Several groups have attempted to investigate the effect of vasectomy on the endocrine function of the human testis.[30-37] The results have been conflicting and difficult to interpret because the changes may have been due to alterations in the sensitivity of the assay.[35] Nevertheless, it does seem that hormone concentrations remain within the normal range after vasectomy, though seasonal variations seem to be lost.[38]

Clearly, then, we need to learn much more about the effect of vasectomy on seminiferous tubules. We need to know about the possibility of different forms of testicular change in different people, predisposing factors such as a history of orchitis or a personal or family history of autoimmune disease, and the relation between the formation of sperm granulomas and testicular changes in man. Most importantly, however, we need further studies to define the risk of testicular cancer after vasectomy and to identify causal factors.

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1 Silber SJ. Vasectomy and vasectomy reversal. *Fertil Steril* 1978;**29**:125-40.
2 Linnet L, Hjort T, Fogh-Anderson P. Association between failure to impregnate after vaso-vasostomy and spermagglutinins in semen. *Lancet* 1981;i:117-9.
3 Fuchs EF, Alexander NJ. Immunologic considerations before and after vasovasostomy. *Fertil Steril* 1983;**40**:497-9.
4 Clarkson TB, Alexander NJ. Long-term vasectomy: effects on the occurrence and extent of atherosclerosis in the rhesus monkey. *J Clin Invest* 1980;**65**:15-25.
5 Campbell WB. Vasectomy and arterial disease. *J R Soc Med* 1988;**81**:683-5.
6 Cale ARJ, Farouk M, Prescot RJ, Wallace IWJ. Does vasectomy accelerate testicular tumour? Importance of testicular examinations before and after vasectomy. *Br Med J* 1990;**300**:370.
7 Thornhill JA, Butler M, Fitzpatrick JM. Could vasectomy accelerate testicular cancer? The importance of prevasectomy examination. *Br J Urol* 1987;**59**:367.
8 Strader CH, Weiss NS, Daling JR. Vasectomy and the incidence of testicular cancer. *Am J Epidemiol* 1988;**128**:56-63.
9 Grewal RS, Sachan MS. Changes in testicle after vasectomy. An experimental study. *Int Surg* 1968;**49**:460-2.
10 Kothari LK, Mishra P, Mishra RK. Effect of bilateral vasectomy on the structure and function of the testis. *Am J Surg* 1973;**126**:84-8.
11 MacDougall MK, McCowin K, Derrick FK, Glover WL, Jacobson CB. The effects of vasectomy on spermatogenesis in the dog, Canis familiaris: a meiotic analysis. *Fertil Steril* 1975;**26**:786-90.
12 Vare AM, Bansal PC. Changes in the canine testis after bilateral vasectomy—an experimental study. *Fertil Steril* 1973;**24**:793-7.
13 Tung KSK. Pathogenesis of testicular pathology in vasectomized guinea pigs. In: Lepow IH, Crozier R, eds. *Vasectomy: immunologic and pathophysiologic effects in animals and man*. New York: Academic Press, 1979:407-21.
14 Bigazzi PE. Immunopathological findings in vasectomized rabbits. In: Lepow IH, Crozier R, eds. *Vasectomy: immunologic and pathophysiologic effects in animals and man*. New York: Academic Press, 1979:339-53.
15 Alexander NJ, Tung KSK. Vasectomy in the rabbit: immunological and morphological effects. In: Lepow IH, Crozier R, eds. *Vasectomy: immunologic and pathophysiologic effects in animals and man*. New York: Academic Press, 1979:355-77.
16 Bedford JM. Adaptations of the male reproductive tract and the fate of spermatozoa following vasectomy in the rabbit, rhesus monkey, hamster and rat. *Biol Reprod* 1976;**14**:118-42.
17 McDonald SW, Falconer JS, Al-Saffar RA, Scothorne RJ. Sperm granuloma formation in the caput epididymidis is associated with testicular degeneration in rats. *Clinical Anatomy* 1990;**3**:65.
18 McDonald SW, Spilg EG, Alexander JA, Scothorne RJ. Testicular atrophy following vasectomy—is the position of the sperm granuloma important? *Clinical Anatomy* 1990;**3**:68.
