

Testosterone release rate and duration of action of testosterone pellet implants

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Summary

OBJECTIVE Testosterone pellets are a highly effective subdermal depot administered at regular intervals with the timing individualized depending upon return of the patient's characteristic androgen deficiency symptoms. Yet the *in vivo* testosterone release rate and effective duration of action of these pellets has been little studied systematically.

DESIGN Analysis of prospectively collected data from three randomized controlled clinical trials. Collection of extruded pellets.

PATIENTS Androgen-deficient men ($n = 136$) undergoing long-term androgen replacement therapy with a standard dose (800 mg) of testosterone pellets implanted subdermally at intervals from 5 to 7 months.

MEASUREMENTS Testosterone release rate of pellets, consisting of pure crystalline testosterone without excipients, is estimated by measuring the dry weight lost by pellets ($n = 179$) over their time *in situ*. The effective duration of the standard regimen, and the influence of extrusion and patient or procedural characteristics on it, was estimated by timing of return for re-implantation due to recurrence of the patient's familiar androgen deficiency symptoms.

RESULTS The loss of dry weight of intact ($n = 112$) pellets was strongly correlated with time *in situ* ($r^2 = 0.969$) providing an estimate of daily testosterone release rate per 200 mg pellet of 1.34 ± 0.02 mg/pellet/day (95% CI 1.30–1.37 mg/day) for the first 3 months. After 756 implantations of the standard dose, men return for re-implantation at 5.8 calendar months following no or only a single pellet extrusion, but the time

to return was significantly shorter after multiple extrusions. No patient or procedural features influenced the timing of return. Among men with primary hypogonadism, increases in plasma LH and FSH were more sensitive than plasma total or free testosterone to changes in testosterone delivery following an extrusion.

CONCLUSION Testosterone pellet implants release testosterone at a steady rate of 1.3 mg/200 mg implant/day (95% CI). The duration of action is about 6 months in an uncomplicated cycle with timing of return shortened by extrusions only in the 3.6% of procedures followed by multiple extrusions. No other patient or procedural features influenced duration of action. Among men with an intact hypothalamo-pituitary unit, plasma gonadotropins are more sensitive than blood total or free testosterone to reduced testosterone delivery following an extrusion.

The low oral bioavailability and short circulating half-life of testosterone, both recognized since the first clinical use of testosterone (Hamilton, 1937), create difficulties for its use in androgen replacement therapy (Handelsman, 2001). Among ways to circumvent these limitations, various parenteral depot testosterone preparations were developed. Among the earliest was intramuscular injectable formulation of fatty acid esters of testosterone dissolved or suspended in a vegetable oil vehicle (Junkman, 1957), a preparation that remains the most cost-effective and widely used worldwide. However, oil vehicle injections of conventional testosterone esters (enanthate, cypionate, decanoate, propionate) have an effective duration of action of at most 2 weeks (Behre & Nieschlag, 1998) as wider spacing between injections leads to progressively more extreme excursions in plasma testosterone concentrations, less well-sustained gonadotropin suppression (Snyder & Lawrence, 1980) and greater symptomatic consequences of these wide fluctuations (Handelsman, 2001). Recently, newer injectable testosterone depots aiming to provide longer intervals between injections have been developed. Biodegradable microspheres (Burris *et al.*, 1988; Bhasin *et al.*, 1992; Amory *et al.*, 2002) and longer acting testosterone ester formulations such as testosterone undecanoate in oil vehicle (Behre *et al.*, 1999; Zhang *et al.*, 1998; von Eckardstein & Nieschlag, 2002) and an aqueous suspension of testosterone buciclate (Behre & Nieschlag, 1992) promise up to 2- to 3-month intervals between injections when they become available commercially.

