EFFECTS OF TESTOSTERONE IMPLANTS IN MEN WITH DEFECTIVE SPERMATOGENESIS

BY

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The causes of defective spermatogenesis in men are largely unknown, and it will generally be agreed that the methods of treatment, correspondingly empirical, are for the most part ineffective. It has seemed justifiable to try any form of treatment which might help at least some men, and, provided sufficiently accurate data are collected, there is no doubt that trials of this kind are fully warranted. Too often, of course, treatment has been given because a single seminal specimen failed to reach acceptable standards; conclusions drawn from such instances are usually misleading. Consequently, lack of adequately controlled observations in most of the literature dealing with this subject has led to a widespread therapeutic nihilism and its attendant apathy. The prevalence of seminal deficiencies, and our ignorance of how to deal with them, demand, of course, a very different attitude.

There is little doubt that testosterone plays a part in spermatogenesis, though its exact role is still uncertain. There is equal certainty that large doses of testosterone will inhibit spermatogenesis, through its action in depressing the production of pituitary gonadotrophin. Heckel *et al.* (1951, 1952), as is now well known, maintain that on cessation of high-dosage testosterone administration the sperm count rises, not only to its pre-treatment level, but, by reason of a rebound effect, to far higher levels. Other workers have been less impressed by this rebound phenomenon, which is certainly missing from many cases treated according to the method of Heckel. It has seemed possible, on the other hand, that continuous low-dosage testosterone administration might actually stimulate spermatogenesis, or improve sperm motility when this is the deficient characteristic. In order to examine this possibility implants of testosterone have been given to a number of men with various kinds of seminal deficiencies. Implantation was chosen as the route of therapy since it is convenient—a single implant remaining effective for some six months—and affords a slow continuous administration of the steroid.

Material and Methods

The men treated in this series were patients attending the Fertility Clinics at University College Hospital and at the Hospital for Women, Soho Square. Seminal analyses on masturbation specimens were made by a standardized technique, which was the same at both hospitals. They involved determination of volume, density, total percentage of abnormal forms and motility indices according to the method of Emmens (1947) at two or more times. The general plan adopted was to obtain three seminal specimens, each preceded by a three-day (at U.C.H.) or five-day (at Soho) period of abstinence (the difference in period of abstinence seems to be immaterial) before treatment; to administer either two or three 100-mg. pellets of testosterone by subcutaneous implantation at the upper outer aspect of the thigh, just below the iliac crest; and to analyse three further seminal specimens, collected one, two, and three months after implantation. Naturally this plan miscarried on several occasions.

In all, 83 implantations were made in 72 men. Of these, 16 men failed to furnish any post-treatment specimens and so must be discarded. There thus remain for analysis 56 men who received 67 implants. Twenty-eight implantations were of two 100-mg. pellets and 39 were of three 100-mg. pellets of testosterone.

Results

General Effects on Seminal Fluid.—In the first place, the mean figures before treatment for each individual for volume, motility, density, and morphology were compared with the corresponding mean figures after treatment. On this basis, it appears that some degree of general improvement in the seminal fluid was found in 28 individuals, of whom 12 had received 200 mg. and 16 had had 300 mg. of testosterone. In 22 men the findings appeared to be unchanged; while in the remaining six men the post-treatment specimens were definitely worse. In this last group, one man had had 200 mg. and five men 300 mg. of testosterone.

The next step in the analysis was to compare the mean figures for all volumes, motilities, densities, and morphologies before treatment with the corresponding figures after treatment. In dealing with motility it was necessary to find a suitable expression for the comparison of different specimens, the motilities for which might have been recorded at different times after production. For this purpose the "five-hour motility" figure has been used. To calculate this, the motility scores, which range from 4 (maximum) to 0, were plotted against the age of the specimen at the time of scoring, a straight line being drawn through the points. The score at five hours was thus interpolated, and was then expressed as a percentage of the maximum figure 4. Thus, if the interpolated motility index at five hours was found

to be 3, the "five-hour motility" would be $\frac{3 \times 100}{4} = 75$.