19 Derrick FC, Glover WL, Kanjuparamban Z, *et al*. Histological changes in the seminiferous tubules after vasectomy. *Fertil Steril* 1974;**25**:649-58.
20 Gupta AS, Kothari LK, Dhruva A, Bapna R. Surgical sterilization by vasectomy and its effect on structure and function of the testis in man. *Br J Surg* 1975;**62**:59-63.
21 Fallon F, Jacobo L, Bunge RE. Restoration of fertility by vasovasostomy. *J Urol* 1978;**119**:85-6.
22 Jenkins JP, Muir VY, Blacklock NJ, Turk JL, Hanley HG. Consequences of vasectomy: an immunological and histological study related to subsequent fertility. *Br J Urol* 1979;**51**:406-10.
23 Bigazzi PE, Alexander NJ, Silber SS. Studies on testicular biopsies from vasectomized men. In: Lepow IH, Crozier R, eds. *Vasectomy: immunologic and pathophysiologic effects in animals and man*. New York: Academic Press, 1979:459-69.
24 Jarow JP, Budin RE, Dym M, Zirken BR, Noren S, Marshall FF. Quantitative pathologic changes in the human testis after vasectomy. A controlled study. *N Engl J Med* 1985;**313**:1252-6.
25 Mehrotra R, Nath P, Singh KM, *et al*. Changes in seminiferous tubules after vasectomy. *Indian J Pathol Microbiol* 1985;**28**:371-8.
26 Howards SS, Johnson AL. Effects of vasectomy on intratubular hydrostatic pressure in the testis and epididymis. In: Lepow IH, Crozier R, eds. *Vasectomy: immunologic and pathophysiologic effects in animals and man*. New York: Academic Press, 1979:55-67.
27 McDonald SW, Scothorne RJ. A quantitative study of the effects of vasectomy on spermatogenesis in rats. *J Anat* 1988;**159**:219-25.
28 Samuel T, Kolk AHJ, Rumke P, Van Lis JMJ. Autoimmunity to sperm antigens in vasectomized men. *Clin Exp Immunol* 1975;**21**:65-74.
29 Ansbacher R, Hodge P, Williams A, Mumford DM. Vas ligation, humoral sperm antibodies. *Int J Fertil* 1976;**21**:258-60.
30 Rosemberg E, Marks SC, Howard PJ, James LP. Serum levels of follicle stimulating and luteinizing hormones before and after vasectomy in men. *J Urol* 1974;**111**:626-9.
31 Kobrinsky NL, Winter JSD, Reyes FI, Fairman C. Endocrine effects of vasectomy in men. *Fertil Steril* 1976;**27**:152-6.
32 Naik VK, Thakur AN, Sheth AR, *et al*. The effect of vasectomy on pituitary-gonadal function in men. *J Reprod Fertil* 1976;**48**:441-2.
33 Smith KD, Tcholakian RK, Chowdhury M, Hsi BP. Endocrine studies in vasectomized men. In: Lepow IH, Crozier R, eds. *Vasectomy: immunologic and pathophysiologic effects in animals and man*. New York: Academic Press, 1979:183-200.
34 Whitby RM, Gordon RD, Blair BR. The endocrine effects of vasectomy: a prospective five-year study. *Fertil Steril* 1979;**31**:518-20.
35 Goebelsmann U, Bernstein GS, Gale JA, *et al*. Serum gonadotrophin, testosterone, estradiol, and estrone levels prior to and following bilateral vasectomy. In: Lepow IH, Crozier R, eds. *Vasectomy: immunologic and pathophysiologic effects in animals and man*. New York: Academic Press, 1979:165-81.
36 Varma MM, Varma RR, Johanson AJ, Kowarski A, Migeon CJ. Long-term effects of vasectomy on pituitary-gonadal function in man. *J Clin Endocrinol Metab* 1975;**40**:868-71.
37 Skegg DCG, Mathews JD, Guillebaud J, *et al*. Hormonal assessment before and after vasectomy. *Br Med J* 1976;i:621-2.
38 Reinberg A, Smith KD, Smolensky MH, Steinberger E, Hallek M. Annual variation in semen characteristics and plasma hormone levels in men undergoing vasectomy. *Fertil Steril* 1988;**49**:309-15.

Hirsutism

Treatable and usually caused by the polycystic ovary syndrome

In the past decade the polycystic ovary has emerged clearly as the source of excess androgens in most hirsute women,[1] and the establishment of effective antiandrogen treatment, combining oestrogen with cyproterone acetate,[2] has resulted in an increased demand for treatment by patients and doctors. We now enter an era in which the long term safety of treatment must be determined to provide a more accurate assessment of the risk-benefit ratio of hormone treatment.

