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Aphrodisiacs

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In Xanadu did Kubla Khan
A stately pleasure-dome decree:

.....

For he on honey-dew hath fed,
And drunk the milk of Paradise.
COLERIDGE

It has been alleged that power is the greatest aphrodisiac. Yet so powerful a conqueror as Kubla Khan sought out such presumed aphrodisiacal agents as honey-dew and the milk of Paradise. Perhaps power was not enough.

In the Bible, the second book of Samuel unfolds a scenario of sexual dysfunction in all its ramifications: first, the introduction of voyeurism as a stimulus to lust unrestrained; then, the insinuation of psychogenic forces, abetted by advancing age resulted in the loss of sexual prowess; and finally, the employment of an age-old aphrodisiacal device to test potentia.

King David, standing on the balcony of his palace, lustfully watched a nude woman bathing on the roof of her house. The woman, Bathsheba, was the wife of a captain serving in the King's army at the battlefront. Sexually aroused, David summoned her to his rooms and seduced her. Soon Bathsheba was with child. When the prophet Nathan admonished the God-fearing David, 'Thou art the man', conscience took reason prisoner; the King's remorse deepened with the years. In time, rumours of his impotence became current, and the Israelites, who equated leadership with virility, applied the test. A young and beautiful Shunamite maiden was chosen to lie with the king, but 'he gat no heat' — 'love's labours' lost. David failed the test and was forced to abdicate in favour of his son Solomon, he of the thousand wives (Greenblatt 1977).

THE ROLE OF THE PSYCHE AND THE NERVOUS SYSTEM IN SEXUAL PERFORMANCE

The eminent British surgeon, John Hunter (1728–93) predated today's physicians when he pointed out that a relationship existed between emotional stress and psychogenic impotence. The mind is subject to many a caprice that affects sexual performance. Thus, in order to overcome sexual inadequacy, men and women have sought means to stimulate sexual ardour by resorting to foodstuffs, plants, herbs, spices, philtres, love potions, alcoholic beverages, imagery, the

body beautiful, and even sacrifices and prayers to the gods. In recent years, pharmacologic agents and hormones have been employed as aphrodisiacs to provoke libidinous drive, enhance or maintain penile erection, and stimulate vaginal lubrication and hyperaemia.

Sexual arousal depends on the five senses in hormonally-prepared individuals, but organic response is dependent on an intact autonomic nervous system conditioned by the state of the mind. Penile erection, however, is not necessarily hormone-dependent, for this phenomenon has been observed in the foetus-in-utero, in boys during early childhood, and in men castrated after adolescence. Parasympathetic nervous system activation dominates the initial phase of sexual excitement while progressive cholinergic impulses are involved in orgasm and ejaculation (Wiedenking, Ziegler, and Lake 1979). In the male frog (*Rana pipiens*), both gonadotropins and adrenergic agents stimulate the sympathetic ganglia to release sperm; a response which adrenolytic drugs can abolish (Greenblatt, Clark, and West 1950) (Fig. 25.1).

