We have preferred the oral route of administration because our results in guinea pigs were obtained by this method. Furthermore, patients prefer to take the drug orally because the relatively mild symptoms noted are less uncomfortable than the distress produced by parenteral injections. It seems probable that the drug undergoes chemical transformation when given by the oral route.

The clinical evaluation of any therapeutic agent in human tuberculosis must be undertaken with the greatest caution. The marked tendency of many forms of the disease is toward steady improvement without treatment. The anticipated clinical course of tuberculosis may be so variable that control evidence is difficult to establish. Therefore we would caution urgently against insecure conclusions in the study of chemotherapy in clinical tuberculosis, recalling the history of tragic disappointments which followed the early use of tuberculin and other forms of treatment. Equal care must be taken lest some treatment be discarded prematurely, especially when there are wide choices of means of administration and dosage. We believe that the drawing of either positive or negative conclusions should be avoided until the force of facts makes these conclusions self evident.

ABSTRACT OF DISCUSSION

DR. J. ARTHUR MYERS, Minneapolis: I had the pleasure of visiting Drs. Hinshaw and Feldman and saw their setup for experimental work and their gross and microscopic postmortem specimens. The difference between the control and the treated animals is almost unbelievable. Finally, after fifty centuries of trial man has found a drug which apparently is capable of controlling tuberculosis in animals. It will be of interest to know what further studies reveal with reference to the presence or absence of tubercle bacilli in the small atypical lesions of the treated animals, whether these animals will live out the natural span of life without developing significant disease, and whether allergy remains or disappears. The medical profession has been misled many times concerning drug therapy because of statements made on insufficient evidence. Drs. Hinshaw and Feldman are ultraconservative in their statements, and this is laudable. They have pointed out that a great deal of work is necessary to determine the effect of the drugs they are studying on tuberculosis in man. However, it appears that with this or some closely related drug we may be approaching the time when tuberculosis in man can be quickly controlled. The time may come when the person who is found to react to tuberculin but has no other evidence of tuberculosis will be treated by chemotherapy, just as the patient who has a positive Wassermann reaction with no other evidence of syphilis is treated by chemotherapy. I should like to suggest that the physicians of this country allow Drs. Hinshaw and Feldman to proceed unmolested. They have a perfect setup for their experimental studies. They have an abundance of clinical material with which they are cautiously determining the efficacy of chemotherapy on tuberculosis in human beings. They have every necessary qualification for the completion of this work. When they have finished their studies with reference to toxicity, safe dosage and efficacy of the drug they will present their findings to the world.

Cold Exhaustion.—As a result of fatigue an individual wandering in the cold surrenders to an overpowering desire to sleep. During this unconscious state, temperature regulation is disturbed and much heat is lost. The body temperature falls; at 68 F. coma sets in and death results. It has been pointed out that a fall of temperature depresses the dissociation of oxyhemoglobin and tends to lower oxidation in the tissues.—Wright, Samson: Applied Physiology, New York, Oxford University Press, 1940.

OBSERVATIONS ON THE IMPLANTATION OF TESTOSTERONE PELLETS

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AND
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Within the past few years the literature on testosterone has become voluminous. In large part it deals with laboratory experiments, animal studies and the like. Carefully controlled clinical observations over long periods of time have been comparatively few. Still, the ultimate goal is the actual clinical application, for without such its importance is reduced and its value largely academic. In our clinic we have treated a large number of patients suffering with a wide diversity of conditions, including the postcastration status, eunuchoidism, hypogonadism of other types such as Lorain-Levi infantilism and hypopituitarism, impotence and others. For clarity and brevity only selected cases will be reported at this time, others being left for later communications.

This report deals with observations on patients chosen from the "hypogenital groups," numbering in all 60, of whom 30 have been given further treatment by implantation, 30 having been treated by injections only. The 30 patients given implantations have received a total of seventy implants.

IMPLANTATION OF TESTOSTERONE PELLETS AS A METHOD OF LONG-CONTINUED TESTOSTERONE THERAPY

Our observations and experiences led us early to realize that the injection therapy would have to be administered frequently, regularly and for long periods. The numerous objections to this soon became apparent to both physician and patient. The work of Brock and Druckrey,[1] Deanesly and Parkes [2] and Noble [3] on animals suggested the subcutaneous implantation of hormone pellets in human beings, and Bishop's [4] report on the implantation of a tablet of estrone in a woman with relief of menopausal symptoms immediately prompted us to apply this form of therapy in males, using testosterone pellets.

Deanesly and Parkes [5] clearly demonstrated the "effectiveness of crystalline gonadal hormones when administered by the subcutaneous implantation of solid tablets of the pure substance" in mice, rats, guinea pigs and rabbits. We readily substantiated this in guinea pigs and rabbits. More recently Vest, Drew and Langworthy [6] have reported similar and more pertinent detailed observations on the monkey. Reviewing Deanesly and Parkes's original reports, they noted that testosterone was absorbed at the rate of approximately 25 per cent a month, giving a calculated average life to an implanted pellet of about four months, although it is possible, and highly probable, that the rate would

The testosterone pellets were supplied by the Schering Corporation through Dr. Max Gilbert.

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Because of lack of space, this article is abbreviated in THE JOURNAL by the omission of some illustrations. The complete article appears in the authors' reprints.