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Yet, the oldest depot testosterone preparation, subdermal testosterone implants (Deansley & Parkes, 1938), still offering the longest duration of action with prolonged zero-order, steady-state delivery characteristics lasting 4–7 months (Handelsman *et al.*, 1990; Jockenhovel *et al.*, 1996; Kelleher *et al.*, 2001). Among patients who have experienced the alternatives of injectable or daily delivery (Conway *et al.*, 1988), the very high continuation rates for implants reflects their convenience and effectiveness (Handelsman *et al.*, 1997). Based on the clinical pharmacokinetics and pharmacodynamics evaluated from monthly blood sampling (Handelsman *et al.*, 1990; Jockenhovel *et al.*, 1996; Kelleher *et al.*, 2001), the standard dosage is four 200 mg pellets (800 mg) implanted subdermally at intervals of 5–7 months (Handelsman, 1998). Yet the *in vivo* testosterone release rate of these testosterone pellets and its determinants have not been studied systematically. Therefore, this study aimed to characterize the testosterone release rate and effective duration of action of testosterone pellets by two different *in vivo*-based estimates which provide convergent estimates confirming the predictions from prior pharmacokinetic and pharmacodynamic studies. One approach was based on the measurement of testosterone released from pellets collected after spontaneous extrusion and providing an estimate of testosterone release rate as measured by the loss of dry weight of intact pellets over the time *in situ*. The other approach was based on prospectively collected patient records used to estimate the time between successive implantations. This was based on the fact that the patient on regular treatment determined the time of return for re-implantation based on recognizing the reappearance of his familiar androgen deficiency symptoms.

Materials and methods

Patients

Patients were recruited from androgen deficient men undergoing regular androgen replacement therapy at the Department of Andrology, Concord Hospital (and Andrology Unit, Royal Prince Alfred Hospital prior to September 1999). Clinical and biochemical data for this study were obtained from three recent prospective randomized clinical trials (Kelleher *et al.*, 1999, 2001, 2002). The cohort for these trials is made up of 136 men having regular androgen replacement of which 60 men have primary hypogonadism, 58 have secondary hypogonadism and 18 have mixed hypogonadism. As > 95% of men who commence pellet implantations choose to continue this treatment modality (Handelsman *et al.*, 1997), the cohort of men already on long-term treatment remained virtually unchanged during the data collection period. The men's age was 45.9 ± 2.5 years (median 41 years, range 18–82 years), height 176.3 ± 2.1 cm (median 176 cm, range 152–194 cm), weight 87.6 ± 10.2 kg (median 84.0 kg, range 49.5–143.7 kg), body mass index (BMI) 27 ± 3 kg/m² (median 26,

range 18–42 kg/m²) and body surface area (BSA) 2.01 ± 0.03 m² (median 2.01, range 1.94–2.09 m²). During the study data collection period, the men had a median of three (range two to nine) implantations. Additional information collected included implantation site, number of previous procedures, postprocedural adverse effects and hormonal data (total and free testosterone, SHBG, LH, FSH).

Testosterone pellet implantation

Testosterone pellets are implanted in an office-type minor surgery procedure as described previously (Handelsman, 1991, 1998). Briefly, four 200 mg testosterone pellets are implanted under the skin of the lateral abdominal wall at about the level of the umbilicus or the lateral aspects of the buttocks along the pants line, according to patient preference. At the first implantation, patients are advised that the likely duration of the treatment varies between patients but is usually between 5 and 7 months. Men are advised to make contact as soon as they become aware of the return of their own characteristic androgen deficiency symptoms (e.g. loss of energy and stamina, mood changes, decreased libido) for re-treatment with another implantation. No routine reminders to return in any form are sent to the patients. Appointments for implantation are routinely available with a waiting time of less than 1 week. At the visit for re-implantation, a blood sample is drawn for hormone (total and free testosterone, SHBG, LH, FSH) measurements prior to the testosterone implantation.