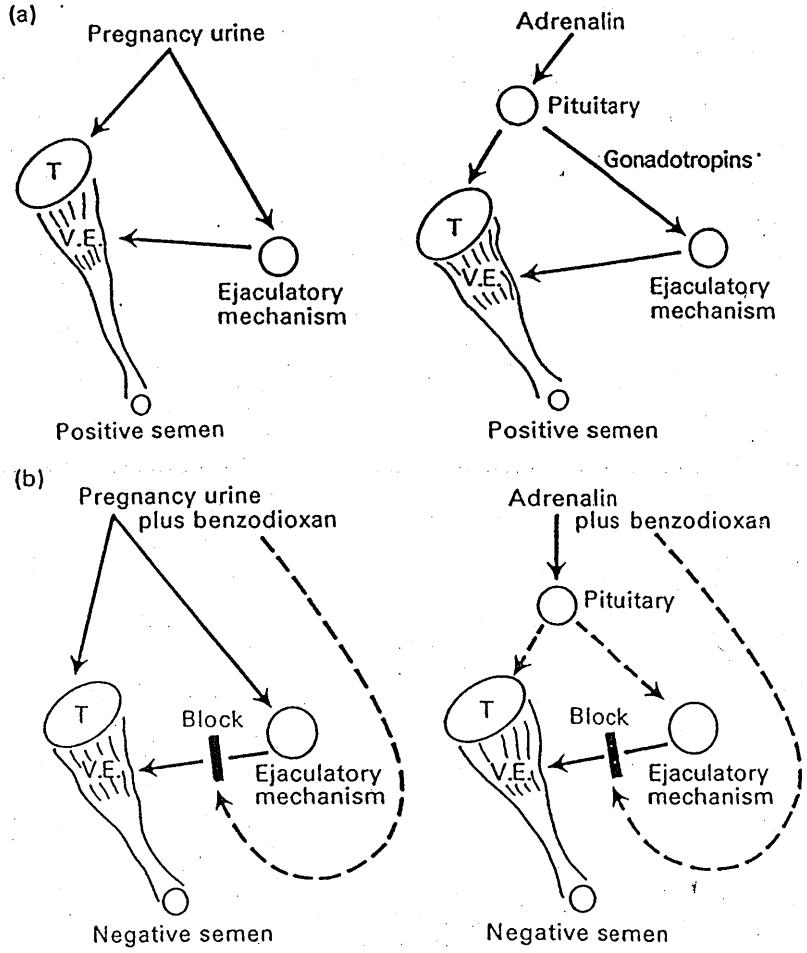

Fig. 25.1. Both pregnancy urine and adrenalin stimulate the ejaculatory mechanism in the *Rana pipiens*. Adrenolytic agents abolish the response. (From Greenblatt 1979).

ASPECTS OF THE NEUROPHYSIOLOGY OF SEXUAL BEHAVIOUR

Sexual behaviour and potency have been associated with alterations in levels of brain serotonin and dopamine. The depletion of serotonin has an invigorating effect on sexually sluggish rats, but no effect on rats whose baseline activity is normal. Hormonal interactions with serotonin and other neurotransmitters may be instrumental in the modification of sexual behaviour (Zitrin, Dement, Barchas *et al.* 1973). In the female rat, castration (*ovariectomization*) results in a rise, oestrogens in a fall of brain noradrenaline. Testosterone administered to one-day-old male rats prevent the usual twelth-day rise in serotonin (Fig. 25.2). When new-born female rats are injected with testosterone, the hypothalamus is masculinized, preventing the initiation of cyclic oestrus (Barraclough and Gorsi 1968). There is a wealth of material defining the role of a variety of pharmacologic agents which influence the neurotransmitters of the brain of experimental animals, but thus far, application of this knowledge to human sexual behaviour has not proved promising (Tucker and File 1983). In the last resort, human reactions can only be studied in man.

Norepinephrine	↑	(rat brain)	Castration
Norepinephrine	↓	(rat brain)	Estrogen
Serotonin	↓	(rat brain)	Testosterone*

*Blocks 12th day rise if injected on day 1.

Fig. 25.2. Oestrogens and androgens influence brain content of neurohormones of the brain.

TEMPORAL ASPECTS OF SEXUAL AROUSAL IN MEN AND WOMEN

Women are subject to episodic changes in hormone levels throughout the menstrual cycle. Dramatic surges of oestradiol (E_2) and luteinizing hormone (LH) initiate ovulation; soon thereafter, progesterone levels rise then fall precipitously to trigger the menstrual process. Testosterone and prolactin levels also show cyclic shifts. Hormonal status may influence sexuality; some women experience their greatest sexual urge at the time of ovulation, others during the luteal or premenstrual phase, and not a few during menstruation. Males, on the other hand, are not subjected to such hormonal swings. Like stags in rutting season, most men remain in a continuous state of readiness. Perhaps Henry Higgins' query in *My Fair Lady*, 'Why can't a woman be more like a man?' referred to the inconstancy of her moods and behaviour – a reflection of the gyrations in hormonal tides.

THE ROLE OF GONADAL STEROIDS IN SEXUAL BEHAVIOUR

Nottebohn (1983), puzzled by the fact that only male canaries sing, injected adult females with testosterone. Within ten days, the female canaries burst into song. He and his associates found an area in the forebrain that increases in volume following testosterone administration. Perhaps women, too, who bemoan their loss of sexual drive can be made 'to sing' following the judicious use of this hormone. The danger of drawing facile parallels is apparent, but the canary experience serves to emphasize that the brain is a target organ.

The metabolic fate of testosterone involves conversion into E_2 and 5α-dihydrotestosterone (DHT); one of the enzymes in the pathway of biosynthesis has aromatase activity. The intracerebral administration of an aromatase blocker (andros-1,4,6-triene-3,17-dione) will inhibit masculine sex behaviour in spite of the systematic presence of testosterone (Baum and Starr 1980). It appears that E_2 and DHT are essential for expression of these behaviours, rather than the parent steroid testosterone (Christensen and Clemens 1975) (Fig. 25.3).