1. Brock, N., and Druckrey, H.: Klin. Wchnschr. **17**: 23 (Jan. 1) 1938.
2. Deanesly, R., and Parkes, A. S.: Proc. Roy. Soc., London **124**: 279 (Dec. 7) 1937.
3. Noble, R. L.: Lancet **2**: 192 (July 23) 1938.
4. Bishop, P. M. F.: Brit. M. J. **1**: 939 (April 30) 1938.
5. Deanesly, R., and Parkes, A. S.: Lancet **2**: 606 (Sept. 10) 1938.
6. Vest, S. A.; Drew, J. E., and Langworthy, O. R.: Endocrinology **27**: 455 (Sept.) 1940.

vary and that, as the pellet became smaller, the amount absorbed would be less per month and the life of the pellet prolonged, but perhaps with decreased efficacy. They also pointed out that "the rate of absorption from a tablet must depend largely on its surface area, and will therefore be absolutely greater, though proportionately less, from a large tablet than from a small one." Also, "the simplest way to increase the intensity of action would be to insert a number of tablets of a size calculated to last for the desired period." Finally, they concluded that "the technic is particularly useful where a long continued steady effect is required" and suggested that "treatment of very long duration following one administration of hormone will be possible by implantation of tablets."

Our original observations on the implantation of testosterone tablets have already been reported.[7] A preliminary report on the implantation of testosterone has also been made by Howard and Vest.[8] This has been carried on until today we have observed a total of 30 patients who have received implants, 7 patients receiving one implant, 14 patients two, 6 patients three and 3 patients their fourth implant, totaling sixty-five implants, plus two occasions on which the implants were ejected spontaneously and three occasions on which the pellets were removed after one, two and three months for weighing and examining them.

It was our original plan to administer treatment by injections of testosterone propionate (25 or 50 mg. three times a week) for a sufficiently long period of time to permit a "build-up" of testosterone effects and then, and then only, to resort to implantations, repeating them at intervals as indicated or required (three to six month intervals). This was carried out in most cases. In some cases no preliminary injections were given, and the desirability or undesirability of this will be further discussed. The first implants were single 200 mg. pellets; later we used two, three or four such pellets in each case, and still later we made observations with one, two, three or four 150 mg. tablets. Finally, bearing in mind Deanesly and Parkes' words that "the simplest way to increase the intensity of action would be to insert a number of tablets of a size calculated to last for the desired period," and that "as the pellet became smaller the amount absorbed would be less per month and the life of the pellet prolonged," we decided to use from six to eight 50 to 75 mg. tablets. Our original method, still employed with the larger pellets, was by the incision and "pocket formation" (to be described later), while our more recent multiple 50 mg. pellet implants were performed with a trocar (described later). Failure of therapeutic response, spontaneous discharge of the pellets and other observations will be described.

REPORT OF CASES

CASE 1.—A. W., a college student aged 20, entered the clinic on May 3, 1938. His family history was irrelevant. When he was 2 years old a right congenital inguinal hernia was repaired, and at 3 he had an uncomplicated attack of mumps. The testicles were never palpated. His growth was entirely normal, pubic hair appeared at 14 but at 16 he became conscious of inadequate sexual growth. A course of treatment with chorionic gonadotropin stimulated the growth of pubic hair, libido and occasional erections. On admission the patient was acutely conscious of genital underdevelopment, absence of facial hair, a high pitched voice and a lack of confidence which he attributed to sexual inadequacy. Physical examination revealed that the patient was of normal height, had feminine contours and had an extremely youthful appearance. The blood pressure was normal. Genital examination alone showed divergence from the normal. The penis was small, the scrotum was flat and no testicles could be felt. His height was 68½ inches (174 cm.), span 71½ inches (182 cm.), the upper measurement 31½ inches (80 cm.) and the lower 37 inches (94 cm.). The basal metabolic rate was minus 7 per cent. Roentgenograms of the skull and the blood chemistry were normal. The dextrose tolerance curve was 85, 105, 115. Treatment begun in May 1938 consisted of testosterone propionate 25 mg. three times a week, then twice a week by intramuscular injection. A total of 3,500 mg. was administered over a period of sixteen months. The results were dramatic and sustained. The genitals increased appreciably in size, the voice deepened, bodily strength increased and he took on a more muscular and masculine appearance. His weight increased many pounds, and his personal confidence matched his physical gains. After ten months of this therapy intercourse was attempted and was completely successful, with mutual satisfaction for the partners. In October 1939 two 200 mg. tablets were implanted successfully after the first attempt was followed by ejection of the tablets. The satisfactory status was maintained. The patient married and leads a normal sex life, though his wife has been informed of his undoubted sterility. The implant maintained its expected activity for nine months, after which "withdrawal symptoms" appeared. He was reimplanted in September 1940 with 400 mg., with renewal of the testosterone effects.

CASE 2.—F. V. A., a musician aged 29, entered our clinic in November 1939. A brother aged 33 presented, according to the patient, an identical problem, which was genital underdevelopment and inadequate secondary sex characteristics. A high pitched voice and feminine contours were also present. The patient was moderately tall, with a hairless, immature face, wide flared hips and small genitalia. The testicles were small and were located in a small scrotum. Measurements were: height 70¼ inches (178 cm.), span 75 inches (190 cm.), upper 30¾ inches (78 cm.) and lower 39½ inches (100 cm.). The basal metabolic rate was minus 16 per cent and the dextrose tolerance curve 80, 90, 75. Roentgenograms of the sella turcica showed it to be 15 per cent undersize, and there was a delay of about ten years in epiphysial development. Treatment from Nov. 11, 1939 to Jan. 4, 1940 consisted of 50 mg. of testosterone propionate three times a week. This was followed by a satisfactory increase in the size of the penis, pubic hair and deepening of the voice. On January 5, 600 mg. of testosterone was implanted, with further improvement. The effects began to run down about August and a new implantation (400 mg.) was done in September. He again reports excellent libido and erections and increased general well-being.

