The Pharmacology of Sexual Function and Dysfunction
J. Bancroft, editor

Testosterone and Prolactin: behavioural and psycho-physiological approaches in men

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Androgens are necessary for normal sexual desire. They are also necessary for production of seminal fluid and hence ejaculation, although their role in male orgasm remains uncertain. However, the relationship between androgens and erectile function is more complex.

In 1970 Ismail et al. (1) and Cooper et al. (2) found that urinary testosterone (T) was lower in psychogenic impotent men than in controls.

Some investigators found that T was lower in men with erectile dysfunction than in controls (3, 4), but others could not confirm this observation (5, 6). Furthermore, androgen replacement therapy had only slight transient effects or even no beneficial effects on functional impotence (7, 8, 9).

O'Carroll and Bancroft (9) reported that T administration by injecton was followed by a modest increase of sexual desire but not of erectile function in eugonadal men complaining of loss of sexual desire. This study indicates that increased plasma T can effect interest even in eugonadal men. On the other hand Schiavi (10) studied subjects with hypoactive sexual desire and found that these men had significantly lower plasma T, measured hourly through the night, than controls, and there was a positive relation between T and frequency of sexual behaviour. The nocturnal penile tumescence and rigidity monitoring (NPTM) parameters of hypoactive sexual desire subjects related with secondary impotence were significantly lower than in non-dysfunctional men. This confirmes that the nocturnal erections are androgen-dependent.

We (11) studied sleep related erections in 8 eugonadal men and found that T enhantate administration was associated with an increase of both maximum rigidity and duration of rigidity higher than 60% but the administration of the androgen had no effects on penile circumference and on frequency of both erections and REM.

In a recent work on the effects of supraphysiological levels of T used for male contraception for up to two months Anderson et al. (12) showed that some aspects of sexual arousability can be improved without a simultaneous stimulation of sexual activity in eugonadal men.

In adult men either primitive or secondary hypogonadism usually results in loss of libido and impairement of penile erection, which can be both restored by adequate T replacement therapy. Therefore, hypogonadism is a clinical situation which helps to understand the effects of androgens, whose precise role in adult male sexual function is not yet completely clear.

The study of sleep-related erections helps to differentiate organic from psychogenic erectile disfunctions (13, 14, 15). Fenwich et al. (16) found a positive correlation between nocturnal erections and both serum total T and free T levels in subjects affected by chronic epilepsy. There are only few studies cocerning the nocturnal penile tumescence and rigidity (NPT) in hypogonadal subjects with and without T replacement therapy (17, 18).

In studies on hypogonadal men who stopped the replacement therapy, Cunningham et al. (19), Zini et al (20) and Carani et al. (21) confirmed impaired NPT and decreased frequency of the nocturnal erections with no differences between patients and controls for what concerns the penile response to visual erotic stimuli (VES). In fig. 1a, 1b and 1c some results are shown (21).