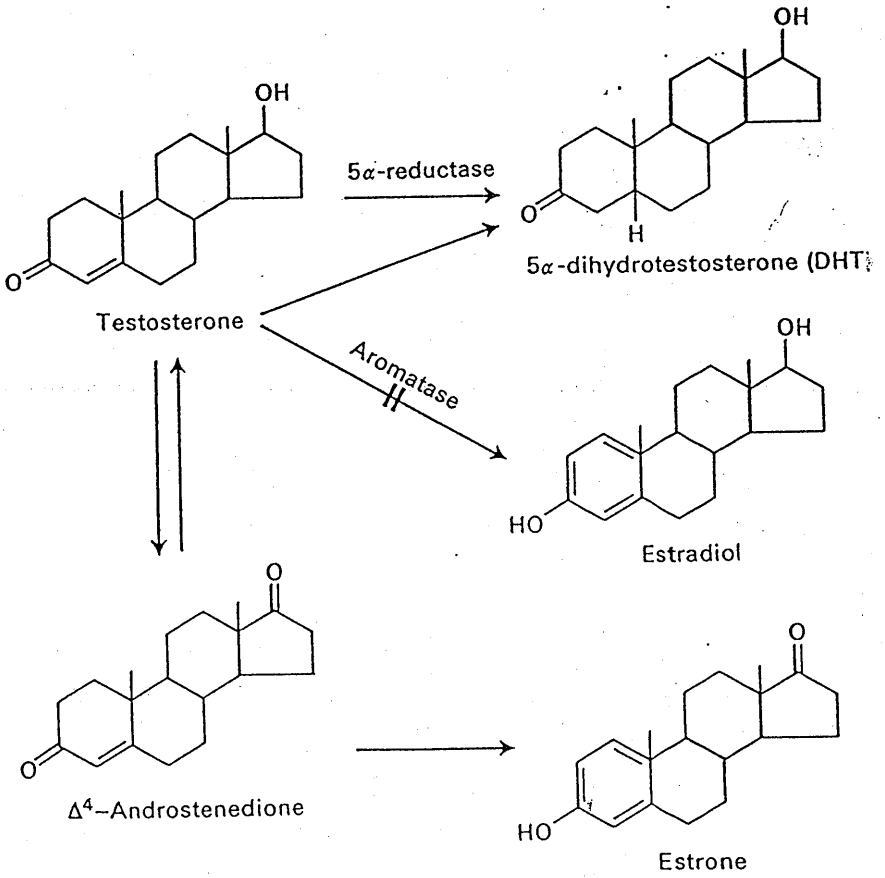

Fig. 25.3. A blockade of aromatase activity will inhibit sexual behaviour in spite of the systemic presence of testosterone. E_2 and DHT are essential for expression of sexual behaviour. (After Christensen and Clemens (1975) *Endocrinology* 97, 1545–51).

Newman and Northup (1983) report that about thirty years ago an experiment was performed in which an adult woman received an intravenous injection of testosterone (then available for experimental use). Within a few minutes there was intense vulvar flushing, vaginal hyperaemia, a rise in uterine temperature accompanied by a distinct increase in libido. Masters and Johnson (1977), in their clinical studies, observed similar changes in females during sexual excitement.

Men and women with hypopituitarism due to an hypothalamic lesion resulting in anosmia and secondary hypopituitarism (Kallmann's syndrome), or those with primary hypopituitarism (idiopathic or caused by a tumour) exhibit all the signs of sexual infantilism, absence of sexual hair, and libidinous drives. In females, the results of hormone replacement therapy are striking. Cyclic oestrogen and progestin therapy will induce regular withdrawal uterine bleeding periods and breast development, but sexual arousal remains poor, and pubic hair fails to appear. When androgen is added to the oestrogen-progestin regimen, sexual hair grows and sex drive becomes very positive (Fig. 25.4). When a placebo is substituted for the androgen, then both sexual hair and libido regress completely (Greenblatt 1945). This human experiment helps delineate the role of gonadal steroids in sexual drive.