CASE 3.—S. L., a medical student aged 20, came to our clinic in December 1939. The past and family histories were irrelevant. His chief concern on admission was inadequate genital development with no change since the age of 15. There was no growth of hair on the face, and the pubic and axillary hair was sparse. The voice was high pitched. On examination, the only divergence from normal was a small penis, shallow scrotum and two small testes. The laboratory data were irrelevant. Treatment, started in December, consisted of 50 mg. of testosterone propionate injected three times a week. Up to Feb. 20, 1940 1,500 mg. was injected. The penis increased decidedly in size, the pubic hair spread, the voice deepened and erections were common. On February 23, 600 mg. of testosterone was implanted. In August after the growth of some facial hair, the effects began to subside, and in September 350 mg. was inserted by trocar (seven 50 mg. pellets). Within two weeks he again described the return of "full" response.

CASE 4.—B. Z., a student aged 17, was admitted to the clinic in November 1939. The family history was irrelevant. He had undergone an operation for bilateral inguinal hernias

7. Eidelsberg, Joseph, and Ornstein, E. A.: Endocrinology **26**: 46 (Jan.) 1940.
8. Howard, J. E., and Vest, S. A.: Am. J. M. Sc. **198**: 823 (Dec.) 1939.

at the age of 6 years. The testicles were undescended and only one was found in the canal at operation, but no correction was attempted. The immediate problem was undescended testes and genital underdevelopment. Physical examination showed him to be well developed and normal in all respects but genitally. There was a moderate amount of axillary and pubic hair, with

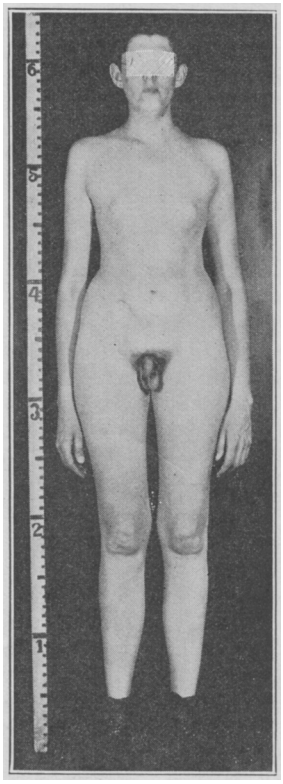

Fig. 26 (case 6).—Appearance in June 1939.

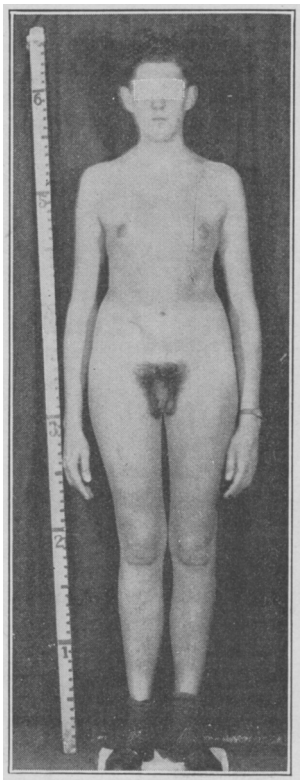

Fig. 27 (case 6).—Appearance in January 1940.

feminine distribution. The penis was 2 inches (5 cm.) long and 3 inches (7.6 cm.) in circumference. The testicles were not felt. The measurements were 67 inches (170 cm.) in height, span 67 inches, upper 30 inches (76 cm.) and lower 37 inches (94 cm.). The basal metabolic rate was normal and the dextrose tolerance curve was flat, with values of 75, 82, 65. Roentgenograms of the wrists showed slight delay in epiphysial union. Treatment begun in December 1939 consisted of 50 mg. of testosterone propionate three times a week. After one month there was a satisfactory increase in the size of the penis. In January 1940 a 200 mg. tablet of testosterone was implanted. After another month, hair appeared on the upper lip, the left testicle was palpated in the inguinal canal and the penis further increased in size. In April the penis was still growing slowly, erections were frequent, masturbation was followed by ejaculation and the tablet was still palpable. In September the effects were "running down" and testosterone (six 50 mg.) pellets were inserted by trocar. He has since maintained what appears to be a normal status.

CASE 5.—T. McH., aged 21, who entered our clinic in March 1940, had been receiving treatment elsewhere for sexual underdevelopment for the past two years with anterior pituitary extracts, a testicular preparation and 5 mg. doses of testosterone propionate, later increased to 25 mg. twice a week. The latter treatment had caused increased growth of the penis, pubic hair, height and weight. Treatment was continued intermittently but with little progress after the initial surge. The patient's height was 69 inches (175 cm.), span 71 inches (180 cm.), upper measurement 29½ inches (75 cm.) and lower 39½ inches (100 cm.). The physical examination was negative except for the genitals. The penis was below average in size, measuring 1½ inches (3.8 cm.) long and 3 inches (7.6 cm.) in circumference. The pubic hair was of female distribution and sparse. The scrotum was shallow and contained two small testicles. The significant laboratory data were a basal metabolic rate of minus 14 per cent, and bone age studies showed a two to three year delay in ossification. In April 1940 400 mg. of testosterone was implanted (two 200 mg. pellets). After two months, the voice deepened and the penis increased in size. Erections were active and a circumcision was performed in August. After five months there was a moderate recession in the size of the penis and number of erections. A second implant was done in September with six 50 mg. tablets, and he again reports general well-being, erections and satisfactory libido.