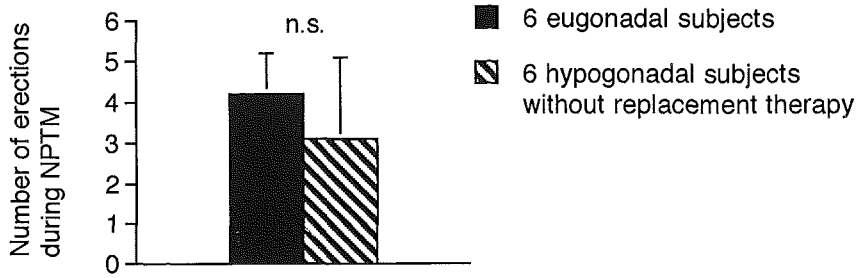

Fig. 1a

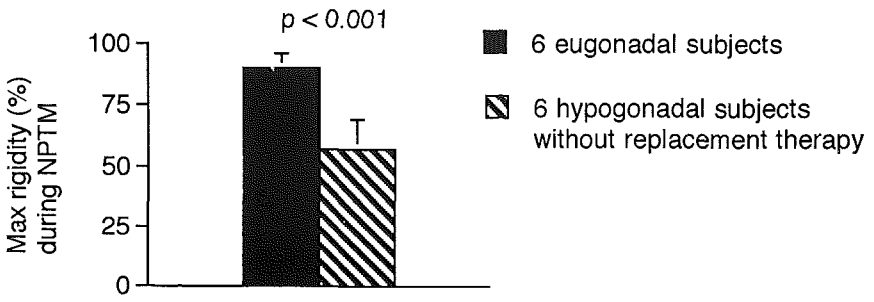

Fig. 1b

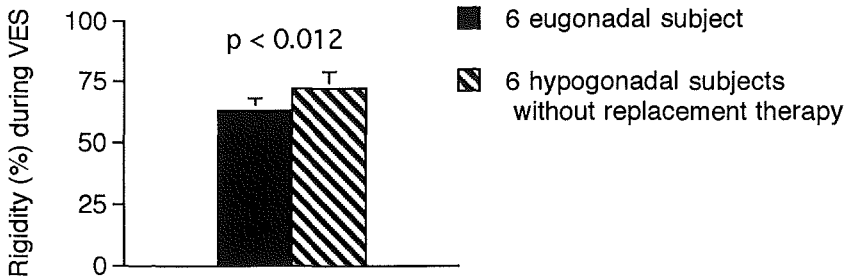

Fig 1c

On the other hand, the administration of T, gonadotropins or gonadotropin releasing hormone (19, 22) was followed by the reapparance of normal NPT in hypogonadal subjects (Fig. 2) (22). In these studies on hypogonadal men the erections in response to VES were also evalued and have seen to be similar to those from eugonadal controls and to have no enhancement from androgen replacement (17, 24), apart from the duration of the penile response. The hypogonadal patients during replacement therapy showed the "time above rigidity $\geq$ 60%" significantly higher than the hypogonadal patients without replacement therapy and with a trend for this parameter to be higher in the patients with therapy than in the controls (Fig. 3) (22).

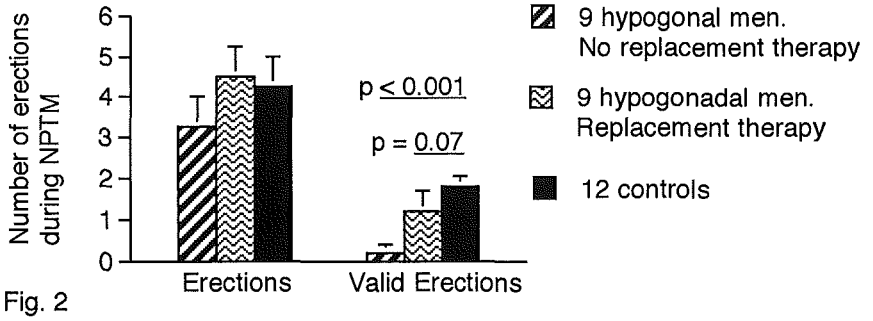

Fig. 2

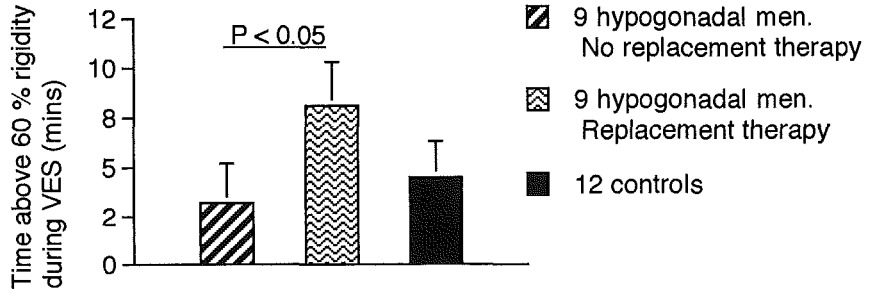

Fig. 3

Our results support previous findings that NPT is androgen-dependent and that erectile response to VES is androgen-independent; however the data on the duration of the response to VES suggest a role of T at least on this parameter and justify further studies.

Hypogonadism is well known to occurr also in male hyperprolactinemia (25) and it is often accompanied by impotence and infertility. It is still unclear why hypogonadism can occurr in men with hyperprolactinemia. Many studies have shown decreased plasma levels of total T and normal, low or sometimes even increased levels of gonadotropins (25) together with high serum prolactin (Prl) levels.