APHRODISIACAL EFFECT OF OESTROGEN-TESTOSTERONE ADMINISTRATION FOR SEXUAL DYSFUNCTION IN WOMEN

Despite the scepticism of the medical establishment concerning the value of hormones in the treatment of sexual dysfunction in women, the many positive reports cannot be ignored (Salmon 1941; Greenblatt, Mortara, and Torpin 1942; Dempsey, Hertz, and Young 1935; Studd 1978). There is no doubt that oestrogens will relieve dyspareunia when due to atrophic vaginitis; and that oestrogens and testosterone properly administered will increase sexual dreams and appetites and will promote orgasmic responses in many women. Oral oestrogens and androgens in the usually recommended doses often prove inadequate because hormones taken orally enter the enterohepatic system where the liver conjugates, detoxifies, and neutralizes, while parenteral hormones avoid the first pass through the liver and, hence, are more effective (Campbell and Whitehead 1977). Our most recent study of 136 depressed menopausal women involves the subcutaneous implantation of one or two pellets of 17β-oestradiol (E_2) (25 mg each) or a combination of one or two E_2 pellets with one or two pellets of testosterone (75 mg each). Almost every woman in this series complained of loss of sexual desire. The hormone therapy resulted in an increase in free and total tryptophan (Alyward 1973) (Table 25.1). We are not certain whether the improvement in emotional status or the changes in tryptophan metabolism were responsible for the increased sexual responsiveness, but what emerged from this study is that gonadal steroids not only exert an anti-