Extruded pellets

Patients are asked to keep any extruded implants noting the date of extrusion. Immediately they extrude, the patient places the recovered pellet into a clean, dry, plastic container for storage until return to the Department. Returned extruded or accidentally desterilized (which serve as contemporaneous un-implanted controls) pellets are stored in individually labelled dry containers. After storage for at least several months at room temperature, the dried weight of all intact pellets was measured on a Sartorius Analytic Balance to the nearest 0.1 mg. Pellets that were not intact or in fragments were not weighed. The number of days *in situ* was calculated for each pellet from the recorded dates of the implantation procedure and the extrusion date. As the pellets consist of pure crystalline testosterone without excipients, the weight of testosterone released during its period *in-situ* was the difference between the mean weight of un-implanted pellets and the weight of the dried extruded pellet.

Hormone assays

Hormone assays were performed in a single laboratory as described previously (Handelsman *et al.*, 1990, 1996; Kelleher

et al., 2001). Plasma LH (AxSYM, Abbott Laboratories, IL, USA; CV 5.0–7.4%), FSH (AxSYM, Abbott Laboratories; CV 3.5–7.4%), SHBG (Immulin, DPC, Los Angeles, CA, USA; 6.1–7.9%) and total testosterone (Immulin, DPC; 7.8–12.7%) were measured by commercial immunoassays as described previously (Ly *et al.*, 2001; Liu *et al.*, 2002). Free testosterone was measured by an in-house centrifugal ultrafiltration assay (Vlahos *et al.*, 1982) using Centrifree columns (Millipore, Bedford, MA, USA) and tritiated testosterone to estimate percentage unbound testosterone from which actual free testosterone (CV 9.6–11.7%) is calculated using total testosterone.

Data analysis

The testosterone release rate per day was calculated by a regression of the weight of testosterone release on the numbers of days the implant was *in situ* before extrusion. Given the relationship between testosterone release and timing, the regression was forced through the origin by setting the intercept to zero. The slope of the orthogonal regression then estimated the testosterone release rate per day. The confidence intervals for the slope were verified by bootstrap re-sampling (Efron & Tibshirani, 1993) procedure (10 000 replicates) implemented with NCSS 2001 software. This computationally intensive numerical method provides unbiased estimates of the confidence intervals for the regression slope without any distributional assumptions.

Nadir testosterone level was defined as the lowest serum testosterone level recorded for that individual including either pretreatment or all trough levels between treatments. Body mass index (kg/m^2) and body surface area (m^2 , using the Gehan-George formula; Bailey & Briars, 1996) were calculated from height and weight data. Statistical analysis including ANOVA, *t*-tests, linear regression and correlation were performed using SPSS Version 10 and NCSS 2001 software.

Results

Testosterone pellets

A total of 179 pellets were available for analysis, 149 pellets from extrusions and 30 un-implanted contemporaneous controls collected over 17 years. Of the extruded pellets, 112 (75%) intact pellets weighed 129.1 ± 7.2 mg had been *in situ* for 58 ± 3 days compared with 30 unused control pellets which weighed $203.4 \text{ mg} \pm 5.9$ mg. Extruded pellets that were recovered intact consistently maintained a cylindrical shape for up to 98 days *in situ* (Fig. 1). The extruded pellets had a smooth, clean surface free of adherent tissue or ingrowth of cells macroscopically and also by inspection of cut surface under light microscope.

The remaining 37 (25%) extruded pellets were fragmented into either more than one piece (29/37, 78%) or available only

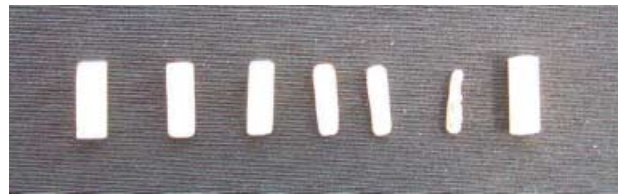


Fig. 1 Pictured are a series of testosterone pellets including unimplanted pellets (extreme left and right) and a series of pellets extruded after various time intervals subdermally (33 days, 60 days, 78 days, 98 days and 143 days from left to right). Note preservation of cylindrical shape throughout the time *in situ* and the smooth clean white pellet surface.

as an incomplete fragment (8/37, 22%). Fragmented pellets had been in place for a median of 115 days (mean 121 ± 5.5 days, range 77–243 days) but were excluded from the regression analysis to estimate testosterone release rate, as it was not certain all fragments had been recovered. The earliest pellet recovered in fragments was *in situ* for 77 days.