The mechanism whereby hyperprolactinemia induces hypogonadism remains conjectural. It is believed that hyperprolactinemia induces excessive endogenous oppiate tone, which inhibits pulsatile release of gonadotropins-releasing hormone by an effect at the median eminence. This, in turn, would reduce the frequency of luteinizing hormone release and the ensuing production of T. It also has been postulated that excessive Prl may inhibit steroidogenesis directly in the testes but this is substantiated poorly, since virtually no Prl receptors have been localized in the male gonads. However reducing the serum level of T is not the only mechanism whereby Prl inhibits erectile function. The administration of exogeneous T in the presence of hyperprolactinemia does not improve sexual function. Thus Prl appears to have a central effect on sexual performance.

Cunningham in 1982 (26) studied the relationship between serum T and Prl levels on one hand and sleep-related erections on the other hand.
He described the data obtained in a group of men with erectile disfunction, including also 12 men with low T plasma levels and/or high Prl plasma levels. He noted a sort of threshold below which for T and over which for Prl a high incidence of impaired NPT occurred.

With the aim to evaluate the role of Prl on the penile erection, we studied NPT and penile response to VES in 4 groups of men:
a) 8 men with severe hypotestosteronemia due to hypogonadotropic hypogonadism (serum T less than 130 ng/100 ml); all the 8 patients complained of erectile disfunction and decreased libido (Fig. 4);
b) 10 men with mild hypotestosteronemia; the serum T level was between 200 ng/100 ml and 340 ng/100 ml; 1 man complained of decreased libido, 2 complained of erectile disfunction and 1 complained of both (Fig. 4);
c) 6 men with severe hyperprolactinemia and mild hypotestosteronemia; the mean serum Prl level was over 300 ng/ml; all the 6 patients complained of a decrease in libido and erectile disfunction (Fig. 4);
d) 10 control men (serum T levels higher than 450 ng/100 ml in all subjects) (Fig. 4).

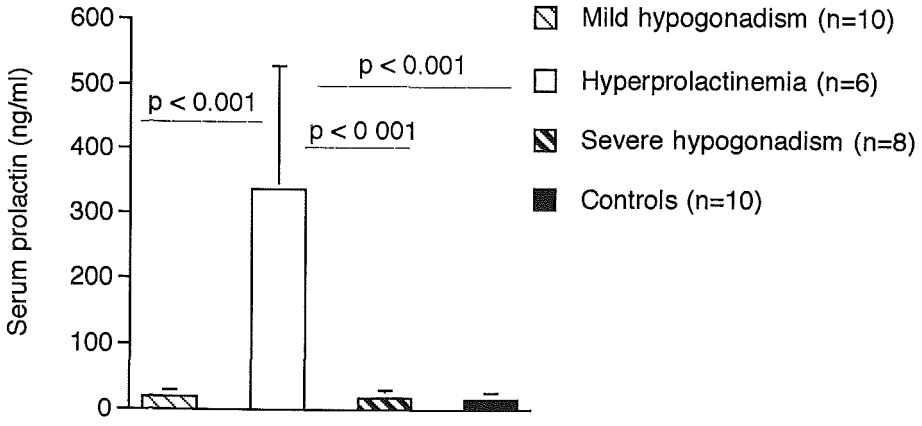

Fig. 4

Only the patients with severe hypogonadism showed significantly impaired NPT when compared with the other 3 groups. No difference was found among the groups for the response to VES (Fig. 5).

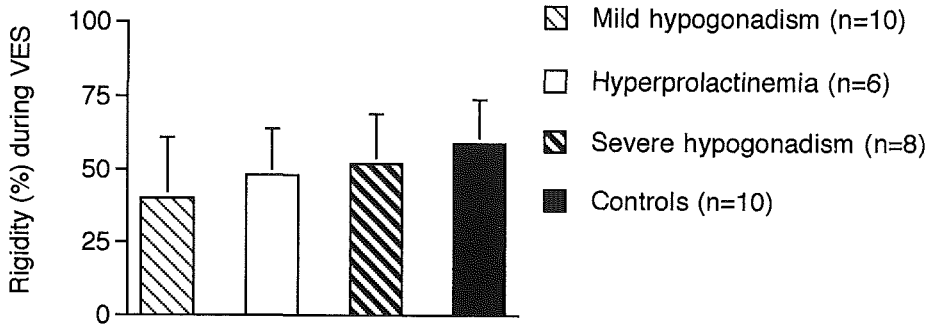

Fig. 5

So it seems possible to assume that there is a threshold for plasma T below which the night erections are impaired. On the other hand, our data suggest that hyperprolactinemia has no evident, direct effects on penile erections and its inhibiting effect on sexual behaviour cannot be removed simply by T administration (27). The men affected by hyperprolactinemia show valid erections during sleep and in response to VES, which put these patients very close to the men affected by psychogenic impotence.