The overall results are given separately for 200-mg. and 300-mg. implants in Table I. From this it is clear that, in general, both doses had similar effects; that little change in volume was observed; that motility appeared to be improved and density increased; and that the percentage of abnormal forms was slightly increased.

TABLE I.—Mean Values and Standard Errors

		Dose of Testosterone	
		2 × 100 mg.	3 × 100 mg.
Volume (ml.)	Before implantation	3.49 ± 0.24	3.42 ± 0.16
	After "	3.81 ± 0.23	3.21 ± 0.15
5-hour motility*	Before "	34.89 ± 4.28	20.55 ± 2.57
	After "	47.27 ± 4.77	35.73 ± 3.43
Density (millions per ml.)	Before "	32.08 ± 9.20	26.62 ± 2.04
	After "	37.31 ± 7.56	40.94 ± 3.39
% abnormal spermatozoa	Before "	37.17 ± 1.99	34.44 ± 2.36
	After "	43.66 ± 2.09	35.55 ± 1.07

* For explanation see text.

Motility.—Inspection of the data for individual men showed clearly that where the initial motility was of an extremely low order—the mean five-hour motility figure being 5 or less—implantation was followed by no improvement whatever. Since extreme asthenospermia is thus not susceptible to this treatment, it seemed reasonable to exclude such cases and to compare the pre- and post-treatment data for the remainder. This is done in Table II, from which it appears that comparable improvement is found in both the 200-mg. and the 300-mg. series. Reference to Table III, which combines the results for 200-mg. and

TABLE II.—Effect on Motility, Excluding Cases of Extreme Asthenospermia before Treatment. Mean Values and Standard Errors

		Dose of Testosterone	
		2 × 100 mg.	3 × 100 mg.
Before implantation		41.11 ± 4.61	25.47 ± 2.92
	After	57.56 ± 4.56	41.67 ± 3.82

300-mg. implants, shows that the difference between the mean pre- and post-treatment motility figures is highly significant ($t=4.08$, $n=258$, $P<0.01$).

TABLE III.—Overall Effects: Combined Results for 200-mg. and 300-mg. Implants

		Mean and S.E.	n	t	P
Volume, ml.	Before implan- tation	3.44 ± 0.13	177	—	—
	After "	3.44 ± 0.13	143		
5-hour motility of selected group (Table II)	Before "	31.55 ± 2.60	139	4.08	<0.01*
	After "	47.68 ± 2.99	119		
Density (mil- lions per ml.)	Before "	29.18 ± 3.56	171	2.035	<0.05 >0.01†
	After "	39.53 ± 3.57	142		
% abnormal spermatozoa	Before "	35.44 ± 1.66	155	1.139	>0.05
	After "	37.79 ± 0.88	177		

* Highly significant. † Significant.

Density.—The combined mean densities before and after treatment with 200 and 300 mg. are shown in Table III. The difference is significant, though not highly so ($t=2.035$, $n=313$, $0.01<P<0.05$). However, when the differences between the mean pre- and post-treatment figures are examined for 200 mg. and 300 mg. separately (Table IV)

TABLE IV.—Effect on Density of 200 mg. and of 300 mg. of Testosterone

		Mean and S.E.	n	t	P
2 × 100 mg.	Before implan- tation	32.08 ± 9.20	62	0.434	>0.05
	After "	37.31 ± 7.56	55		
3 × 100 mg.	Before "	26.62 ± 2.04	109	3.780	<0.01*
	After "	40.94 ± 3.39	87		

* Highly significant.

it becomes apparent that, while for the former the difference is not significant ($t=0.434$, $n=117$, $P>0.05$), for the latter it is highly significant ($t=3.780$, $n=196$, $P<0.01$). One may conclude, therefore, that an implant of 300 mg. is superior to one of 200 mg. in its effect on sperm density.

Volume and Morphology.—It is clear, from Table III, that implantation was without significant effects on the volume of the ejaculate or on the proportion of total spermatozoal abnormalities.