Estimated testosterone release rate from extruded pellets

Estimating testosterone release from the loss of dry pellet weight, the testosterone release rate per day was obtained from a linear least-squares regression ($r^2 = 0.969$) of the slope of the plot of testosterone release vs. time; the implant was *in situ* (Fig. 2). The estimated testosterone release rate was 1.31 ± 0.02 mg/day for each 200 mg pellet with 95% confidence interval (CI) of

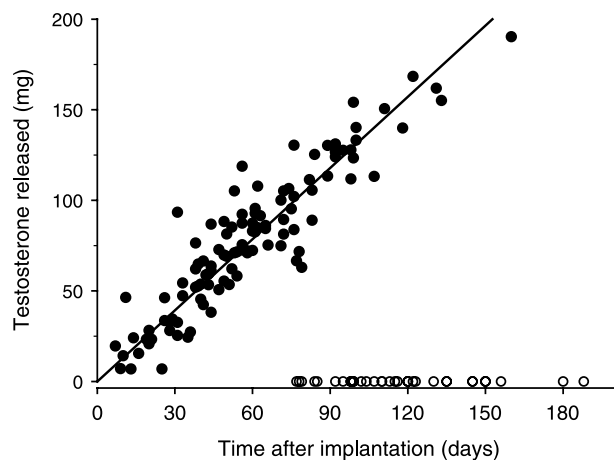


Fig. 2 Plot of testosterone released (in mg) according to the numbers of days *in situ* for 113 pellets recovered intact. Plotted along the x-axis are 37 pellets recovered in fragments at various times. The plot for fragmented pellets indicates time only, not weight. Note the earliest a fragmented pellet is observed is after 77 days *in situ*. The regression of testosterone released on time ($r^2 = 0.969$) gives an estimate of testosterone release rate of 1.31 mg/day. For further details see text.

Table 1 Time between successive testosterone pellet implantations

Implant procedures	Extruded pellets	Days to first extrusion	Pellet-days between implants	Days between implants
703	0		700 ± 6	175 ± 2
44	1	52 ± 6	593 ± 22*	175 ± 6
19	2	48 ± 9	431 ± 32*	158 ± 9*
9	= 3	46 ± 11	352 ± 45*	148 ± 15*

*Indicates significantly different ($P < 0.05$) from no extrusions.

1.27–1.35 mg/day from conventional regression estimates. Using a bootstrapping procedure with 10 000 resampling replicates, the mean testosterone release rate was identical with CIs of 1.29–1.38 (95%) and 1.27–1.40 (99%) mg/day. These estimates were valid for the first 3 months where linearity was well maintained with minimal pellet fragmentation.

The testosterone release rate was not influenced by the potential covariables height ($P = 0.80$), weight ($P = 0.22$), BMI ($P = 0.38$) or BSA ($P = 0.60$). Additionally, the site of implantation did not influence the testosterone release rate as there was no difference ($P = 0.98$) in the linear regression comparing the 13 pellets extruded from the hip vs. 99 (88%) extruded from abdominal site of implantation.

Time till return for re-implantation

There were 889 implant procedures performed over 5 years during three randomized controlled trials in which testosterone pellets were implanted in individuals on at least two consecutive occasions (so the number of days between procedures was known). Of these, 756 (85%) involved four 200 mg implants (total 800 mg) while the remaining 133 (15%) involved fewer (36) or more (97) than four pellets implanted and were excluded from this analysis.