There is wide consensus that patients with hyperprolactinemia present an unusual prevalence of depressive disorders and it could be suggested that in this desease two different mechanisms take place: a) the high Prl serum levels probably play a role on the mood; b) the low T serum levels may be the most important organic side of this desease.

Surprisingly, to our knowledge only one study to date has evalued the use of L-dopa in patients with sexual disfunction (28). Although the authors concluded that L-dopa had little value in the treatment of erectile disorders, the exclusion of patients with psychogenic erectile difficulties or desire disorders, and absence of concomitant sex therapy interventions, may have contributed to the lack of positive out-come in this study. Overall there is increasing evidence of the role of dopaminergic stimulating activity and Prl inhibiting activity in the mediation of sexual desire and arousal.

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Discussion - TESTOSTERONE AND PROLACTIN: BEHAVIOURAL AND PSYCHO-PHYSIOLOGICAL APPROACHES IN MEN

J.G. Pfaus

How do you differentiate between a valid and an invalid erection?

C. Carani

We consider an erection valid when we have an increase of tumescence of at least 30 mm lasting at least for 5 minutes and an increase in rigidity greater than 60%, lasting at least for 5 minutes.

J.G. Pfaus

Specially in the case of erectile responses to erotic films, what might testosterone do to the erectile response of control non-hypogonadal men? Might it facilitate it like it does in the hypogonadal men?

J. Bancroft

There are not any studies giving testosterone to normal men and assessing their effects to visual erotic stimuli but in a study in which testosterone was given to eugonadal men and sleep erections were recorded, there was a significant increase in rigidity of the sleep erections induced by testosterone administration.

J. Herbert

The absence of effect of low testosterone on a variety of parameters apart from the NPT is striking. Do you have any indication of the sexual activity of these various groups? Also, did you measure mood, and particularly aggressivity?

C. Carani

We detected loss of libido and impaired erection in all men with severe hypogonadism. Among cases of mild hypogonadism, I found only one man with loss of libido and impaired erection, one with impaired erection and one with loss of libido. Concerning the second question, we used some tests to evaluate depression in

hyperprolactinemic men with mild hypogonadism, but we did not do a complete study.

D. Vanderschueren

Just a technical question. I noticed that you used rigidity as an endpoint, but I believe that John Bancroft claims that tumescence is a better endpoint for measurement of erections.

C. Carani

I measured tumescence at the same time but rigidity is more connected with high testosterone levels. I had more results when comparing testosterone levels and rigidity than when comparing testosterone levels and tumescence.

J. Bancroft

We are less confident in the rigidity measure than the circumference measure with this particular device. We had problems getting reproducible results from different machines and it is difficult to calibrate and so on. But I think the results with rigidity are quite striking in these hypogonadal men. Concerning the increase in rigidity in hypogonadal men in response to erotic stimuli when they are given testosterone, it seems to me that there are two possible explanations for that. One is that there is a transient enhanced response to testosterone when you increase the levels in hypogonadal men which then declines. In the clinic, I have seen that when one starts treating a hypogonadal man for the first two or three weeks one sometimes gets a stronger effect of the hormone and then it settles down. Whether this is because of a down-regulation of receptors or whether this is because of some testosterone-related increase in inhibitory as well as excitatory mechanisms, I am not sure but I believe that we are probably seeing an early effect. Perhaps if we repeated those results after the men had been on testosterone treatment for several months, the difference may not have been there. The other possible explanation is that in hypogonadal men the penises tend to be smaller and with a small penis you may get a higher degree of rigidity for the same response.