CASE 6.—F. P., aged 32, an accountant, was first seen by us in May 1939. His family and past histories were irrelevant. He was tall and well built, and his main wish was to have something done about the "size of his genitals," which were considered totally inadequate. He had little or no sex consciousness and had never shaved or masturbated. His testicles had always been small and in the scrotum. Breast tissue had developed in the past two years. The skin was smooth and clear, and there was no beard or axillary hair. The physical examination was of no significance, except for the genitals. The hips were wide, the pubic hair was slight in amount and the penis was small. The height was 73 inches (185 cm.), span 81 inches (206 cm.), the upper measurement 32 inches (81 cm.) and the lower 41 inches (104 cm.). The laboratory data revealed a basal metabolic rate of minus 15 per cent. Treatment started in July 1939 consisted of 25 mg. of testosterone propionate three times a week for two months. There followed considerable enlargement of the penis. The testicles and scrotum also increased in size. The voice deepened and more pubic hair appeared. On September 19, 200 mg. of testosterone was implanted, but by Jan. 5 1940 the tablet was not palpable and the effect had subsided. However, an extremely

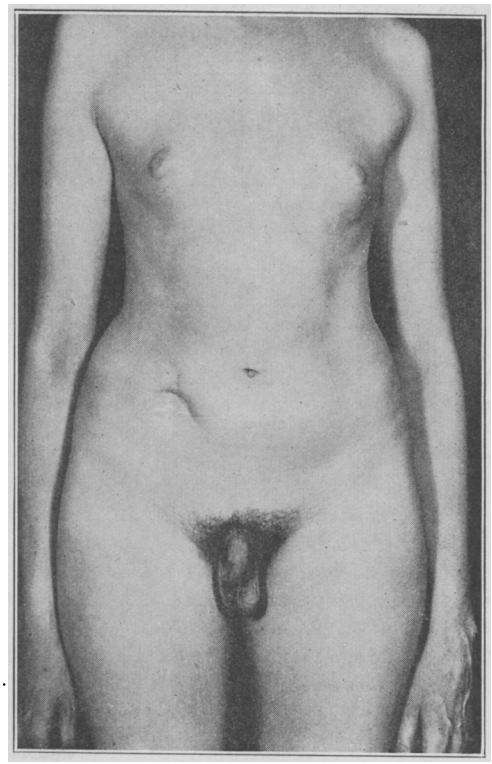

Fig. 28 (case 6).—Appearance in June 1939.

severe facial acne appeared which was treated locally. Circumcision was also performed. At this time, January 1940, 600 mg. was implanted—three 200 mg. tablets. The effect continued most satisfactorily until July and then began to decline. On October 2 350 mg. was implanted again with considerable and excellent effects.

CASE 7.—F. B., aged 27, who came under observation on Nov. 14, 1939, had the usual chief complaints of small genitalia, rare erections, absence of facial and axillary hair and sparse pubic hair. Physical examination was negative, aside from these abnormalities. His basal metabolic rate was minus 2 per cent. Blood pressure was normal. He weighed 144 pounds

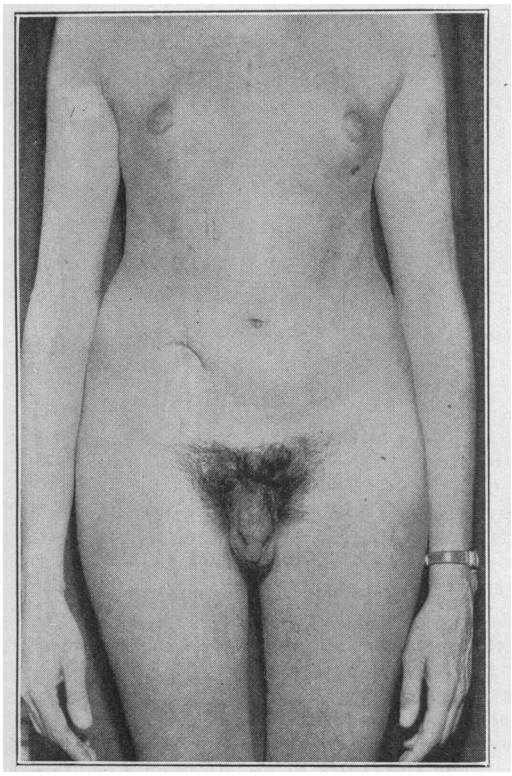

Fig. 29 (case 6).—Appearance in January 1940.

(65.3 Kg.). He received 700 mg. of testosterone propionate by injection from Nov. 16, 1939 to Jan. 1, 1940. The response was well defined. On January 2 two 200 mg. tablets of testosterone were implanted. The effect was maintained satisfactorily until July, when it began to decline, and by August he complained of a decrease in the size of the penis, absence of libido and a loss of 15 pounds (6.8 Kg.) (from 160 to 145 pounds [72.6 to 65.8 Kg.]). October 1, 300 mg. was again implanted, and the original satisfactory status returned in about two weeks.

