CLINICAL EXPERIMENTS WITH ANDROGENS

IV. A METHOD OF IMPLANTATION OF CRYSTALLINE TESTOSTERONE

SAMUEL A. VEST, M.D.
CHARLOTTESVILLE, VA.
AND
JOHN E. HOWARD, M.D.
BALTIMORE

From experimental observations it is well known that androgenic substances are chemically changed and excreted after entering the circulation. The effectiveness of any androgenic preparation depends on many factors. One of the most important, besides the frequency of administration and the dosage, is the method of administration. The use of various solvents, the addition of fatty acids to the androgenic solutions, esterification of the substances and many other variations have been studied in an attempt to increase the efficiency of administration of androgenic substances.

The fact that pure crystalline testosterone is readily absorbed by the body fluids undoubtedly leads to waste when excess material is given. In order to overcome this difficulty and to decrease the rate of absorption, testosterone has usually been injected in an oily solution as the propionate. Injection of testosterone propionate has proved far more effective than the equivalent amounts of free testosterone. The intensity and duration of the action of testosterone has been thus enhanced, and treatment of hypogonadism in human beings has been satisfactorily carried out with injections at intervals of from three to four days. From the results of animal experiments it would appear that when large amounts of testosterone propionate are injected at such intervals an appreciable proportion of the substance is wasted. Testosterone has also been used clinically in the form of inunctions and by oral administration. It is not entirely satisfactory in the form of inunctions and when given by mouth enormous amounts are necessary to elicit clinical response. A method of administration which would tend to simulate the secretion of this hormone by the testis has been sought. If androgenic substance can be administered so that the amount absorbed daily is not in excess of the physiologic requirements, waste will be eliminated and expense can be kept to a minimum. Before the prevalent intramuscular injection of the testosterone propionate in an oily solution is supplanted, a new method must prove to be more convenient, more efficient, less expensive and devoid of harmful consequences.

The first use of pure androgens and estrogens by subcutaneous implantation of crystals or pellets was reported by Deanesly and Parkes in 1937 and 1938. Their work indicated that tablets of compressed crystals implanted subcutaneously produced stronger and longer effects of stimulation than similar doses given by injection. Schoeller and Gehrke later showed the superior effect of implanted testosterone and testosterone propionate tablets in fowls. Having knowledge at the time of the work that Deanesly was carrying out in experimental animals, we first implanted pellets of crystalline testosterone subcutaneously into a patient with hypogonadism in the fall of 1937, but these pellets were too small to produce any significant clinical results. Three recent reports have referred to the implantation of small pellets of testosterone in human beings with questionable results. In the fall of 1938, soon after Thorn began his work with the implantation of small pellets of testosterone in human beings with questionable results. In the fall of 1938, soon after Thorn began his work with the

Fig. 1.—The instruments used to make pellets of various sizes. A, the press; B, the die with three sizes of pellets; C, the punches; D, the assembled press with a punch in place; E, the heavy metal mallet.
tion of moderate sized pellets of desoxycorticosterone acetate, we began to make and implant pure testosterone in large pellets weighing up to 800 mg. We have now implanted these pellets into a series of thirteen patients with hypogonadism. We have implanted pellets subcutaneously or intramuscularly in the leg, arm, back and scrotum. The pellets have been removed later and reweighed in order to calculate the average amount that has been absorbed daily. The actual curve of absorption probably shows a gradual decrease as the size of the pellet becomes smaller. Tissues surrounding the pellets, which are foreign bodies, have been removed and studied pathologically. Assays of the urinary androgens and estrogens have been made before and after implantation. A systematic study of various aspects of pellet implantation with both crystalline testosterone and some of its esters is now being completed and an evaluation of the clinical results will be discussed in a forthcoming report. A study of the effects of testosterone and its esters in the monkey, comparing the method of injection with the implantation of pellets, is also in progress.

Our purpose in this report is to present a new technic for the subcutaneous implantation of solids such as pellets of pure crystalline androgenic substance by the use of an "injector" instrument. If the slow absorption of subcutaneous androgenic substance in pellet form was to be more efficient per unit weight of material utilized, this advantage would be offset somewhat by the impracticability of the necessary incision for implantation. To obviate an operating room procedure, the following method was devised. Figure 1A, B, and C shows the press, die and punches used to make pellets of three different sizes. The pellets are shown in their corresponding slots. Figure 1D shows the assembled press with a punch in place. Figure 1E shows the heavy metal hammer used to pound the previously sterilized, powdered testosterone into a very hard and compact pellet. These implements can be boiled and the pellets are made under sterile technique. It has been impossible to make pellets of uniform size and weight with such an apparatus, but for practical purposes it has served for our study. Many factors probably affect the absorption rate, the foremost of which are the surface area and the density of the pellet. Other possible factors are the vascularity of the site of implantation, the extent of the reaction to the foreign body and the degree of hormone deficiency. For absolute comparative values regarding absorption and clinical effect in a series of cases it would have been ideal to implant pellets of identical size and weight, but this was not possible.

Figure 2A shows one of several instruments which we have devised on the principle of the syringe in order that solid pellets might be injected subcutaneously or intramuscularly in the office instead of in an operating room. It shows the instrument with the fenestra closed and the obturator slightly withdrawn. A scalpel-like point serves to pierce the skin, leaving a clean linear opening. Figure 2B shows pellets of different caliber for which three sizes of instruments can be used, depending on the amount of material one desires to inject. The maximum amount injected with such

---

Footnotes:
9. This instrument was developed with the assistance of Mr. Frederick C. Wappler, of the American Cystoscope Makers, Inc.