I would also like to comment on Herbert's question about mood and aggression. Certainly, in the studies that we did earlier, there was little effect on mood. You do get

effect in some individuals in improving the mood when you treat hypogonadism, but on average it is a rather weak effect and less predictable than the effect on sexual interest. Similarly, with aggression, if anything, there is a tendency for aggression to go down and this has also been suggested by a recent study from Seattle, published in JCEM this summer, giving LHRH antagonists to normal men. There was not very much effect on mood or aggression, if anything there was a slight increase in aggression as testosterone levels went down, if I remember correctly. Julia Heiman was involved in that study, perhaps she could comment on that.

J.R. Heiman

I really am not very convinced that we had a good aggression measure. We tried to look at hostility and aggression but the standard scales included a number of items that we would not expect to be influenced, and so we had to select items off those scales. As a consequence, we did not have a scale, we had individual items and so I ended up not completely satisfied with our measure. Nonetheless, I am still convinced that probably not much happened with aggression in that particular study, if that conflicting statement makes any sense. I think that the aggression, hostility and anger responses need to be more carefully teased out for human endocrine studies measuring daily experiences.

J. Bancroft

I would agree entirely that all these studies have used very limited measures. We are starting a WHO study which is directly aimed at assessing the effect of increased testosterone on aggression in eugonadal men, because we believe that it has not been adequately tested.

B.D. Sachs

I would like to come back to the microprolactinoma subjects that you were talking about. You mentioned that they had no impairment in sleep erections nor in response to erotic films, but they came to you because they were reporting low libido and erectile dysfunction. What were the symptoms of erectile dysfunction, and to what do you attribute the erectile dysfunction that they were reporting?

C. Carani

This is my question too, because I analyzed these men during the night and during the day but I didn't arrive to a conclusion. These patients suffered from sexual impairment, they had low sexual desire and impairment of erection, but the result is the same as in normal men or in men with psychogenic impotence. My question is, have these men the same problem as the ones with psychogenic impotence? I presented only one man with microprolactinoma and with very low testosterone levels. I have only three men with microprolactinoma and with very low testosterone levels. It seems that the nocturnal erection is linked to low testosterone levels but not to high prolactin levels. The nocturnal erections in hyperprolactinemic men are androgen-dependent.

J. Bancroft

I would like to mention the case of a hyperprolactinemic man. We discovered his hyperprolactinemia after we had treated him psychologically. His erectile problem was resolved by sex therapy. He was left with relatively low sexual desire and in a placebo controlled evaluation we found that reducing his prolactin levels improved his sexual desire. So it appeared that in his case the erectile problem was a psychological reaction to his low sexual desire and the problems that caused in his relationship with his partner.

K. Demyttenaere

I would like to come back to the discussion on mood because we have focused only on mood and testosterone. I think it is also important to have a look to mood and prolactin because if it is true that these patients complain about low sexual interest and erectile failure while they have normal reactions in the lab, this could reflect a depressive situation. It has been shown in depressive patients that they complain about sexual dysfunction or loss of libido, while, in fact, in experimental situations they show normal reactions. It has been suggested that prolactin could have a neuroleptic activity, and it is known that hyperprolactinemic patients have high depression and anxiety and it has been shown that if you reduce prolactin levels with bromocriptine they are better psychologically or if you give them autogenic training the prolactin levels go down. So, we should take mood into account and look at the conflicting data between self-report

and what they are doing in the lab.

R.T. Segraves

Clinically these patients can be quite confusing because I remember one patient that came in and reported that he was impotent with his wife but potent with his secretary and he had early morning erections. The sex therapist said there was nothing wrong with this man psychologically, but subsequently we measured his prolactin levels and we found that he had a fairly large adenoma. These can be very tricky cases.

W. Everaerd

I have a rather technical question. I am curious about the variation within groups of the effects of testosterone in replacement therapy. How large are they?

C. Carani

Probably there is a correlation between testosterone levels and response. In the study in which I gave testosterone to hypogonadal men the average levels of testosterone were higher than in the control group. This higher testosterone may be playing an important role not only during the night but also during the day.

J. Bancroft

I think that a lot of the variance that one sees in men's sexuality is not dependent on testosterone and therefore if you take hypogonadal men you will restore them to the level that they would be at if they were eugonadal, that is going to be quite variable from one man to another. So you cannot expect to get homogenous sexuality by giving people the same amount of testosterone.