RATE OF ABSORPTION OF IMPLANTED PELLETS

Deanesly and Parkes'[5] original animal studies suggested that approximately 24 or 25 per cent of the implanted pellet of testosterone was absorbed per month when pellets weighing 29 mg. and 100 mg. were used, the determinations of amounts absorbed made after forty-five and forty-one days. One must remember the size of their pellets and the animals used (guinea pigs). Vest, Drew and Langworthy,[6] in the monkey, demonstrated that 184.5 mg. was absorbed in ninety-two days from two pellets (166.5 mg. and 243 mg.) and 325 mg. absorbed in one hundred days from two pellets (225 mg. and 267 mg.). The calculated average amounts of substance absorbed per day were about 2 mg. and 3.25 mg., the extremes being 1.4 mg. and 4.7 mg. for single pellets.

On three occasions we removed implanted pellets from patients after one, two and three months.

EXPERIMENT 1.—Two pellets were inserted weighing 150 mg. each, a total of 300 mg. After one month they were removed and weighed, one pellet weighed 95 mg. and the second 115 mg., totaling 210 mg. This represented an absorption of 90 mg. in this, the first, month, or 30 per cent. The average amount of substance absorbed per day was therefore 3 mg.

EXPERIMENT 2.—Two pellets were inserted weighing 150 mg. each, a total of 300 mg. After two months they were removed and weighed, one pellet weighing 85 mg. and the second 55 mg., totaling 140 mg. This represented an absorption of 160 mg. in two months, or 53 per cent. The average amount of substance absorbed per day was therefore 2.66 mg.

EXPERIMENT 3.—Two pellets weighing 300 mg. on insertion were removed after three months and weighed a total of 95 mg. (35 mg. and 60 mg.). This represents a total absorption of 205 mg., or 68 per cent, or an average absorption of 2.28 mg. a day.

However, one must note the wide range of the weight of the removed pellets and the possibilities resulting from overlying or overlapping of pellets. Unquestionably the size of the pellet would make a further variation. However, the constancy of the daily average is striking. Also it appears that the first month's absorption was about 30 per cent, the first two months about 53 per cent (or 23 per cent in the second month) and 68 per cent absorbed in the first three months (or about 15 per cent in the third month). Thus with each passing month the rate of absorption decreased, probably as the total surface exposed decreased, as surrounding tissue reaction progressed and for other possible reasons.

Nevertheless, the clinical observations add up to one fact, namely that most patients were definitely benefited by implantation, just as they were by injections, and that as time progressed the effects gradually subsided. However, reimplantation could be performed readily, and with it there were renewed effects of testosterone therapy. As demonstrated, some patients returned for reimplants in four months, others in six months, while still others were not given reimplantations for eight or ten months. This was to be expected as the so-called regression or withdrawal symptoms appear at variable times, or even fail to appear in occasional cases.

ENCAPSULATION OF IMPLANTED PELLETS

In several animals (rabbits), pellets of testosterone (50 and 150 mg.) were inserted and removed at varying intervals. At no time were surrounding reactions sufficient to warrant a description of capsule formation. However, several clinical observations are worthy of special note.

CASE 8.—B. C., aged 32, came under observation on Nov. 20, 1939. His family history was irrelevant. He had a congenital dislocation of the left hip and had had a number of operations thereon. He had always been conscious of a lack or failure of genital development and of inadequate sex characteristics, especially so since the age of 17. There had never been any facial or axillary hair, but there had been a slight growth of suprapubic hair. His voice was feeble and high pitched. Erections occurred on rare occasions. Physical examination revealed that he was tall and thin, with long extremities, distinct genital underdevelopment, no facial or axillary hair and a slightly female escutcheon. There was a wide scar of the operations performed on his left hip. His physical examination was otherwise negative. The blood pressure was 130 systolic and 75 diastolic; his weight was 136 pounds 61.7 Kg.) and his height 70¼ inches (178 cm.). The basal metabolic rate was minus 13 per cent. The dextrose tolerance curve was 65, 85, 67. Roentgenograms revealed a rather small, shallow sella turcica. The testes were very small, the scrotum was thin and small and the penis small and shrunken. From December 1 to December 26 he received a total of 500 mg. of testosterone propionate by injection. Erections appeared frequently, onanism

with orgasm was reported, his voice became husky and the genitals showed unmistakable evidence of improvement and growth. On December 26 one 200 mg. tablet was inserted. On Feb. 2, 1940 he reported that there was no further progression but rather a stationary status for the past several weeks. The pellet was definitely palpable, and, in comparison to other cases six to eight weeks following implantation, it seemed to be large. On March 26 the tablet was still very large, the erections had ceased and the genitals had receded somewhat in size. On March 29 600 mg. of testosterone was implanted (three 200 mg. pellets). April 12 the penis again was larger, erections were frequent and he weighed 148 pounds (67.1 Kg.), but by May 3 the maximum effect had passed and the newly implanted pellets were still distinctly palpable, as was the pellet implanted in December. On June 7 the pellet inserted on Dec. 26, 1939 was removed (five and one-half months after implantation). There appeared to be a definite dense capsule surrounding the hard center (the pellet). The laboratory reported that the specimen was an irregular, oval mass of fat and fibrous tissue 17 by 10 by 8 mm. On section, a band of gray fibrous tissue 2 mm. thick surrounded a yellow calcific mass about 5 mm. in diameter. Microscopically the specimen revealed a thick capsule of connective tissue which was moderately dense and contained a number of giant cells of foreign body type. No foreign bodies were seen in them, however. The diagnosis was foreign body granuloma (Dr. M. M. Richter). During July and August all testosterone effects were practically absent. In September injections were resumed, 25 mg. three times a week, with renewal of testosterone effects—growth of genitalia, erections, change in voice and others.