Until recently most patients with excess hair growth were labelled as having idiopathic hirsutism because they had no discernible abnormality of the menstrual cycle or of gonadotrophin or androgen secretion. Two lines of investigation have altered our understanding of the pathogenesis of hirsutism. Firstly, the total serum testosterone concentration, which is normal in many hirsute patients, has been shown to be an inaccurate reflection of androgen production. More subtle investigation has shown that excess androgen concentrations exist in nearly all patients.[3-5] Moreover, specific venous sampling has shown the ovary rather than the adrenal gland to be the source of androgen excess.[6] Secondly, ultrasonographic examination of the ovary has shown the typical morphology of the polycystic ovary in 92% of women with hirsutism.[7] Most hirsute women have symptomatic and biochemical hyperandrogenism together with polycystic ovaries. Hirsutism is therefore one of the components of the polycystic ovary syndrome, even when the menstrual cycles and gonadotrophin concentrations are normal.

Many investigators have been tempted by the notion of a single mechanism to explain hyperandrogenism, but it is probably the result of defects in several metabolic and endocrine pathways. Induction of excessive synthesis of ovarian androgens through stimulation by luteinising hormone,[8,9] insulin,[9,10] or corticotrophin[11] or through overactivity of the cytochrome *P*-450c17α enzyme complex[12] have all been postulated. Applying molecular techniques to the study of hormone production should define subgroups of women with

hirsutism in whom specific genetic defects underlie their symptoms.[13]

Hirsute women tend to be more obese than non-hirsute women,[8] although the relation between obesity and excess hair growth is complex. In hirsute women there is a direct correlation between body mass index and the total serum testosterone concentration despite a fall in the concentration of sex hormone binding globulin in obese people.[14] Possibly the hyperinsulinaemia of obesity lowers the sex hormone binding globulin concentrations[15] and also stimulates the theca cells of the ovary to secrete more androgen in response to luteinising hormone.[16] In addition, increased release of adrenocorticotrophin may contribute to excess androgen in obesity.[17] The practical implications are, however, clear: weight loss must be a priority in treating overweight women with excess hair growth. Raised serum insulin concentrations and deranged lipid profiles[18] are also more prevalent in lean women with the polycystic ovary syndrome than in women with normal ovaries.[9 16] The cause of this hyperinsulinaemia is not clear but the consequence may be to increase the risk of cardiovascular disease in hirsute women.[18] These processes, and the effect of treatments on them, require further evaluation.

The physical treatments of shaving, bleaching, and electrolysis are all complementary to antiandrogen treatment and do not stimulate hair growth. Only one preparation is licensed in Britain for treating hirsutism: Dianette contains 35 μg of ethinyloestradiol, which suppresses ovarian androgen production and raises the concentration of circulating sex hormone binding globulin, and 2 mg of cyproterone acetate, a progestogen and antiandrogen that competes with dihydrotestosterone at the hair follicle. Though Dianette is an effective maintenance treatment for many hirsute patients, it is rarely sufficient for reversing excess hair growth. Its components may be prescribed separately as ethinyloestradiol (30-50 μg) administered on days 5-26 of the menstrual cycle and cyproterone acetate (licensed for the control of libido in male hypersexuality) 50-150 mg on days 5-15. Such antiandrogen treatment is effective in most hirsute patients, who usually require 12-18 months of treatment before the doses can be reduced to maintenance levels. Patients with severe hirsutism may require indefinite treatment with a substantial dose of antiandrogen. Conversely, the most sensitive responders can be treated intermittently. Flutamide, a new non-steroidal antiandrogen licensed for palliative treatment of advanced prostatic cancer, is now available for evaluation as an alternative to cyproterone acetate. As it is not a gestagen, even when combined with oestrogen, it is not contraceptive. For most women, therefore, it will need to be given with an oral contraceptive because of potential risks to a male fetus.

An important concern in treating a benign condition is that the treatment should be safe. Rarely is the risk-benefit ratio of long term treatment low enough to justify the use of alternatives to combined oestrogen and antiandrogen treatment. The Committee on Safety of Medicines has advised against the long term use of spironolactone, except in certain specific conditions, because of concern over the results of animal studies. Glucocorticoids should be used only if a defect of adrenal steroid synthesis is clearly shown. Analogues of luteinising hormone releasing hormone are used as an alternative and effective method of suppressing ovarian androgen production. The nasal or parenteral route makes them unacceptable for many patients, however, and the long term effect on bone demineralisation is a point of concern.