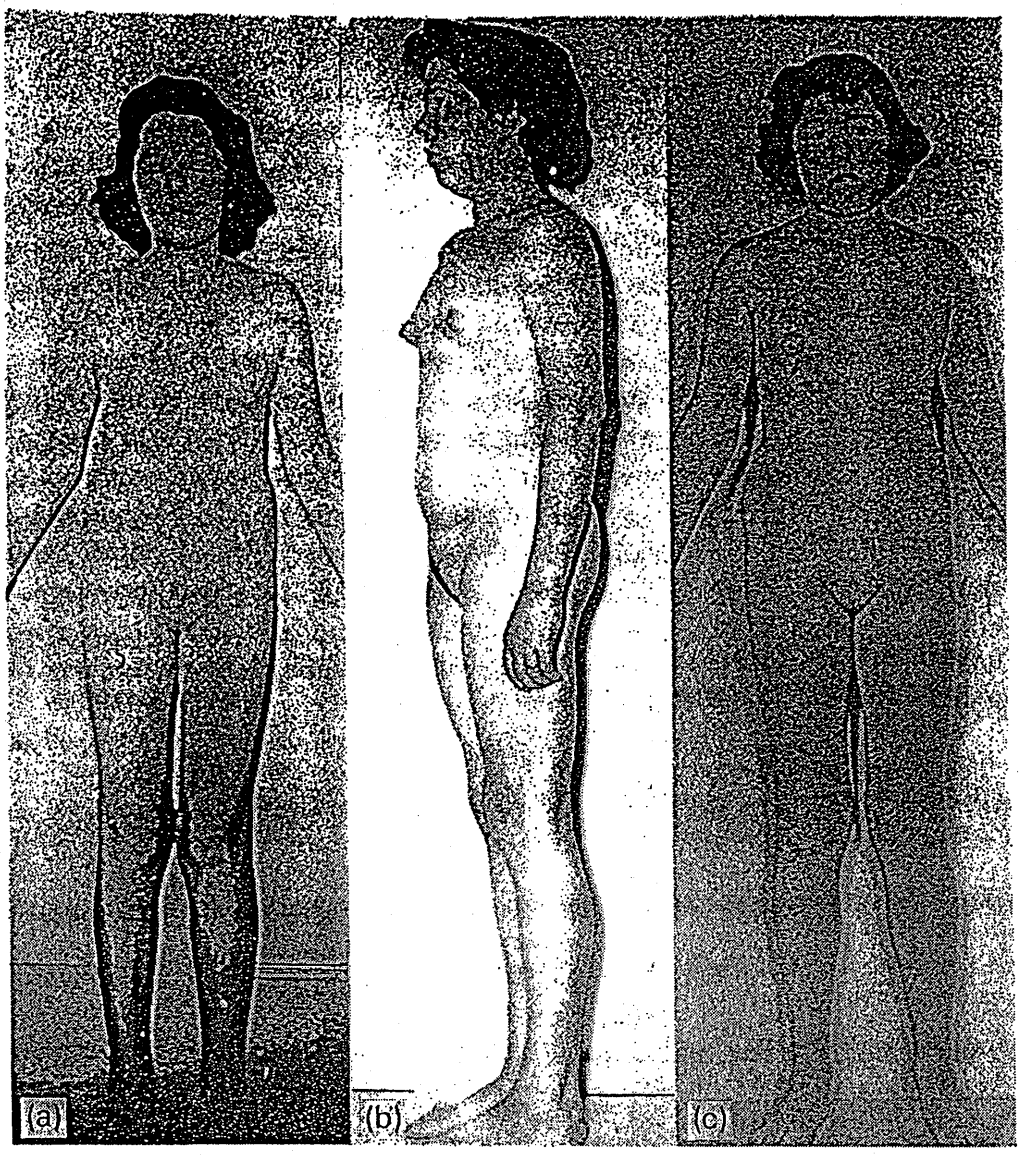

Fig. 25.4. (a) Sexual infantilism in a 23-year-old girl. Sequential oestrogen-progestin therapy-induced breast development and withdrawal uterine bleeding periods, but neither pubic hair nor libido. (b) The addition of an oral androgen resulted in sexual-hair growth and stimulated libido. (c) The replacement of the androgen with a placebo caused complete regression of the hair growth, with loss of sexual desire. (From Greenblatt (1945) *West. J. Surg.* 53, 222–6).

depressant effect (Herrmann and Beach 1976), but that such therapy is associated with a return of sexual drives.

The question will be asked, What about untoward reactions and possible risks of cancer? The answer is that only a few women on such a regimen develop hairiness, mild acne, and more rarely, voice changes or slight enlargement of the clitoris. Reversal of the untoward signs usually takes place if further androgen therapy is discontinued. Many women, however, do not wish to eliminate

TABLE 25.1. *Tryptophan† in depressed menopausal women with loss of libido*

Serum free and total tryptophan increased to almost normal values on hormone replacement therapy in depressed menopausal women. The more frequent sexual response to the oestrogen-testosterone regimen over that of oestrogens alone suggests that the role of androgen is more important than the simple increase in free tryptophan.

Free		Total		Libido	Depression
Before	After	Before	After	25–100% Improvement	
3.76 ± 0.09	4.41* ± 0.19	34.66 ± 0.89	35.51 ± 1.28	50% on E_2	70% on E_2
				90% on E_2 + T	70% on E_2 + T
n = 136	n = 90	n = 136	n = 90		

*p = <0.05 E_2 = Estradiol pellets T = Testosterone.

	Free	Total
†Non-depressed menopausal patients	5.12 ± 0.34 n = 20	44.8 ± 2.87 n = 20

androgen medication because, for them, the benefits far outweigh the undesirable reactions. The risk of endometrial cancer on prolonged oestrogen therapy can be reduced to less than the normally expected incidence by the administration of an oral progestin for seven to ten days each month (Gambrell 1980; Greenblatt and Gambrell 1980). As to breast cancer, we feel that there is no hard evidence to support the allegation of an association. Horwitz and Stewart (1984) reviewed eleven of the most recent studies dealing with the subject. Their verdict was that with the removal of bias factors, there appears to be no increased risk.

THE USE OF PARENTERAL TESTOSTERONE (IMPLANTS OR INJECTIONS) IN NORMAL MEN WITH SEXUAL DYSFUNCTION

The male, complaining of loss of libido and/or erectile capacity, may have low or normal serum testosterone values. Normal values do not necessarily reflect the interaction between the hormone and the target cells, nor the receptivity of testosterone receptors. We have previously reported on a double-blind study in

which less than 50 per cent of men experienced mild to moderate response to oral androgens (Greenblatt, Oettinger, and Bohler 1976; Greenblatt, Nezhat, Roesel, and Natrajan 1979). However, parenteral androgen therapy (implants of 75 mg pellets, one per 10–15 lb of body weight at six month intervals or injections of 100–200 mg of a long-acting testosterone, enanthate or cypionate, preparation (every 7–14 days) is far more effective than oral therapy. In our experience improvement in sexual drive and/or erections may be expected in about two-thirds of the patients (Greenblatt and Karpas 1983), (Figures 25.6 and 25.7). Men on drugs (antiphypertensives, α-β-blockers, tranquillizers), alcoholics, and diabetics, usually fail to benefit.

Untoward reactions are few, and these are prostatic enlargement and physiologic polycythemia. In the former, medication is discontinued, and in the latter, old-fashioned phlebotomy may be practised (donation of a pint of blood to a blood bank at six week intervals) to reduce haemoglobin concentration and elevated hematocrit. Occasionally, nipple tenderness is experienced. A decided increase in low and very low density lipoproteins and a decrease in high-density lipoproteins has been found to occur following oral synthetic androgens (Solym 1971), but we have not seen any significant changes after implantation of pure testosterone (Fig. 25.8).