Among men who received the standard pellet implantation (800 mg), when all pellets remained *in situ*, the mean number of days to the next treatment was 175 ± 2 days (5.8 months) (Table 1). This was not significantly different after a single extrusion (175 ± 6 days, 5.8 months) but was significantly shorter after two (158 ± 9 days, 5.2 months) and three or more (148 ± 15 days, 4.9 months) extrusions. These time intervals lagged behind estimates of the numbers of pellet-days between procedures mainly due to the relatively late time of occurrence of the extrusions within treatment cycles (Table 1). Extrusions occurred after 9.2% (72/775) of implantations, most (44/72, 61% of extrusions) being a single extrusion with the remainder having two (19) or more (9) pellets extruded. Multiple extrusions occurred after 3.2% (25/775) of implantations.

The number of days until re-implantation was not related to anthropometric variables height ($P = 0.31$), weight ($P = 0.92$), adiposity (BMI, $P = 0.64$), body size (BSA, $P = 0.55$) or to

diagnosis ($P = 0.41$). Nor were any procedural features such as site ($P = 0.78$), number of previous implantation procedures ($P = 0.42$), occurrence of bruising ($P = 0.22$) or nonextrusion-related infection ($P = 0.91$) related to the number of days until return for re-implantation.

Serum total and free testosterone and SHBG concentrations (Table 2) were significantly higher ($P \leq 0.001$) on the day of return for re-implantation, compared with blood levels on the day of the nadir testosterone concentrations. Among men with primary (hypergonadotrophic) hypogonadism (302 implantations in 60 men), plasma LH and FSH concentrations were also significantly less elevated on the day of return for re-implantation compared with the concentrations at the time of nadir testosterone concentrations (Table 2).

Among men with primary (hypergonadotrophic) hypogonadism, plasma LH and FSH were significantly higher at the time of re-implantation among those who had one or more extrusions (Table 3). There was no significant differences in total or free testosterone or SHBG concentrations on the day of re-implantation regardless of extrusions (Table 3).

Discussion

The pharmacological features of testosterone, notably its short half-life and low oral bioavailability, pose problems for practical clinical treatment which led to the development of oral androgens and depot testosterone preparations. Most oral androgens are synthetic, 17- β alkylated androgens whose class-specific hepatotoxicity (Ishak & Zimmerman, 1987) has rendered them obsolete for modern clinical use given the availability of nonhepatotoxic testosterone preparations. Recently, old oral testosterone delivery technologies (Lisser *et al.*, 1942) that avoid gastrointestinal and portal transit have been revived, resulting in testosterone preparations for transdermal delivery via scrotal (Bals-Pratsch *et al.*, 1986) and nonscrotal (Meikle *et al.*, 1992) skin patches or gel (Wang *et al.*, 2000), topical application to sublingual (Stuenkel *et al.*, 1991; Salehian *et al.*, 1995; Wang *et al.*, 1996) or buccal (Baisley *et al.*, 2002; Dobs *et al.*, 1998) mucosa or oral ingestion of oil-filled capsules (Nieschlag *et al.*, 1975; Tauber *et al.*, 1986). However, these preparations require daily or more frequent administration and are more expensive than

Hormone		<i>n</i>	Nadir level (mean $\pm$ SEM)	Symptomatic level (mean $\pm$ SEM)
Total testosterone (nmol/l)	Procedures	693	5.4 $\pm$ 0.1	10.4 $\pm$ 0.2*
	Patients	136	5.4 $\pm$ 0.2	10.3 $\pm$ 0.5*
Free testosterone (pmol/l)	Procedures	672	76.4 $\pm$ 1.8	153.5 $\pm$ 3.7*
	Patients	136	79.2 $\pm$ 1.1	152.2 $\pm$ 7.5*
SHBG (nmol/l)	Procedures	674	33.4 $\pm$ 0.6	30.4 $\pm$ 0.6*
	Patients	136	33.6 $\pm$ 1.4	30.4 $\pm$ 1.5*
LH (IU/l)†	Procedures	302	22.6 $\pm$ 0.7	15.6 $\pm$ 0.8*
	Patients	60	22.4 $\pm$ 0.6	15.3 $\pm$ 1.8*
FSH (IU/l)†	Procedures	302	40 $\pm$ 1.2	29.5 $\pm$ 1.4*
	Patients	60	39.4 $\pm$ 2.1	30.5 $\pm$ 3.4

* $P < 0.001$.

