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Type V phosphodiesterase inhibitor treatments for erectile dysfunction increase testosterone levels

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OBJECTIVE Lack of sexual activity due to erectile dysfunction (ED) decreases testosterone (T) levels through a central effect on the hypothalamic–pituitary axis. In this paper we studied the effect of different type V phosphodiesterase (PDE5) inhibitor treatments for ED on the reversibility of this endocrine pattern.

DESIGN Open-label, retrospective study.

PATIENTS Seventy-four consecutive patients were treated on demand with sildenafil (Sild) (50 mg) and tadalafil (Tad) 20 mg.

MEASUREMENTS The success in sexual intercourse was recorded and total (tT) and free testosterone (fT) levels were studied before and after 3 months of treatment.

RESULTS Basal level of tT and fT were at the bottom of the normal range and LH levels were at the top of the high normal range. After treatments, this endocrine pattern was reversed in both groups. However, the T increase in Sild-treated patients was significantly lower than in those treated with Tad (4·7 ± 2·7 *vs.* 5·1 ± 0·9, $P < 0·001$). fT levels followed a directly proportional pattern, while the inverse was found when LH production was studied. The intercourse rate reflected this effect: in fact, the Sild group showed a 4·9 ± 2·9/month full sexual intercourse rate while in the Tad group a significantly higher rate of sexual intercourse was found (6·9 ± 4·6/month, $P = 0·04$). However, drug consumption was comparable between the groups (Sild 4·9 ± 2·9 *vs.* Tad 4·4 ± 2·8 pills/month, $P = 0·72$).

CONCLUSIONS As it is unlikely that the two drugs have a different direct effect on the pituitary–testis axis, this effect is probably due to the higher frequency of full sexual intercourse in the Tad-treated group, because of the drug's longer half-life.

The availability of the first selective inhibitor of the erectolytic enzyme type V phosphodiesterase (PDE5), sildenafil citrate (Sild), has dramatically changed the prognosis of erectile dysfunction (ED) (Jannini *et al*., 2003). The recent marketing of two other PDE5 inhibitors has now expanded the therapeutic possibilities. Vardenafil (Klotz *et al*., 2001), like Sild (Goldstein *et al*., 1998), is characterized by a relatively short half-life (4–5 h). By contrast, tadalafil (Tad) ($t_{1/2}$ = 17·5 h) (Padma-Nathan *et al*., 2001) can be considered as a long-acting drug, as its different structural formula means that it has high affinity for PDE5 (Sung *et al*., 2003).

While the overall effectiveness of these drugs appears comparable (for review see Corbin & Francis, 2003; Jannini *et al*., 2003), it is not known whether there are differences in hormonal and/or behavioural responses to these treatments.

We have previously demonstrated that men suffering from impotence, irrespective of its aetiology, have androgen levels significantly lower than normal controls, although still in the normal range (Fabbri *et al*., 1988; Jannini *et al*., 1999). This is due to reduced LH bioactivity, a marker of impaired GnRH secretion (Fabbri *et al*., 1988; Carosa *et al*., 2002). As psychological (behavioural therapy), pharmacological (Prostaglandin E1, Yohimbine), and mechanical (penile prostheses, surgery, vacuum device) therapies are able to restore testosterone levels and LH bioactivity (Jannini *et al*., 1999; Carosa *et al*., 2002), we wanted to verify whether the same effect occurs in patients treated with PDE5 inhibitors.

Therefore, we designed a retrospective protocol studying the pituitary–testis axis and sexual behaviour in Sild- and Tad-treated patients.

Subjects and methods

This was a multicentre, open-label, retrospective study on behavioural output and endocrine response to two oral pharmacological

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regimens for ED. The 97 patients with chronic ED reported in this study were consecutive, random, ambulatory patients seen at our andrological clinics, who met all of the following inclusion criteria: (1) age between 18 and 70 years at first examination; (2) mild to severe ED of at least 1 year's duration with or without loss of libido, as established by a clinical questionnaire (Fabbri *et al*., 1989) and the International Index of Erectile Function (IIEF) (Rosen *et al*., 1997); (3) stable relationship of at least 1 year; (4) return for the therapy follow-up. We excluded patients with: (1) history of cryptorchidism and varicocele; (2) clinically evident hypogonadism; (3) past or current use of illicit drugs; (4) unresponsiveness to the drugs used in this study at the 3-month follow-up. The definition of success was the patient's, which was always defined as achieving successful penetrative intercourse. Failure was not being able to get an erection firm enough to penetrate (Tomlinson & Wright, 2004). On the basis of this criterion, 74 patients were evaluated.