Thus in an occasional case a definite reaction occurs about the implanted pellet. This seems characteristic of the individual patient and may reappear with subsequent implantations. On the other hand, we have repeatedly reimplanted into sites of the original implantations at intervals of three, six and ten months, without finding any evidences of the originally implanted pellets, or evidences suggesting capsule or scar tissue formation. There were no evidences of interference with the absorption of the pellets inserted at the second or third implantation.

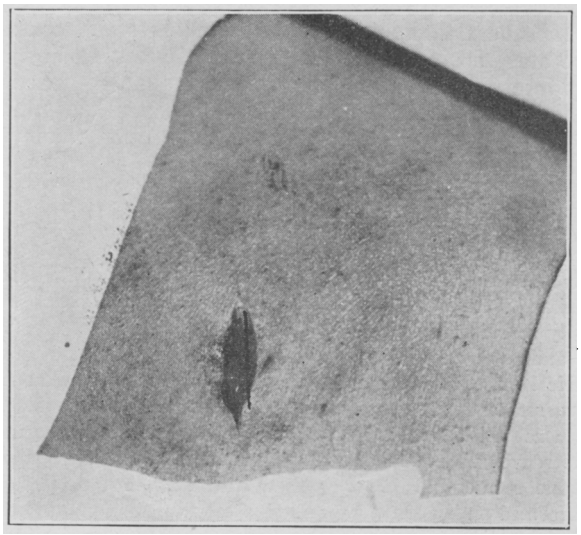

Fig. 46.—Step 2 in implantation technic.

Another experience is worthy of note and further emphasizes this observation:

CASE 9.—E. J. S., a man aged 52, single, was first seen by us Dec. 2, 1939. The only important facts in his previous history were as follows: He was well and normal in every way until at the age of 20 he had an episode of hemoptysis and was told he had pulmonary tuberculosis. He spent one year in a sanatorium and was discharged as "cured." His life from 21 to 40 years of age was that of any normal adult. He had begun to shave regularly at 16. He was normal sexually and had no complaints. At 40 a right orchiectomy was done because of tuberculosis; about two years later a left

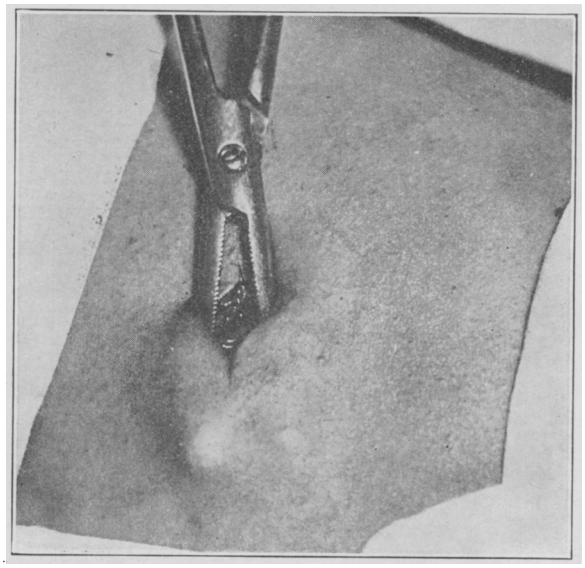

Fig. 47.—Step 3 in implantation technic.

orchiectomy was performed for the same reason. Since then he gradually gained about 25 pounds (11.3 Kg.), became nervous and irritable, frequently became hot and flushed and would break into profuse sweats. His facial hair disappeared almost entirely and his penis slowly grew smaller. The breasts slowly increased in size. All libido disappeared and no erections occurred. His physical examination revealed the status described but was otherwise negative. The blood pressure was 130 systolic and 75 diastolic, and all laboratory studies were negative. He was considered to be a true postoperative castrate or eunuch, and on March 6, 1940 a total of 450 mg. of testosterone was implanted in the form of three 150 mg. tablets. For about four or five weeks thereafter the nervousness, tremulousness, sweating and weak feeling decreased and then disappeared. His sallow, yellowish skin took on a more ruddy appearance. There was some growth of axillary and facial hair. His penis lost its shrunken appearance and seemed to grow, and many erections occurred. He even practiced some masturbation. But by April 21, seven weeks after the implantation, he noticed complete subsidence of the testosterone effects, and he gradually returned to the original status. The pellets were still distinctly palpable. On May 18 eight 50 mg. pellets (400 mg.) were inserted. For two or three weeks there was a suggestion of testosterone effect, but on June 8 it was decided that the effect was negligible. Several more weeks were allowed to elapse, and since he had again returned to the original status he was given a total of 1,000 mg. of testosterone propionate by injection over a period of six weeks during July and August. Feeling improved and disliking the injections, he ceased treatment, believing he was now cured, despite advice to the contrary.

This patient undoubtedly derived some benefit from the first implant, but there was less by far than would be expected, and the duration was much too short. In addition, the pellets remained distinctly palpable. Reimplantation led to a similar experience. It was concluded that we were again dealing with the process of encapsulation. Injections led to what appeared to be definite full response. Of the 30 patients treated by implantation, 3 have failed to respond sufficiently, and we believe that the failure was due to the process of encapsulation which prevented or retarded absorption.