Although the role of suggestion may be strong, the proof that implants do not act as placebos, is the fact that as the pellets are absorbed in four to five months there is, in most cases, an abrupt loss of libido and/or erectile capacity corresponding to a fall in serum testosterone levels (Fig. 25.5(a)), and a concommitant rise in serum FSH and LH levels (Fig. 25.5(b)).

IS THERE A TRUE APHRODISIAC?

The view generally held is that one expressed by Benkert (1980): 'No pharmacotherapy is known that has been experimentally substantiated. The therapeutic results obtained in controlled studies were no better than placebos.' For more than forty years we have evaluated various endocrine preparations, i.e. oestrogens, progestogens, androgens, corticoids, gonadotrophins, etc. Many of our studies were double-blind and only one effective regimen consistently has stood the test of time, and that is a preparation that contained an androgen (Albeaux-Fernet, Bohler, and Karpas 1978; Greenblatt, Barfield, and Garner *et al.* 1950) (Table 25.2).

No one will deny that testosterone administration to the hypogonadal male will result in sexual drive and erection, but what is debatable is its usefulness in the treatment of sexual dysfunction in men with normal or even subnormal serum testosterone values, and in women. It is futile to offer a course of oral therapy for a few weeks and come to a conclusion, as Bancroft (1983) did, that there were no 'significant differences between androstenedione and placebo'. Androstenedione is a very weak androgen and quite inappropriate for such a study. The key to success, it appears, is persistent therapy with potent hor-

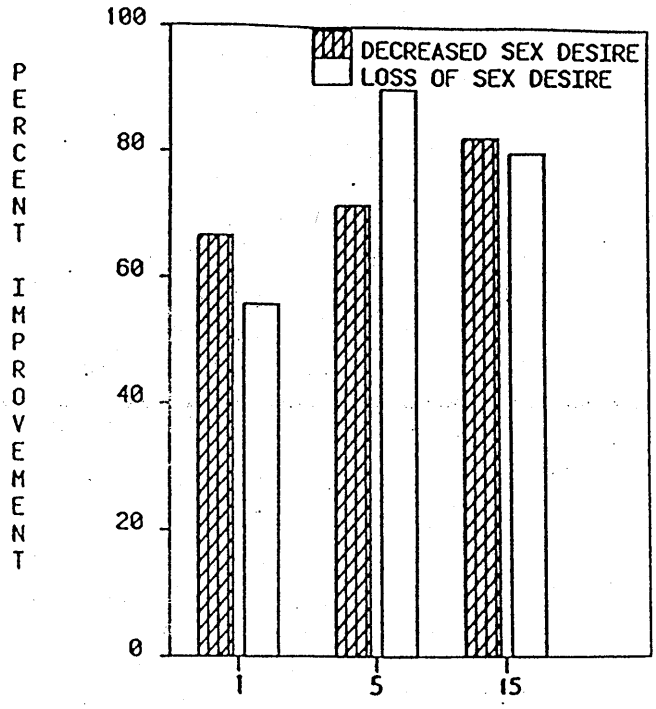

Fig. 25.6. One hundred men received testosterone pellet implants every six months. Note degree of improvement of libido after first, fifth, and fifteenth implantation.