In most patients impotence was chronic and absolute, that is present with any partner, even if to a differing degree. Aetiological diagnosis of ED was performed on the basis of the following data (Korenman, 1995): laboratory (glycaemic, hepatic, lipid and renal profiles), psychiatric (Minnesota Multiphasic Personality Inventory and State Trait Anxiety Index), neurological (bulbocavernous reflex latency time) and vascular (penile-brachial pressure index before and after exercise; two-dimensional Doppler assessment before and after vasodilatator infusion) parameters. Pharmacocavernosometry, pharmacocavernosography and angiography were used when indicated to study patency of major vessels and the veno-occlusive mechanism.

Reproductive endocrine axis was evaluated using commercial kits for immunoreactive LH (I-LH; normal range 1·5–10·0 IU/l), total testosterone (tT; normal range 8·6–34·6 nmol/l) and free testosterone (fT; normal range 40–140 pmol/l). The intra- and interassay coefficients of variance (CVs) were 1·0% and 1·9%, respectively, for I-LH; 4·6% and 4·9% for tT; and 3·8% and 4·2% for fT. As androgens and gonadotrophins are secreted episodically and vary both diurnally and seasonally, tT, fT and LH were measured in duplicate, both at entry and after 3 months of treatment, on serum collected every 15 min for 90 min, starting at 0800 h. Samples were pooled using the same volume of serum and stored at −70 °C. For each hormone, each pair of serum samples (i.e. pre- and post-therapy) from a given patient was assayed in the same run. Because patient treatments were scattered throughout the year, seasonal variations in the pituitary–testicular axis did not affect the results.

Patients were assigned to the following treatment regimens: the Sild group (Viagra, Pfizer, New York, NY, USA, 50 mg p.o. on demand, as needed); $n = 32$, mean age 42·3 ± 13·8 years (range 19–67 years); and the Tad group (Cialis, Lilly-Icos, Indianapolis, IN USA, 20 mg p.o. on demand, as needed); $n = 42$, mean age 41·4 ± 11·9 years (range 21–70 years) (*P vs.* Sild = 0·4). As stated above, only patients responsive to the drugs were considered. However, the number of responsive patients and drop-outs was similar in both groups (not shown). No differences were found between groups for body mass index (BMI), prevalence of organic/nonorganic aetiologies, duration of ED, degree of impotence, as judged by IIEF, and sexological and marital recall.

Patients and partners recorded their sexual encounters in the Padma-Nathan Sexual Encounter Profile (SEP) diaries, consisting of a series of yes/no questions regarding specific aspects of each sexual encounter (Padma-Nathan *et al*., 2001). Patients were instructed to take a maximum of one dose daily as needed over a period of 3 months, at least 1 h before the sexual attempt. Food and alcohol intake were restricted before each assumption. At the end of the 3-month period, IIEF scores were obtained, SEP diary cards were reviewed and new blood samples obtained for tT, fT and LH measurement. Also evaluated were the number of pills consumed and how often full sexual intercourse was performed, on the basis of patient and partner logs.

Statistical analysis

The results are expressed as mean ± SD. Mean differences in hormone levels were analysed with the paired and unpaired *t*-test as appropriate, by setting the level of significance at $P < 0·05$.

Results

Hormone profile

The mean values of serum tT in the 75 patients as a whole group were low, within the low normal range of 11·9 ± 3·1 nmol/l, confirming the reduction in androgen production previously demonstrated in impotent patients without sexual activity (Jannini *et al*., 1999; Carosa *et al*., 2002). As free levels more clearly reflect the biological activity of circulating testosterone than do tT levels, we measured fT in our patients. These values of 59·9 ± 23·6 pmol/l paralleled those for total testosterone. LH levels were 4·7 ± 2·1 IU/l, in the high normal range.