†Men with primary (hypergonadotrophic) hypogonadism only.

Data are tabulation of mean blood hormone concentrations according to either per patient or per treatment cycle as the primary unit of analysis. Note similarity of both estimates indicates the absence of bias despite the theoretical risk associated with using the larger per treatment cycle data due to proportionately greater influence of men with more compared with those with fewer implant treatments.

Table 2 Comparison of blood hormone concentrations in androgen-deficient men at time of nadir blood testosterone level and at times of return for re-implantation

	0	1	2	3 +	<i>P</i>
Total testosterone (nm/l)	10.4 $\pm$ 0.2	9.5 $\pm$ 0.6	8.6 $\pm$ 1	10.7 $\pm$ 2	0.8
[<i>n</i>]	[544]	[37]	[12]	[7]	
Free testosterone (pm/l)	155 $\pm$ 4	121 $\pm$ 10	141 $\pm$ 25	155 $\pm$ 74	0.2
[<i>n</i>]	[529]	[36]	[12]	[7]	
SHBG (nm/l)	30.1 $\pm$ 0.6	33.1 $\pm$ 2	29.9 $\pm$ 7	30.3 $\pm$ 5	0.5
[<i>n</i>]	[539]	[36]	[12]	[7]	
LH* (IU/l)	14.5 $\pm$ 0.9	24.5 $\pm$ 3	29 $\pm$ 6	N/A	0.005
[<i>n</i>]	[243]	[17]	[7]		
FSH* (IU/l)	27.9 $\pm$ 1.3	43.3 $\pm$ 5	53.2 $\pm$ 9	N/A	0.004
[<i>n</i>]	[243]	[17]	[7]		

*Men with hypergonadotrophic hypogonadism.

Table 3 Hormone levels on re-implantation day in the presence of none, one or more extrusions

parenteral testosterone. For younger androgen-deficient men requiring life-long treatment, regimens involving frequent administration often result in suboptimal efficacy due to unreliable adherence to more demanding and prolonged treatment schedules (McDonald *et al.*, 2002). In a random sequence cross-over study we found that younger androgen-deficient men preferred 6-monthly testosterone implants to the more expensive option of oral testosterone undecanoate taken twice daily (Conway *et al.*, 1988; Handelsman, 2001). Whether the same applies to daily application of a testosterone gel, currently costing six to eight times more than injectable or implantable testosterone, has yet to be tested.

Previous pharmacological studies of testosterone pellet implants have clearly established that circulating testosterone levels rise rapidly into the physiological range where they are maintained at stable levels from day to day for months before gradual

decrease to pretreatment levels between 4 and 7 months, depending upon dose, after implantation as pellets undergo full absorption *in vivo* (Handelsman *et al.*, 1990; Jockenhovel *et al.*, 1996; Kelleher *et al.*, 2001). The present study is consistent with previous findings (Handelsman *et al.*, 1990; Jockenhovel *et al.*, 1996) showing prolonged steady-state kinetics of fused testosterone pellets with stable release rate over time (Fig. 1). This most probably reflects a constant rate of gradual dissolution of testosterone from the pellet – considered effectively as a very large reservoir of solid crystalline steroid – into the extracellular fluid, in which testosterone has very low solubility. The present study provides an estimate that each 200 mg testosterone pellet releases 1.3 mg testosterone per day. Assuming a constant daily testosterone release until complete dissolution, this provides a crude estimate that four testosterone pellets should last ~154 days