DOSE IMPLANTED AND USE OF FEW LARGE PELLETS VERSUS MULTIPLE SMALL PELLETS

As described, amounts varying from 150 mg. to 900 mg. were inserted. Unquestionably the largest dose gave greater response than the smallest. However, it is conceivable that an optimum dose should be ascertained if possible, for the substance is too valuable to be wasted unnecessarily and indiscriminately. From our observations it appears that from 300 to 450 mg. usually appeared adequate for satisfactory results, but allowances must be made for individual cases. Further, should one implant two 200 mg. pellets, three 150 mg. pellets or six or eight 50 mg. pellets for the most economical and most satisfactory effects? Certainly, overlapping of pellet surfaces reduces the total surface exposed and the amount absorbed per day. Also larger pellets are more likely to fragment, crush and give irregular waves of hasty absorption. Further, the larger pellets require a longer incision and a pocket formation, while smaller pellets are readily inserted without the formation of a scar through a trocar (to be described later). By this method, the small pellets are "strung out" end to end without overlapping and are less likely to fragment, assuring longest possible life with greater efficiency. The surface area of eight 50 mg. pellets is thus greater than four 200 mg. pellets, and probably remains proportionately greater as time and absorption proceeds.

IMPLANTATION METHODS

We chose the posterior axillary line, at about the level of the sixth to the ninth rib. We felt that there was little subcutaneous fat at this site, a likelihood of less trauma, little interference with motion and probably a minimal and uniform effect of muscular and bodily activity.

For the implantation of the larger pellets (150 and 200 mg.) an incision about ¾ inch (2 cm.) in length was made under procaine hydrochloride anesthesia and

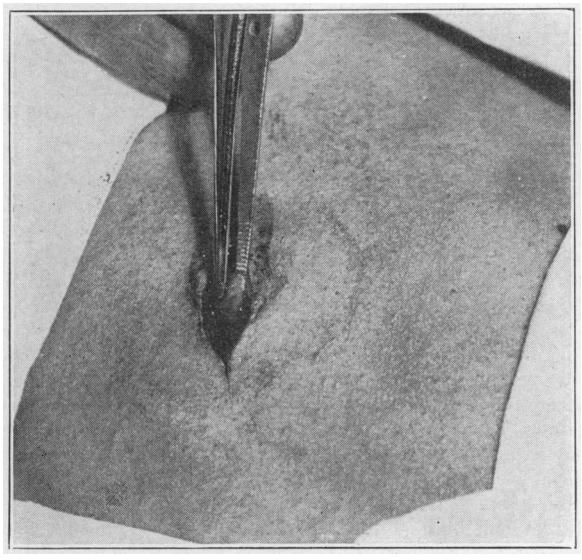

Fig. 48.—Step 4 in implantation technic.

by blunt dissection a pocket about 1 or 2 inches in diameter was made below and away from the incision. Into this pocket the pellets were inserted, and the incision was closed with two or three sutures. Although care was taken to insert the pellets without overlapping, they undoubtedly frequently "bunched" themselves, nevertheless. The sutures were not removed until the seventh day.

For the 50 mg. pellets a trocar was specially constructed so that the diameter of the pellets was that of the trocar. After injection of procaine hydrochloride a minute cutaneous puncture or incision was made (about

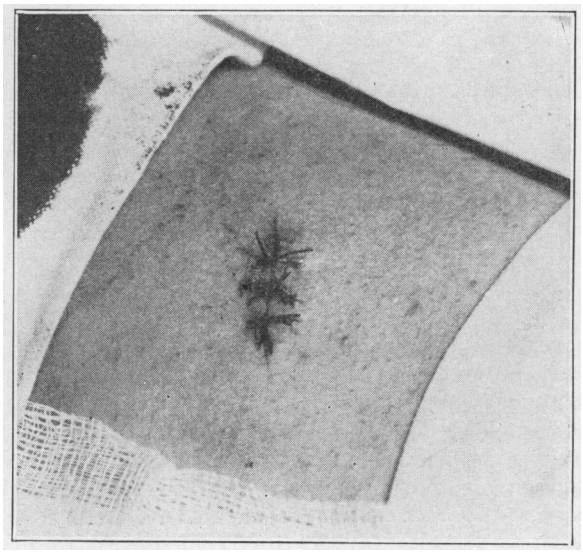

Fig. 49.—Step 5 in implantation technic.

¼ inch [0.64 cm.]) with a sharp pointed scalpel. This facilitated the introduction of the trocar. It was then slowly pushed forward under the skin and the stilet withdrawn. Three or four pellets were then slipped into the hollow and held in place with a plunger, while the trocar cuff was withdrawn and the process repeated at another site, the work being done through the one original puncture wound. By this method the pellets remained in a fixed position end to end as inserted, and with less trauma or bleeding. The puncture wound was closed with one suture to insure prevention of the pellets working their way up and out. Repeated implantations could be made at the same site if desired.

ADVERSE RESULTS AND OBSERVATIONS

Of the total of seventy implantations two were terminated spontaneously at the end of the second and third week by failure of the incision wound to heal with resultant ejection of the pellets. In these instances, both among the earlier implants, the sutures were removed on the fifth day. Also, the pocket formation was so small that the pellets lay too near the incision and were too superficial. After the technic was modified this has failed to recur. There has been no excessive bleeding and no infection. There has been no pain, not even discomfort. The ejection has not occurred with the smaller (50 mg.) pellets inserted with the trocar.

