly requires looking at, though the maintenance of a Mediterranean fuzzi even in immigrants residing permanently in the United Kingdom, and the complex action of ultraviolet radiation on hair growth,¹¹ suggests that this cannot explain much of the problem. As I implied above, this notion may well explode on first testing: I suspect that the entity of primary cutaneous virilism will prove more resistant.

Any Questions?

We publish below a selection of questions and answers of general interest

Frederickson's Classification of Hyperlipoproteinaemia

Do all persons having a raised serum cholesterol level fall into one or other of Frederickson's five types of hyperlipoproteinaemia? If not, what proportion is outside that classification?

Not all types of hyperlipoproteinaemia fall conveniently into one of Fredrickson's five categories. Strisower *et al.*¹ found an elevation of both low density lipoprotein and very low density lipoprotein (β and pre β lipoprotein) in 17 of 72 patients with hyperlipoproteinaemia whom they examined. The closest Fredrickson group to this is type IV but in such patients low-density lipoprotein levels are normal or low. In patients with hereditary lipoproteinaemias, the tendency to have raised plasma lipids is aggravated by an increased carbohydrate and fat intake. Conversely, control of obesity and restriction of saturated fats form an essential part of the treatment.

¹ Strisower, E. H., Adamson, G., and Strisower, B., *American Journal of Medicine*, 1968, 45, 488.

North Sea Gas

What ill effects, if any, proved or suspected, are attributed to North Sea gas?

Natural gas is composed almost entirely of methane. An artificial odorant is added. Unburnt natural gas is a simple asphyxiant, and a subject breathing it in sufficient quantities would suffer anoxia with marked symptoms when its concentration in the atmosphere reaches about 50%; 75% is fatal in a few minutes.¹ Incomplete combustion of methane (or of town gas or other common fuels) produces carbon monoxide, which is highly toxic. (Threshold limit value: 50 parts per million).² The products of combustion of natural gas can exceptionally contain trace amounts of oxides of nitrogen or formaldehyde, but the latter is likely to occur only if combustion is incomplete. In theory formaldehyde can act as a local irritant and if traces were present in the burnt gas it would cause lacrymation, but would be unlikely to cause any serious skin reaction.

¹ Sax, N. I., *Dangerous Properties of Industrial Materials*, 3rd edn., New York, Reinhold, 1968.

² Department of Employment and Productivity. *Threshold Limit Values, H.M. Factories Inspector Document: Technical Data*, Note 2/69, 1969.

References

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- ⁷ Shuster, S., *World Medicine*, 1971, 6, 46.
- ⁸ Bottoms, E., and Shuster, S., *Nature*, 1963, 199, 192.
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- ¹⁰ Knox, J. M., Cockerell, E. G., and Freeman, R. G., *Journal of the American Medical Association*, 1962, 179, 630.
- ¹¹ Johnson, B. E., *Advances in Biology of the Skin*, 1969, 9, 323.

Splenic Flexure Syndrome

What is the aetiology of splenic flexure syndrome (Payr's syndrome), and is there any treatment for it?

The aetiology of the splenic flexure syndrome is unknown, and the mechanism of symptoms is based more on conjecture than on experimental observations. Patients with pain and distension under the left costal margin can be shown to have excessive gas shadows distending the colon in this area.¹ Distension of a hollow viscus is known to be painful, and hyperactive segmental motor activity of the bowel probably delays rather than accelerates the transit of colonic contents. It is possible, therefore, that the gas accumulates in the splenic flexure proximal to an area of hypersegmentation, the latter constituting a kind of functional obstruction. Though hypersegmentation of the pelvic colon may be associated with abdominal pain,² there are no data to confirm or refute this hypothesis with regard to the splenic flexure.

There is no specific treatment for the syndrome, but some relief can normally be gained from symptomatic remedies. Aerophagy should be watched for and corrected. High residue diet with added bulk (e.g., methyl cellulose or bran) may be helpful. Smooth muscle inhibitors such as diphenoxylate HCl or mebeverine (Colofac) are useful; if constipation is troublesome, standard Senokot tablets are good. Surgery should, if possible, be avoided.

¹ Palmer, E. D., *Clinical Gastroenterology*, 2nd edn., New York, Harper and Row, 1963.

² Holdstock, D. J., Misiewicz, J. J., and Waller, S. L., *Gut*, 1969, 10, 19.

Notes and Comments

Pink Napkins.—Mr. M. J. Erith (St. Bartholomew's Hospital, London E.C.1.) writes: With reference to the answer to this question ("Any Questions?" 11 March, p. 683) your expert fails to mention that uric acid crystals may cause a pink spot on the napkin, which may be mistaken for haematuria. This is most common in boys since their stream of urine is directed to one area, giving a higher concentration of crystals.¹ From personal observation over-enthusiastic application of Drapolene cream results in a pale pink staining of the napkin.

¹ Jolly, H., *Diseases of Children*, 2nd edn. Oxford, Blackwell Scientific Publications, 1968.