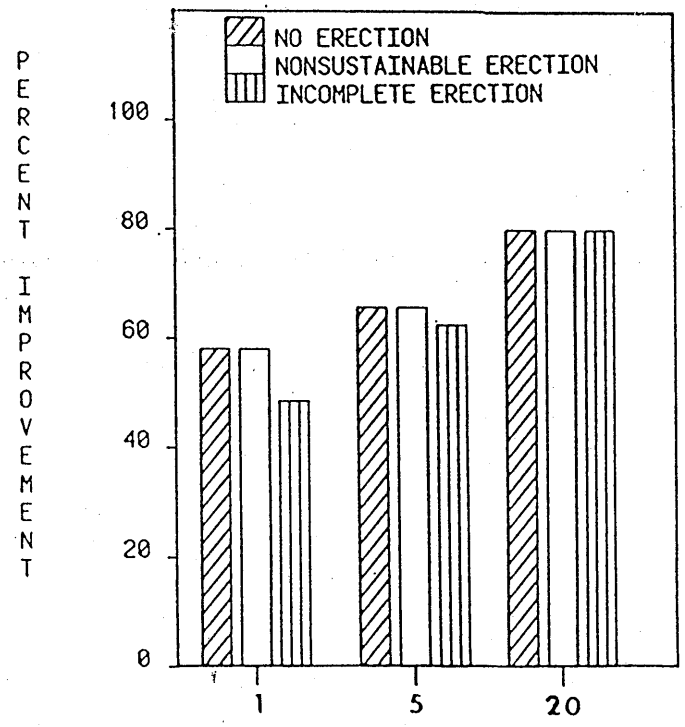

Fig. 25.7. Note degree of improvement in erectile capacity after first, fifth, and twentieth implantation.

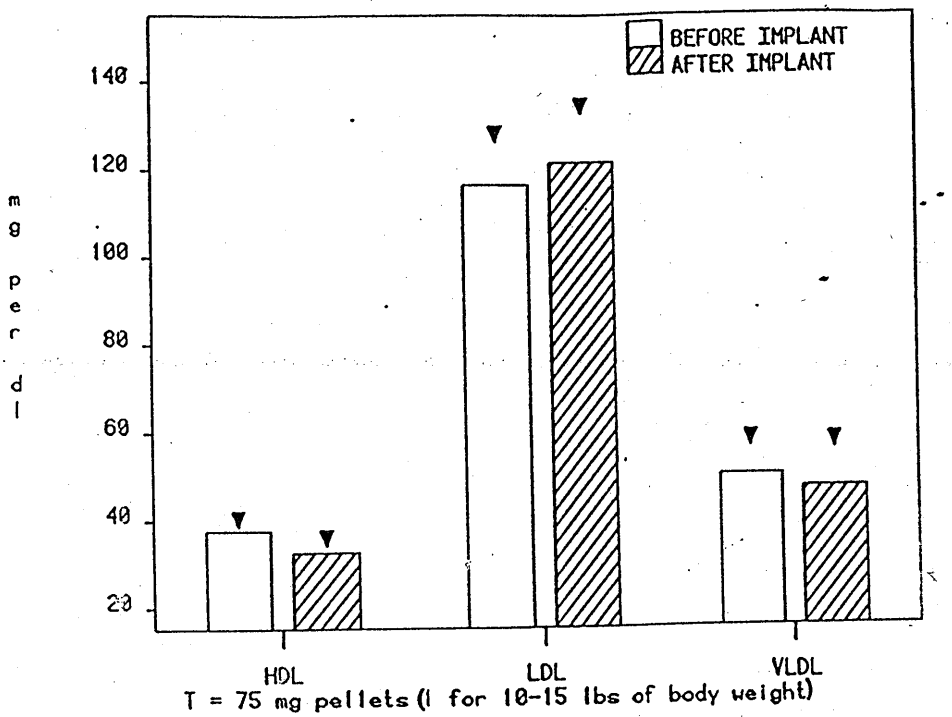

Fig. 25.8. No significant changes in high (HDL), low (LDL), and very low-density lipoproteins (VLDL) were observed after testosterone pellet implantation.