The lack of response, as described, probably due to encapsulation, must necessarily be considered as an adverse result. Several other instances of decreased or partial response did present themselves, probably explainable on the basis of a decrease in absorption due to peri-tablet reaction, or inadequate dosage. That the latter was usually the cause was demonstrated by increased response following reimplantation of larger doses.

In two instances the response seemed exaggerated or excessive, although neither could be classified as severe. These were characterized by excessive libido and erec-

tions and soon disappeared. On reimplanting these patients we used smaller doses, and the response was then considered good and normal.

There have been no unsightly scars, even when reimplantation was performed through the original site. Of course with the trocar method the scar is minimal, negligible or absent.

DURATION OF EFFECTS

The duration of the effects, as determined clinically, has varied from two months to as long as six months, with four months as the average. The shorter periods seemed to occur with pellets that were not well compressed or friable. Fragmentation of the pellets on insertion, or when in situ, would probably hasten their absorption. Of course periodic urinary determination of androgenic content would be a more objective criterion but entails added labor and expense. However, it seems to us that the clinical history and course is an excellent criterion and, if augmented by the urinary androgen determination, offers an excellent means of indication for reimplantation. As observed with injections, some patients regress so slowly that the interval between treatments may be lengthened in individual cases.

SUMMARY AND CONCLUSIONS

We feel that this series of observations justifies the following conclusions:

1. Many patients need continued testosterone therapy, but occasional patients may discontinue therapy after long-continued treatment, or at least may postpone the resumption of treatment after intervals of rest periods.

2. The implantation of pure testosterone tablets offers a means of prolonged and continued therapy which is simple and practicable.

3. Although there may be some exceptions or untoward sequelae, these are thus far so few as not to contraindicate the procedure in general.

4. Undoubtedly much further work is required to determine the best procedure, dosage, frequency and the like.

5. Following seventy implantations, no real accident or complication has occurred, suggesting the comparatively safe and benign character of the method.

6. Finally, we believe that a patient suffering a lack of androgenic substance should first be given injections of testosterone propionate to demonstrate to the patient (and physician) the effects of testosterone administration before implantation is suggested. The patient would then be able to evaluate the effects of the implants. If implants are performed as the primary treatment, the patient has no established criterion to measure the efficacy of this method.

ADDENDUM

Since the foregoing report was submitted, sixty additional implants have been performed, a total of about one hundred and thirty. These are now done with a new trocar, which has a simple beveled point and requires no incision whatever and no suture on removal. The only dressing used is a collodion dressing, removed on the seventh day. The observations and findings, as reported, hold without any modification for the entire group.

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SPOROTRICHOSIS

REPORT OF SIX CASES AMONG FLORISTS

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Sporotrichosis is a rather rare disease clinically seen as one of four general types, namely lymphatic, disseminated nodular, disseminated ulcerated and visceral.[1] The type commonly encountered is the lymphatic, characterized generally by an initial traumatic abscess of the skin followed by a chain of subcutaneous nodules along the course of the lymphatics in two to three weeks. These nodules are painless and later ulcerate. The ulcers resemble tuberculosis of the skin, syphilitic gumma, staphylococcic infections or tularemia. If the condition remains undiagnosed, the course is prolonged and disabling.

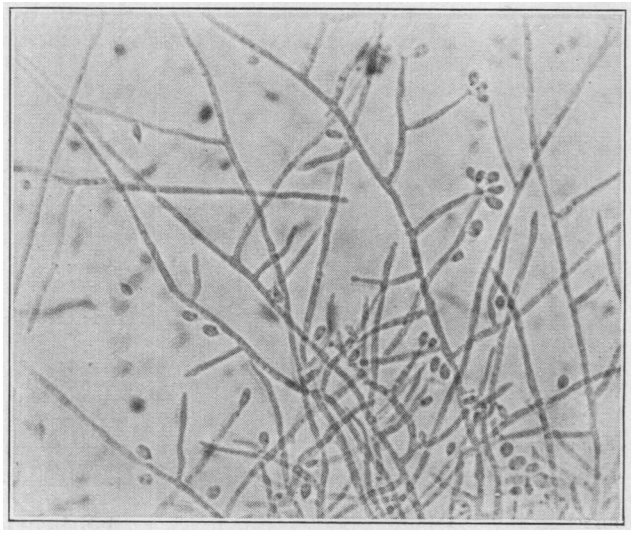

Fig. 1.—Sporotrichum schencki, recovered by aspiration.

The etiologic agent is the fungus Sporotrichum schencki, named after Schenck, who in 1898 originally described the disease in this country. The fungus is a widespread saprophyte being found in every country. Microscopically the myceliums appear hyaline, fine branching organisms 1 to 2 microns in diameter. The spores are oval to pear shaped and are attached to short lateral branches or longer hyphae.

REPORT OF CASES

CASE 1.—G. F., a youth aged 18, a florist's assistant, was referred by his physician to our office on March 4, 1939. On January 2, he stated, he had run a small piece of steel into the middle finger of the right hand. The injury was considered trivial except that it would not heal. Prior to referral, local medications had been applied, and surgical incisions of the abscess had been performed. About the first of February he had noted a number of "boil-like" lesions ascending the right forearm.

Examination revealed that the boy was well developed and had no abnormalities except the lesion of the right forearm. About the nail of the middle finger one could see an infected

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1. Templeton, H. J., and Lunsford, C. J.: Sporotrichosis on Pacific Coast, Northwest Med. **30**: 132-136 (March) 1931.