To test whether recovery of sexual activity by either treatment affects the pituitary–testis axis of impotent patients, we repeated hormone assays 3 months after the beginning of each therapy. Considering our patient group as a whole, tT rose to 16·3 ± 3·5 nmol/l, fT rose to 80·4 ± 23·2 pmol/l, and LH fell to 2·7 ± 1·6 IU/l ($P < 0·001$ for each with respect to basal values). However, differences were found in the hormone profile when the two subgroups were compared. In fact, in the Sild group, androgen increase and LH decrease were less marked than seen with Tad (Table 1). Although at the baseline no statistical differences in hormone levels were found between the two groups, significant differences were found (tT: $P < 0·001$, fT: $P < 0·05$, and

Table 1 Hormonal values before and after 3 months of impotence therapy

	tT (nmol/l)	*P vs.* basal	*P vs.* Sild	fT (pmol/l)	*P vs.* basal	*P vs.* Sild	LH (IU/l)	*P vs.* basal	*P vs.* Sild
Before Sild	11·8 ± 3·1	–	–	62·1 ± 26·7	–	–	4·3 ± 2·3	–	–
After Sild	16·3 ± 9·4	0·000	–	75·2 ± 18·4	0·010	–	3·1 ± 1·6	0·000	–
Before Tad	11·4 ± 2·8	–	0·297	56·2 ± 20·8	–	0·142	5·0 ± 1·9	–	0·075
After Tad	17·7 ± 3·1	0·001	0·001	84·6 ± 25·7	0·000	0·040	2·5 ± 1·5	0·000	0·040

For each group, differences were calculated with respect to baseline and with respect to the same time of the other group.

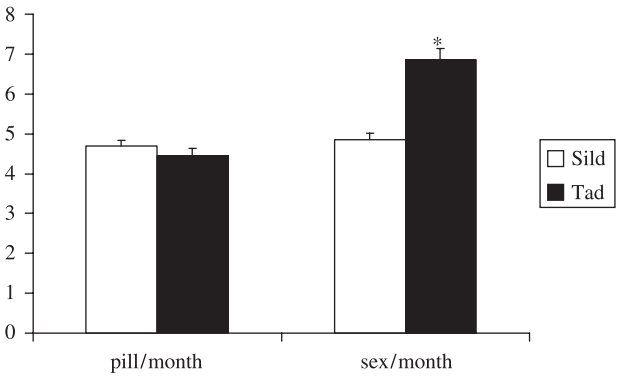

Fig. 1 Number of pills (pill) consumed and frequency of full sexual intercourse (sex) per month in sildenafil (Sild)- and tadalafil (Tad)-treated patients, as recorded by SEP diaries. *$P = 0·036$.

LH: $P < 0·05$) at the 3-month therapy follow-up. Tad thus appears to be more effective than Sild in reverting the ED-induced endocrine pattern.

On the basis of the SEP and IIEF questionnaires, we then tested differences in the therapeutic activity of the drugs. They were equally effective in restoring sexual potency (data not shown). However, the frequency of full sexual intercourse was significantly higher in Tad-treated patients (Fig. 1). As this may have been due to differences in drug use and frequency of assumption, these parameters were analysed.

Patients of both groups were allowed to use the drugs on demand as needed. On the basis of the SEP diary, we found that Sild consumption (2–12 pills/month) was comparable to that of Tad (2–12 pills/month, $P = 0·716$), strongly suggesting that the greater normalization of hormonal values in Tad-treated patients was due to the higher number of sexual acts. Finally, no differences between groups in coital activity were found after the end of the pharmacological effect of both drugs, that is after 12–24 h from Sild administration and 48–72 h from Tad administration.

Discussion

In this study we confirm, in a new population of selected impotent patients, that total and free testosterone serum levels are low in the low normal range and LH levels are high in the high normal range. We also demonstrate the reversibility of this endocrine pattern upon the resumption of sexual activity obtained with PDE5 inhibitor therapies. Even if this cannot be considered a comparative, controlled study, another interesting finding was that with identical pill consumption, patients treated with Tad appear significantly more sexually active than those under Sild treatment. This is reflected by the differences between the two drugs seen in increased T and decreased LH after 3 months of treatment.