(5.0 months) following implantation, which corresponds reasonably well with the actual times till re-implantation determined by return of patient's androgen deficiency symptoms. Conversely, according to these estimates, the standard dose of four 200 mg pellets releasing an estimated 5.2 mg testosterone per day, a figure quite consistent with the best available estimates of endogenous testosterone production rate for eugonadal men of 5–7 mg per day using tritiated (Southren *et al.*, 1968) or stable isotope tracers (Vierhapper *et al.*, 1998a, 1998b, 2000, 2003). Lower estimates of testosterone production rate using stable isotopes are most likely influenced by the interference of low specific activity of tracers suppressing endogenous production rate (Vierhapper *et al.*, 1997). The methodology of the present estimates, while novel, resembles somewhat the widely accepted estimates of nominal testosterone release rate from transdermal testosterone patches. Our estimates, based on testosterone actually released at relatively high local concentration into the subdermal tissues, are likely to be more accurate than estimates of testosterone release rate based on residual testosterone left in patches removed after 24 h of use (Meikle *et al.*, 1992). Losses of testosterone from the patch reservoir may include steroid that does not traverse the full thickness of the skin and survive local skin androgen metabolism.

There are important caveats on our estimate of testosterone release rate. One is that the estimate is derived primarily from data for the first 3 months, when virtually all pellets remain intact and retain their original cylindrical shape consistent with dissolution primarily by surface erosion. After that time, pellet fragmentation becomes common and probably the invariable fate of all pellets. This would have the effect after the first 3 months of increasing the surface area for absorption relative to the decreasing residual amount of testosterone. The net effect of these two opposite influences on testosterone release rate make it hard to predict the net effect on testosterone release rate after the first 3 months while the diminishing sized pellets continue to dissolve until disappearance. A further caveat is that all estimates were based on extruded pellets. Extrusion occurred in this study data at a rate (9.2%) consistent with our long-term experience (Handelsman *et al.*, 1997; Kelleher *et al.*, 1999, 2001, 2002). An inflammatory process often accompanies extrusion, but as no organisms have been identified nor is it prevented by broad-spectrum antibiotic pretreatment of pellets (Kelleher *et al.*, 2002), it is believed to be a foreign body type reaction. Although we cannot exclude the possibility that an inflammatory process might influence the absorption rate, this seems given the consistent evidence that the dissolution of pellets is governed solely by the solubility of testosterone in extracellular fluid. This is further supported by the lack of tissues adherent to, or invading, the extruded pellets that may be the result of the steroid crystal surface lacking the biomatrix coating, which facilitates cellular adhesion and inward migration. If, however, the pellets had any

dissolution-governing membrane surface coating, an inflammatory process might be more likely to influence its steroid permeability.

The other independent approach we have utilized in this study to determine the duration of action of this testosterone pellet implant regimen, is based on the timing of the return for re-implantation. This is reasonable as all men involved had been on long-term androgen replacement therapy and were very familiar with their own stereotypical sequence of return of androgen deficiency symptoms. Our standard approach to await return of androgen deficiency symptoms as well as baseline testosterone concentrations, prevents the accumulation of testosterone which can follow fixed re-implantations schedules as was observed with estradiol implants (Garnett *et al.*, 1990; Buckler *et al.*, 1995). Patients are routinely encouraged at the time of implantation to make phone contact as soon as they re-experienced their familiar symptoms to book a re-implantation but no routine reminders of any sort were sent. As our clinical service provides bookings for implantation procedures within a week of phone contact, the timing of return for re-implantation is a realistic estimate of the return of androgen deficiency symptoms. As this is routinely less than 1 week, this delay considered as a consistent, nondifferential bias inflating the time estimate (by < 1 week) would not bias estimates of the influence of any other between-subject factors. The fact that androgen deficient men return for reimplantation when their plasma testosterone concentrations are well above their own nadir reflects their familiarity with their own characteristic androgen deficiency symptoms. Using the time to return for re-implantation, our direct estimate of duration of action of the standard dose of 800 mg testosterone is 5.8 months as the time during which sufficient testosterone is delivered to avert symptoms of androgen deficiency, in the absence of any extrusion. An important caveat is that this estimate refers to the total testosterone dose of 800 mg, whereas it is clear that a higher dose prolongs the time for plasma testosterone to return to baseline (Handelsman *et al.*, 1990).