---
an instrument to date is two pellets of more than 400 mg.
each at one time. Figure 2 C shows the instrument
with the fenestra open and the obturator withdrawn.
Figure 2 D shows the end of the "injector" or
"implanter" with the fenestra open through which the
obturator is extruding a pellet. Figure 2 E shows how
two pellets can be injected, one following the other.
The obturator can be entirely withdrawn and the pellets
inserted into the proximal end of the barrel as desired
instead of through the open fenestra. The fenestra
can be opened and closed at will by means of the rotary
barrel mechanism controlled at the handle.

The instrument is used in the following manner, as
shown in figure 3. A wheal is made in the skin of the
thigh with a solution of nupercaine. The instrument
with the pellets of testosterone inside and the fenestra
closed is pushed painlessly through the skin and, if
desired, beneath the fascia lata (fig. 3 A). In figure 3 B
the fenestra has been opened and the obturator is being
pushed forward to extrude the pellets in the muscle of
the thigh. The fenestra is then closed and the instru-
mament is withdrawn, leaving the pellet in place as shown
in fig. 3 C. A silver clip has been used to close the
puncture wound. A clip is not always necessary
because the margins of the skin of the 6 to 8 mm.
puncture wound usually approximate themselves.

The following two cases are reported as examples of
the clinical activity of testosterone when it is
implanted into man in the form of pure crystalline
pellets of large size:

CASE 1.—History.—W. A., a white youth aged 21, admitted
to the James Buchanan Brady Urological Institute March 21,
1939, complained of having "never matured sexually." His
two brothers developed normally. The usual changes of puberty,
with the exception of the appearance of a few pubic hairs at
the age of 13 to 16, did not occur in the patient. He stopped
school in the eleventh grade because of his underdevelopment.
His psychologic content was definitely male. Erections had
occurred frequently in the mornings since the age of 17, and
he masturbated several times a year but without ejaculation.

Examination.—Figure 4 A shows the typical eunuchoid
appearance. The patient was 5 feet 10 1/2 inches (149 cm.) tall
and weighed 142 1/2 pounds (64.8 Kg.). Roentgenograms showed
a normal skull and sella, but there was retardation in the
epiphyseal closure of the bones. There was more than 25 but
less than 50 rat units of follicle stimulating factor per liter of

Fig. 4 (case 1).—Appearance of patient, aged 21, with hypogonadism
before and after implantation of pellets of crystalline testosterone in muscle
of back. A, full view and genitalia before implantation; B, same ninety
days later.
ANDROGEN IMPLANTATION—VEST AND HOWARD

TREATMENT.—March 25 three pellets of crystalline testosterone weighing 277, 219 and 175 mg. were implanted in the right lumbar muscles. (In this case we used three relatively small pellets instead of one or two large ones because we wished to study the absorption rate of pellets of this size compared with the larger ones.)

RESULT.—The second day after implantation the patient began to notice an increased frequency of erections and he masturbated eight times in the subsequent three months. Ejaculation occurred for the first time in his life. The nipples soon became tender with the appearance of small lumps underneath, more marked on the left. At the end of the first month the voice had been two B, fibrous tissue, of which is hyaline, and a dense collection of round cells.

In figure 6 A shows the patient's appearance two and one-half months after implantation, at which time he seemed to palpation that only about one third of the pellet had been absorbed. During this time he complained of erections practically all night and frequently during the day. The testes descended to the bottom of the scrotum so that the left became just adjacent to the pellet. The voice became deeper. He gained 4 pounds (1,814 Gm.) the first two weeks and 3 pounds (1,307 Gm.) the following two weeks. He began to masturbate three or four times a week, with ejaculation. Slight tenderness appeared in both breasts, especially the left. Hair began to grow on the lower legs and the upper lip. In two and one-half months (fig. 5 B) the penis had increased in size and was now 6.3 cm. in complete extension. The prostate had developed to about two thirds normal size. It was normal in contour, shape and consistency. Several drops of secretion could be expressed which were normal in appearance and normal microscopically. The seminal vesicles were easily palpable and almost normal in size.

The clinical results, though just beginning in these patients, is indicative of the activity of crystalline testosterone when implanted subcutaneously in the form of pellets. The method may prove to have important clinical applications, but more extensive work is necessary to establish this with certainty.

It has been of interest to study the type of tissue reactions which occur around pellets of testosterone. Figure 6 A and B shows photomicrographs of the tissue encapsulating pellets four months after implantation. In figure 6 A the cavity in which the pellet was situated is visible. Surrounding this cavity is granulation tissue containing many foreign-body giant cells, an occasional leukocyte and some round cells, all lying in a fibroblastic matrix. In 6 B (another case) there is less reaction to the foreign body, with only a rare giant cell. Much fibrous scar tissue has developed, some of which is hyaline. Some diffuse round cells are seen. There is no evidence of unusual cellular reaction, metaplasia or carcinogenic activity.

It is possible that such an instrument as we have developed and presented here might be applicable to injection of other solid medicinal materials.

University Hospital, Charlottesville, Va.—24 East Eager Street, Baltimore.