Although some reports did not show a relationship between T levels and ED prevalence and severity (Rhoden *et al*., 2002a,b), the direct correlation of serum T levels and self-reported sexual activity has been reported in many papers, confirming our findings. Indeed, this idea was formulated more than 30 years ago when it was shown that androgen-dependent beard growth is a direct function of sexual activity (Anonymous, 1970). The short-term exposure of males to females provokes temporary increases in T concentrations in animals (Graham & Desjardins, 1980) and humans (Fox *et al*., 1972). In healthy young men, peaks in salivary T levels coincided with periods of intense sexual activity (Hirshenhauser *et al*., 2002). Penile and systemic T significantly increases during excitation and erection in both normal (Rubin *et al*., 1979; Lange *et al*., 1980; Stoleru *et al*., 1993; Becker *et al*., 2000) and impotent subjects (Becker *et al*., 2001). A retrospective medical review of 180 men attending a hospital-based ED clinic showed that total (around 10·4 nmol/l) and free (around 34·67 pmol/l) T levels were in the low normal range (Ansong & Punwaney, 1999). In 213 men with various degrees of ED, fT levels were significantly correlated with erectile function and, interestingly, with orgasmic function (Ahn *et al*., 2002). Men over 60 in the lowest age-adjusted tertile for sexual outlet had lower serum T levels ($P < 0·05$) than those in the middle or upper tertiles (Tsitouras *et al*., 1982). Men with coronary artery disease, a condition in which sexual activity is impaired, scarce or absent, have significantly lower levels of fT than aged-matched healthy controls (English *et al*., 2002; Sieminska *et al*., 2003). In either normotensive or hypertensive men, a positive correlation has been demonstrated between T levels and sexual activity (Fogari *et al*., 2002). In men with ED, fT directly correlates to the degree of impotence measured by penile arterial inflow

(Aversa *et al*., 2000, 2003). In men successfully treated with apomorphine, tT rose from 13·5 ± 3·5 (baseline) to 20·5 ± 4·5 nmol/l in 2 weeks (Caruso *et al*., 2003). In line with these observations, our data demonstrate that sexual activity per se can affect T levels. In fact, we show that reduced T levels characterize the loss of sexual activity of impotent patients, while androgen levels rise when sexual activity is started anew – no matter what was the cause of the impotence or how it was treated.

At the most commonly used dosages, we found Tad and Sild to be equally effective in treating impotence. However, in this retrospective, open-label study, patients treated with Tad had significantly more full sexual intercourse per pill than those treated with Sild. Because of the comparable pharmacological profile (Jannini *et al*., 2003), similar results may be expected using vardenafil instead of Sild. As this was not a comparative double-blind protocol, patients were informed of Tad's long half-life. Although they did not receive instructions about the number of full sexual acts to perform, this is a heavy bias when comparing results with Sild outcome. Furthermore, the model we studied was a highly selected group of stable couples. Clearly, other groups such as single men or those in an occasional relationship may produce different results. However, independently of this, we have demonstrated for the first time that impotent patients in a stable marital relationship and treated with Tad have more than one sexual act per pill (mean 1·5). As expected, because of its short half-life, the rate of full sexual intercourse per Sild pill is close to one (mean 1·05). This correlates with T levels, which were significantly higher in the Tad than in the Sild group. It could be hypothesized that this endocrine difference may be due to a specific action of Tad on the pituitary–testis axis. In fact, human testis expresses a quite high level of PDE5 (Morelli *et al*., 2004). Hence, it is possible that PDE5 inhibitors act directly on T production in the testis. In addition, no report is so far available on the hypothalamic or pituitary expression of PDE5 and it is possible that these tissues express the enzyme. The chance of a direct effect either on the testis or on the hypothalamic–pituitary axis cannot be ruled out at present, but it seems unlikely, considering that similar effects have been demonstrated previously with many different successful treatments of ED, from talking therapy to surgery (Jannini *et al*., 1999; Carosa *et al*., 2002). We thus hypothesize that the more evident increase in T level is caused by the higher number of complete sexual acts performed by Tad-treated impotent men. In the context of a couple, this can be considered as an important benefit of Tad and a cost-effective advantage.

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References

Ahn, H.S., Park, C.M. & Lee, S.W. (2002) The clinical relevance of sex hormone levels and sexual activity in the ageing male. *British Journal of Urology International*, **89**, 526–530.

Anonymous (1970) Effects of sexual activity on beard growth in man. *Nature*, **226**, 869–870.