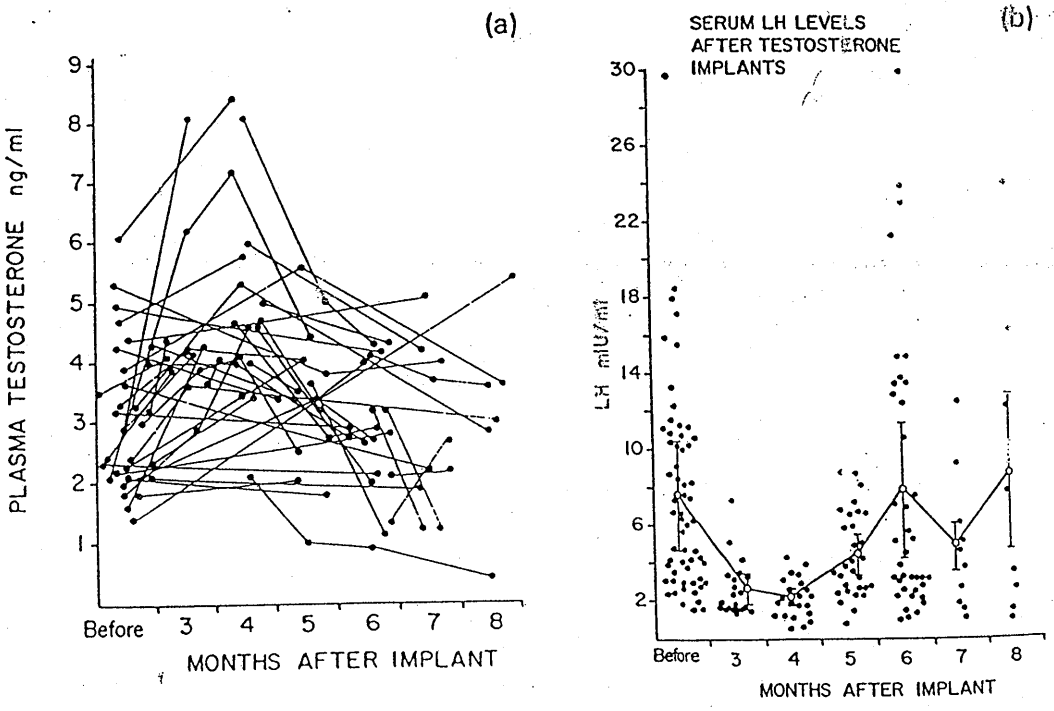

Fig. 25.5. (a) Serum testosterone levels fall after the fourth month of implantation, usually accompanied by a loss of libido and/or erectile capacity. (b) LH levels fall after testosterone pellet implantation and begin to rise coincident with loss of libido and/or erectile capacity.

TABLE 25.2.

In a double-blind study using an oestrogen (AE1), an oestrogen-androgen (AE2). an androgen (AE3), and a placebo (AE4) in the treatment of menopausal hot flushes, 12.3 per cent of the patients volunteered the information that the oestrogen increased libidinous drives, 65.5 per cent after androgens, and only 1.8 per cent on the placebo. (From Greenblatt *et al.* 1950.)

Mrs J.S., w.f. 52. Menopause. Hot flushes and formication. (Hysterectomy)

AE	1	2	3	4	
July	X				Complete relief. Slight increase in libido.
Aug.					Symptoms returned 3 wks. after stopping AE-1.
Sept.		X			90% relief. Increased libido, nervousness.
Oct.					
Nov.			X		Better than AE-2 or AE-1.
Dec.					Recurrence of symptoms.
Jan.				X	No relief. Smear 2-3 plus.
Feb.			X		80% relief. Occasional hot flushes. Smear 3 plus.
Mar.			X		Not as good as AE-1 now.
Apr.				X	No relief. Complete return of symptoms.

mones, preferably by the parenteral route. Specific agents can restore sexual function in individuals with certain disorders, such as thyroxin in the hypothyroid; and propylthiouracil in the hyperthyroid; bromocriptine in individuals with hyperprolactinaemia and acromegaly; and L-DOPA in Parkinson's disease (Calne and Sandler 1977; Spark, White, and Connolly 1980; Thorner and Besser 1976). These very agents proved of little value in normal individuals with sexual dysfunction (Ambrosi, Bara, and Fagler 1977). Although oestrogens may increase a woman's sexual ardour, and progestins may do so for others, it is our experience that women who once have known libido but lost it respond almost universally to oestrogen-androgen therapy.

CONCLUSIONS

Psychodelic drugs, serotonin-antagonists, pharmacologic drugs with vasodilator action, adrenergic blocking agents, nephrogenital irritants, plants and herbs, foodstuffs, alcoholic beverages, and organic material that have some semblance to male genitalia – Paracelsus's doctrine of signatures (i.e. tubers, rhinoceros horn) – are believed to be sexual stimulants. For some, they indeed are, but only temporarily. Suggestion is a powerful ally and, in this regard, pornography does actually stimulate sexual arousal and fantasies.

The psychophysiological complexity of the normal sexual response involves

central, spinal, vascular, sympathetic, and parasympathetic elements. Oestrogens and androgens modulate the neurotransmitters of the brain and indirectly influence the autonomic nervous system. In the female, androgens are powerful stimulants of sexual dreams and fantasies, while improving vaginal hyperaemia and lubrication, often increasing clitoral sensitivity and turgescence and orgasmic experience. In the male, testosterone in large doses, preferably administered parenterally, over a sufficient length of time, has proved in our hands capable of overcoming sexual dysfunction in about two-thirds of normal men with low or normal testosterone levels. Gonadal hormones are psychotrophic drugs, participating in both physiological and psychological components of sexual behaviour.

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