The risks of combined oestrogen and antiandrogen treatment may be compared with those of oral contraceptives. With adequate patient selection (excluding those who smoke and those with hypertension or a strong family history of thrombosis) the incidence of cardiovascular complications in women taking oral contraceptives is reduced. We regard a strong family history of breast cancer as a relative contraindication to antiandrogen treatment and advocate a low threshold for mammography screening in patients who need long term combined oestrogen-antiandrogen treatment. As treatment with cyproterone acetate may exacerbate both hyperinsulinism and adverse profiles of cholesterol and its subfractions associated with hirsutism[19] the need for new approaches to treatment of this problem becomes apparent.

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1 Franks S. Polycystic ovary syndrome: a changing perspective. *Clin Endocrinol* 1989;**31**:87-120.
2 Miller JA, Jacobs HS. Treatment of hirsutism and acne with cyproterone acetate. *Clinics in Endocrinology and Metabolism* 1986;**15**:373-89.
3 Rosenfield RL. Plasma free androgen patterns in hirsute women and their diagnostic implications. *Am J Med* 1979;**66**:417-21.
4 Lobo RA. Disturbances of androgen secretion and metabolism in polycystic ovary syndrome. *Clin Obstet Gynecol* 1985;**12**:633-47.
5 Baxendale PM, Jacobs HS, James VHT. Salivary testosterone: relationship to unbound plasma testosterone in normal and hyperandrogenic women. *Clin Endocrinol* 1982;**16**:595-603.
6 Kirschner MA, Zucker IR, Jespersen D. Idiopathic hirsutism—an ovarian abnormality. *N Engl J Med* 1976;**294**:637-40.
7 Adams J, Polson DW, Franks S. Prevalence of polycystic ovaries in women with anovulation and idiopathic hirsutism. *Br Med J* 1986;**293**:355-9.
8 Conway GS, Honour JW, Jacobs HS. Heterogeneity of the polycystic ovary syndrome: clinical, endocrine and ultrasound features in 556 patients. *Clin Endocrinol* 1989;**30**:459-70.
9 Conway GS, Jacobs HS, Holly JMP, Wass JAS. Effects of luteinizing hormone, insulin, insulin-like growth factor I and insulin-like growth factor small binding protein in the polycystic ovary syndrome. *Clin Endocrinol* (in press).
10 Barbeiri RL, Hornstein MD. Hyperinsulinemia and ovarian hyperandrogenism. *Endocrinol Metab Clin North Am* 1988;**17**:685-703.
11 Lobo RA. The role of the adrenal in polycystic ovary syndrome. *Semin Reprod Endocrinol* 1984;**2**:251-62.
12 Rosenfield RL, Barnes RB, Cara JF, Lucky AW. Dysregulation of cytochrome P450c 17 alpha as the cause of polycystic ovarian syndrome. *Fertil Steril* 1990;**53**:785-91.
13 Miller WL. Molecular biology of steroid hormone synthesis. *Endocr Rev* 1988;**9**:295-318.
14 Evans DJ, Hoffman RG, Kalkhoff RK, Kissebah AH. Relationship of androgenic activity to body fat topography, fat cell morphology, and metabolic aberrations in premenopausal women. *J Clin Endocrinol Metab* 1983;**57**:304-10.
15 Kiddy DS, Hamilton-Fairley D, Seppela M, *et al.* Diet-induced changes in sex hormone-binding globulin and free testosterone in women with normal and polycystic ovaries: correlation with serum insulin and insulin-like growth factor-1. *Clin Endocrinol* 1989;**31**:757-63.
16 Conway GS. Insulin resistance and the polycystic ovary syndrome. *Contemporary Reviews in Obstetrics and Gynaecology* 1990;**2**:34-9.
17 Glass AR, Burman KD, Dahms WT, Boehm TM. Endocrine function in human obesity. *Metabolism* 1981;**30**:89-104.
18 Graf MJ, Richards CJ, Brown V, Meissner L, Dunaif A. The independent effects of hyperandrogenaemia, hyperinsulinaemia, and obesity in lipid and lipoprotein profiles in women. *Clin Endocrinol* 1990;**33**:119-31.
19 Seed M, Godsland IF, Wynn V, Jacobs HS. The effects of cyproterone acetate and ethinyl oestradiol on carbohydrate metabolism. *Clin Endocrinol* 1984;**21**:689-99.