Ansong, K.S. & Punwaney, R.B. (1999) An assessment of the clinical relevance of serum testosterone level determination in the evaluation of men with low sexual drive. *Journal of Urology*, **162**, 719–721.

Aversa, A., Isidori, A.M., De Martino, M.U., Caprio, M., Fabbrini, E., Rocchietti-March, M., Frajese, G. & Fabbri, A. (2000) Androgens and penile erection: evidence for a direct relationship between free testosterone and cavernous vasodilatation in men with erectile dysfunction. *Clinical Endocrinology*, **53**, 517–522.

Aversa, A., Isidori, A.M., Spera, G., Lenzi, A. & Fabbri, A. (2003) Androgens improve cavernous vasodilatation and response to sildenafil in patients with erectile dysfunction. *Clinical Endocrinology*, **58**, 632–638.

Becker, A.J., Uckert, S., Stief, C.G., Truss, M.C., Machtens, S., Sheller, F., Knapp, W.H., Hartmann, U. & Jonas, U. (2000) Cavernous and systemic testosterone levels in different phases of human penile erection. *Urology*, **56**, 125–129.

Becker, A.J., Uckert, S., Stief, C.G., Sheller, F., Knapp, W.H., Hartmann, U. & Jonas, U. (2001) Cavernous and systemic testosterone plasma levels during different conditions in healthy males and patients with erectile dysfunction. *Urology*, **58**, 435–440.

Carosa, E., Benvenga, S., Trimarchi, F., Lenzi, A., Pepe, M., Simonelli, C. & Jannini, E.A. (2002) Lack of sexual activity for erectile dysfunction causes a reversible reduction of LH bioavailability. *International Journal of Impotence Research*, **14**, 93–99.

Caruso, A., Intelisano, G., Farina, M., Di Mari, L., Agnello, C. & Giammusso, B. (2003) Efficacy and safety of daily intake of apomorphine SL in men affected by erectile dysfunction and mild hyperprolactinemia: a prospective, open-label, pilot study. *Urology*, **62**, 922–927.

Corbin, J.D. & Francis, S.H. (2003) Molecular biology and pharmacology of PDE-5-inhibitor therapy for erectile dysfunction. *Journal of Andrology*, **6**, S38–S41.

English, K.M., Mandour, O., Steeds, R.P., Diver, M.J., Jones, T.H. & Channer, K.S. (2000) Men with coronary disease have lower levels of androgens than men with normal coronary angiograms. *European Heart Journal*, **21**, 890–894.

Fabbri, A., Jannini, E.A., Ulisse, S., Gnessi, L., Moretti, C., Frajese, G. & Isidori, A. (1988) Low bioactive luteinizing hormone in nonorganic male impotence: possible relationship with altered gonadotropin-releasing hormone. *Journal of Clinical Endocrinology and Metabolism*, **67**, 867–875.

Fabbri, A., Jannini, E.A., Gnessi, L., Moretti, C., Ulisse, S., Franzese, A., Lazzari, R., Fraioli, F., Frajese, G. & Isidori, A. (1989) Endorphins in male impotence: evidence for naltrexone stimulation of erectile activity in patient therapy. *Psychoneuroendocrinology*, **14**, 103–111.

Fogari, R., Zoppi, A., Preti, P., Rinaldi, A., Marasi, G., Vanesia, A. & Mugellini, A. (2002) Sexual activity and plasma testosterone levels in hypertensive males. *American Journal of Hypertension*, **15**, 217–221.

Fox, C.A., Ismail, A.A., Love, D.N., Kirkham, K.E. & Loraine, J.A. (1972) Studies on the relationship between plasma testosterone levels and human sexual activity. *Journal of Endocrinology*, **52**, 51–58.

Goldstein, I., Lue, T.F., Padma-Nathan, H., Rosen, R.C., Steers, W.D. &

Wicker, P.A. (1998) Oral sildenafil in the treatment of erectile dysfunction. *New England Journal of Medicine*, **338**, 1397–1404.

Graham, J.M. & Desjardins, C. (1980) Classical conditioning: induction of luteinizing hormone and testosterone secretion in anticipation of sexual activity. *Science*, **210**, 1039–1041.

Hirschenhauser, K., Frigerio, D., Grammer, K. & Magnusson, M.S. (2002) Monthly patterns of testosterone and behavior in prospective fathers. *Hormones and Behavior*, **42**, 172–181.