This study confirms that extrusion follows ~10% of implantation procedures, most (61%) being single extrusions with < 4% of all implantations experiencing multiple extrusions (Handelsman *et al.*, 1997; Kelleher *et al.*, 1999, 2001, 2002). It is logical that an extrusion, removing a fraction of the testosterone depot, should reduce in vivo testosterone delivery subsequently. Our data help clarify the uncertainty over how much an extrusion influences the clinical duration of action of the standard testosterone pellet regimen. Because the men having an extrusion may have returned earlier, however, minor foreshortening of duration of efficacy may have been missed. Indeed, among the fewer than 4% of men who had multiple extrusions following an implantation the time of return for re-implantation was up to 1 month earlier. By contrast, the findings show that after extrusion of a single implant, the time to return for reimplantation was not shortened compared with those who did not have any extrusion. This

supports the impression from extensive clinical experience that a single extrusion does not make a major difference to the subsequent course of testosterone effects. While seeming counter-intuitive, it is probable that the late timing of typical extrusions during a treatment cycle minimizes the net loss of testosterone over the full treatment cycle. Nevertheless, the findings of elevated plasma LH and FSH without significant changes in plasma total and free testosterone (among men with an intact hypothalamo–pituitary system), indicates that negative feedback on gonadotropins may be more sensitive to subtle diminution of testosterone delivery than plasma testosterone or the patient's or doctor's perceptions of androgen deficiency symptoms. This is consistent with the established utility of gonadotrophin suppression as a pharmacodynamic measure of testosterone action in men with an intact hypothalamo–pituitary unit (Snyder & Lawrence, 1980; Handelsman *et al.*, 1990). Further, this reinforces the utility of plasma LH as an indicator of adequacy of androgen replacement in men with primary (hypergonadotrophic) hypogonadism. While directly analogous to the use of TSH as an index of net thyroid hormone effects in primary hypothyroidism, this analogous and convenient biochemical index of adequacy of androgen replacement remains surprisingly under-utilized in clinical practice.

The fact that neither anthropometric nor procedural factors influenced the length of time between implantations or the dry weight of extruded pellets, indicates that the dissolution rate of testosterone pellets is not influenced by such physical features. This supports the concept that testosterone is simply absorbed from the surface of the pellets, consistent with retention of shape during dissolution of the pellets. Pellets appear to remain intact for ~3 months after implantation and then begin to fragment. Whether the increased available surface area of pellet pieces after fragmentation increases the release rate of testosterone cannot be verified at present with the available knowledge. The interpretation of testosterone release from pellets by gradual surface dissolution is also consistent with a previous study showing no detectable influence on plasma testosterone time profiles according to the geometry of pellets *in situ* (end-on-end vs. isolated placement; Kelleher *et al.*, 2001), although we previously also reported minor effects of pellet surface area controlling for dose (Handelsman *et al.*, 1990). It is therefore most likely that the very low aqueous solubility of testosterone in extracellular fluid may primarily govern the dissolution rate from, in effect, an infinite depot of crystalline testosterone, rather than true dissolution of the implants whereby the kinetics may depend upon the size, geometry and composition of the implant (Chien, 1992).

We conclude that the 200-mg testosterone implant releases 1.3 mg testosterone per day so that the standard dosage of 800 mg (four 200 mg pellet) of subdermal testosterone provides testosterone release rate of 5.2 mg/day, constituting effective androgen replacement therapy for about 6 months in young men with

androgen deficiency, irrespective of physical anthropometric or procedural features. Extrusion of a single pellet does not significantly shorten clinical duration of action of testosterone implants according to return of androgen deficiency symptoms nor of circulating plasma testosterone concentrations. Plasma gonadotrophin concentrations proved a sensitive marker of subtle decreases in parenteral testosterone delivery in men with a normal hypothalamo–pituitary unit.

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