Pregnancies.—The wives of 20 men became pregnant on 22 occasions, all within six months of implantation. Five of these pregnancies ended with an abortion, the incidence thus being 22.75%. This compares with an abortion incidence of 19.1% in a series of 220 pregnancies in women who attended the Fertility Clinic at University College Hospital; an incidence which, it has been shown, is probably not in excess of the general spontaneous abortion rate (Swyer, 1953). Comparison of the mean pre- and post-treatment figures for the individuals whose wives conceived showed, an apparent improvement after treatment in 17 cases, no change in 4, and deterioration in 1. These results suggest that conception may indeed have been assisted by the treatment given.

Complications of Treatment.—Testosterone implantation is an innocuous, simple, out-patient procedure which entails no discomfort and does not prevent the man continuing with his work. No patients had any complaints as a result of the implantations, but extrusion of a pellet was encountered on three occasions. This incident is of no serious consequence, and merely requires the application of a dry sterile dressing until the wound has healed.

Discussion

While the statistical analysis of the results of treatment with testosterone implants strongly suggests that motility and density are, in general, improved, inspection of the individual data has made it quite clear that by no means every patient benefited. There can be no doubt that the patients in this series must have presented a very heterogeneous collection of lesions, and it is entirely probable

that testicular biopsies before treatment would have shown the unlikelihood of improvement—from any treatment—in many cases. Extreme oligospermia (mean density before treatment 5 millions per ml. or less) and extreme asthenospermia (mean five-hour motility before treatment less than 5) invariably remain unaffected by testosterone implantation. Clearly, the more the series is weighted with unsusceptible cases the less obvious will be the results of treatment; just as if, for example, in attempting to demonstrate the efficiency of penicillin in combating infections the series of cases studied contained a high proportion in which the tubercle bacillus was the infective agent.

Assuming, as appears to be justifiable, that the kind of treatment used here is effective in some cases of defective spermatogenesis, it becomes desirable to determine, so far as possible, which patients are most likely to benefit. It is difficult to lay down hard-and-fast rules, but the following impressions may offer some guidance. As mentioned above, men with extreme oligospermia and extreme asthenospermia (regardless of sperm density) are unsuitable for testosterone implantation. Moderate oligospermia (15–20 millions per ml.) with fair or good sperm activity was improved in 12 cases, remained unchanged in 3, and deteriorated in 3. Poor motility (five-hour motility 15–30) with fair or good density was improved in 14 cases, remained unchanged in 3, but deteriorated in 3 others. These two, then, would seem to be the principal varieties of seminal deficiency for which this treatment might prove of value.

It is suggested as a practical basis that three pre-treatment specimens should be examined, to obtain a fair estimate of the general characteristics of the seminal fluid, and that monthly specimens should be tested for three months after implantation. If these show improvement, but no conception occurs within six months, a further specimen should be examined. If this shows deterioration, a second implantation might be desirable. Obviously, the examination of specimens after implantation is of as much importance to the patient as of interest to the physician, since the decision to use further implants will be governed by the response, if any, to the first one.

In our present state of ignorance, no useful purpose is served by speculating on the *modus operandi* of testosterone in this treatment.

Summary

The effect of implanting two and three 100-mg. pellets of testosterone subcutaneously has been studied in 56 men presenting seminal deficiencies of one kind or another. These men received a total of 67 implants—28 of 200 mg. and 39 of 300 mg. The seminal fluid appeared to improve in 28 individuals (12 received 200 mg., 16 received 300 mg.); to be unchanged in 22 men; and to deteriorate in 6 others (1 received 200 mg., 5 received 300 mg.). No significant overall effects on volume and seminal morphology were seen, but there was a highly significant overall increase in motility with both doses of testosterone and in density with 300-mg. implants. Extreme asthenospermia and extreme oligospermia were invariably unaffected by the treatment.

The wives of 20 of the men became pregnant on 22 occasions, all within six months of implantation; 5 pregnancies ended in abortion (22.75%), the remainder going to term.

It is suggested that moderate depression of sperm density (15–20 millions per ml.) or poor motility (other than extreme asthenospermia) with fair or good density offers the best chances of improvement after testosterone implantation.

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