Jannini, E.A., Screponi, E., Carosa, E., Pepe, M., Lo Giudice, F., Trimarchi, F. & Benvenga, S. (1999) Lack of sexual activity from erectile dysfunction is associated with a reversible reduction in serum testosterone. *International Journal of Andrology*, **22**, 385–392.

Jannini, E.A., Lenzi, A. & Wagner, G. (2003) New perspectives in the pharmacotherapy of erectile dysfunction. *Idrugs*, **6**, 1165–1172.

Klotz, T., Sachse, R., Heidrich, A., Jockenhovel, F., Rohde, G., Wensing, G., Horstmann, R. & Engelmann, R. (2001) Vardenafil increases penile rigidity and tumescence in erectile dysfunction patients: a Rigiscan and pharmacokinetic study. *World Journal of Urology*, **19**, 32–39.

Korenman, S.G. (1995) Advances in the understanding and management of erectile dysfunction. *Journal of Clinical Endocrinology and Metabolism*, **80**, 1985–1988.

Lange, J.D., Brown, W.A., Wincze, J.P. & Zwick, W. (1980) Serum testosterone concentration and penile tumescence changes in men. *Hormones and Behavior*, **14**, 267–270.

Morelli, A., Filippi, S., Mancina, R., Luconi, M., Vignozzi, L., Marini, M., Orlando, C., Vannelli, G.B., Aversa, A., Natali, A., Forti, G., Giorgi, M., Jannini, E.A., Ledda, F. & Maggi, M. (2004) Androgens regulate phosphodiesterase type 5 expression and functional activity in corpora cavernosa. *Endocrinology*, **145**, 2253–2263.

Padma-Nathan, H., McMurray, J.G., Pullman, W.E., Whitaker, J.S., Saoud, J.B., Ferguson, K.M. & Rosen, R.C. (2001) On-demand IC351 (Cialis™) enhances erectile function in patients with erectile dysfunction. *International Journal of Impotence Research*, **13**, 2–9.

Rhoden, E.L., Teloken, C., Mafessoni, R. & Vargas Souto, C.A. (2002a) Is there a relation between serum levels of total testosterone and the severity of erectile dysfunction? *International Journal of Impotence Research*, **14**, 167–171.

Rhoden, E.L., Teloken, C., Sogari, P.R. & Vargas Souto, C.A. (2002b) The relationship of serum testosterone to erectile function in normal aging men. *Journal of Urology*, **167**, 1745–1748.

Rosen, R.C., Riley, A., Wagner, G., Osterloh, I.H., Kirkpatrick, J. & Mishra, A. (1997) The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. *Urology*, **49**, 822–830.

Rubin, H., Henson, D., Falvo, R. & High, R.W. (1979) The relationship between men's endogenous levels of testosterone and their penile response to erotic stimuli. *Behavior Research and Therapy*, **17**, 305–312.

Sieminska, L., Wojciechowska, C., Swietochowska, E., Marek, B., Kos-Kudla, B., Kajdaniuk, D. & Nowalany-Kozielska, E. (2003) Serum free testosterone in men with coronary artery atherosclerosis. *Medical Science Monitor*, **9**, CR214–218.

Stoleru, S.G., Ennaji, A., Cournot, A. & Spira, A. (1993) LH pulsatile secretion and testosterone levels are influenced by sexual arousal in human males. *Psychoneuroendocrinology*, **18**, 205–218.

Sung, B.-J., Hwang, K.Y., Jeon, Y.H., Lee, J.I.I., Heo, Y.-S., Kim, J.H., Moon, J., Yoon, J.M., Hyun, Y.-L., Kim, E., Eum, S.J., Park, S.-Y., Lee, J.-O., Lee, T.G., Ro, S. & Cho, J.M. (2003) Structure of the catalytic domain of human phosphodiesterases 5 with bound drug molecules. *Nature*, **425**, 98–102.

Tomlinson, J.M. & Wright, D. (2004) Impact of erectile dysfunction and its subsequent treatment with sildenafil: qualitative study. *British Medical Journal*, **328**, 1037–1039.

Tsitouras, P.D., Martin, C.E. & Barman, S.M. (1982) Relationship of serum testosterone to sexual activity in healthy elderly men. *Journal of Gerontology*, **37**, 288–293.