SUBCUTANEOUS IMPLANTATION OF FEMALE AND MALE HORMONE IN TABLET FORM IN WOMEN

BY

ALFRED A. LOESER, M.D.

Female and male hormones in tablet form can be implanted subcutaneously, and in this way accurately controlled use of the hormones over long periods is obtained (Deanesly and Parkes, 1938; Parkes, 1938). In human beings this method has not yet been extensively tried (Bishop, 1938; Foss, 1939; Geist, Salmon, and Walter, 1939).

Below are given reports of twelve patients who were given in all sixteen implantations of hormone tablets. Female hormone was implanted in the case of two patients and male hormone in the case of the remaining ten.

Implantation of Tablets of Oestradiol

Both of the women whose cases are here recorded had hitherto been sterile; in both the uterus was infantile; both desired children and had on many occasions been treated unsuccessfully with female hormones and anterior lobe preparations.

Case 1.—The result of the implantation was negative, as the tablets were expelled again ten days after insertion. This woman was very thin and had a scanty subcutaneous layer of fat; the tablets had been implanted too near the skin.

Case 2.—The patient is 32 years of age; she did not conceive either with her first husband or with her present one. Mud-bath and diathermic treatment and dilatations and curettage of the uterus were of no avail. Tubes were open. Menstruation was regular. Uterus was very firm; measurement with a probe gave barely two inches. After injections of almost one million units of oestrogenic preparation during six months the uterus became softer in consistency and its size also seemed to increase, but it reverted to its old firm consistency immediately the treatment was left off. In order to apply continuous stimulation to the uterus, five tablets of oestradiol were implanted deep in the subcutaneous fat of the right hypogastric region on September 6, 1938. (Each tablet weighed 15 mg.) The last normal menstruation occurred on September 14, and then, as expected, menstruation ceased. On January 1, 1939, the periods returned, and in February and March there were haemorrhages lasting up to three weeks. In April they increased still more, as had been previously expected. Curetting revealed a uterus more than three inches in length and a definite cystically proliferated mucous membrane. The Aschheim-Zondek reaction was negative. On May 13—that is, 249 days after the implantation—the tablets were removed by means of a small skin incision, and the amount of hormone absorbed was determined. Then menstruation was again normal, the last period being on October 4, 1939, when the uterus was the same size as during the curetting. In November signs of pregnancy were observed, and on the 10th of that month the Aschheim-Zondek reaction was positive.

In March, 1940, the uterus corresponded in size to that of a fifth-month pregnancy; the Aschheim-Zondek reaction was again positive. The pregnancy so greatly desired by the patient has undoubtedly been attained, so far without complications.

Implantation of Testosterone Tablets

Five women with fibroids of the uterus complicated by menorrhagia were treated; one woman with functional bleeding; two patients with chronically recurring mastitis and multiple nodules in the breast; and, finally, two with

cancer of the breast, one of whom, after numerous operations and x-ray treatment, was to be regarded as hopeless, while the other, after a radical operation and frequent x-ray treatment, had continual recurrences.

Case 3.—The patient, 42 years of age and childless, had previously had a laparotomy on account of an ovarian cyst, now a cervical fibroid larger than a fist, of intraligamentary development. Menstruation lasted up to fourteen days, with much flow of blood. In 1937 and 1938 I gave her injections with testosterone propionate and inunctions into the skin of an alcoholic solution of the same hormone. Results were good, but only temporary. On September 12, 1938, twelve tablets of testosterone propionate, amounting altogether to 600 mg., were implanted. From September 2 to 16 occurred the last profuse menstruation; on the 24th there was a haemorrhage lasting five days; and then there was amenorrhoea until February 20, 1939. After that there were apparently two very short periods, and from April to July there was amenorrhoea. In July there was a haemorrhage lasting six days, followed by complete amenorrhoea until the present time, without the appearance of menopausal symptoms. The fibroid has not changed its size or consistency. The patient, who had refused operation, is well satisfied with her present condition. Time of observation after the implantation amounts to sixteen months.

Case 4.—Patient 29 years of age. In April, 1937, I enucleated three intramural fibroids from the retroflexed uterus. Nevertheless menstruation remained as severe as previously and lasted over a week; severe, at times intolerable, premenstrual breast pains persisted. On August 19, 1938, two tablets of testosterone propionate (in all 948 mg.) were implanted. Amenorrhoea followed. The first period was on November 22. On November 28—that is, 101 days after the implantation—the two tablets were expelled as a result of a severe traumatic haematoma of the abdominal wall. During the first year after the implantation periods were normal, and there was hardly any complaint of premenstrual breast pains. The condition of the generative organs was normal. From October, 1939, onwards—that is, fifteen months after the implantation—the periods once again became menorrhagic. Time of observation was eighteen months.

Case 5.—The patient, 43 years of age, with a submucous fibroid the size of a fist, had periods lasting ten days with much loss of blood. Operation was refused. On October 15, 1938, twelve tablets of testosterone (each tablet containing 50 mg.) were implanted. On October 24 a haemorrhage lasted ten days; after that there was amenorrhoea until January 28, 1939. Regular periods of five days' duration followed, the fibroid being unchanged. Last examination was in July, 1939. Time of observation lasted nine months.

Case 6.—The patient, 40 years of age, had been previously curetted and treated by x rays in Vienna for menorrhagia. For some months past the periods had again been very severe, lasting fourteen days. There were a few hard fibroids in a uterus almost the size of a fist. Operation was refused. On February 1, 1939, twelve tablets of testosterone (in all 600 mg.) were implanted. There was amenorrhoea until June 5, 1939, and after that normal five-day menstruation. Final examination in the middle of January, 1940, revealed the fibroids the same size as previously. Periods were normal, lasting five to six days, and there was far less loss of blood than hitherto. Time of observation after the implantation—nearly one year.

Case 7.—Patient 34 years of age. There was definite masculine distribution of hair on the legs and abdomen. Previously removal of an ovarian cyst and a fibroid had been performed. The menorrhagia then disappeared for one year only. Intolerable breast pains occurred one week before each menstruation. For some months past the menorrhagia had recurred. A small fibroid the size of a walnut could be felt in the uterus. On May 13 386 mg. (eight tablets) of testosterone were implanted. The breast pains disappeared entirely but the menorrhagia was not affected; in fact, the impression is that the periods became still more severe. On August 22 the uterus was curetted and the endometrium was

found to be atrophic. On the same day the implanted tablets were removed; only three were found, and they were much thinner and greatly reduced in size. During the next four months the premenstrual breast pains disappeared, but the menorrhagia had diminished by two days only, though the loss of blood was still considerable.

Case 8.—The patient, 38 years of age, had so severe a menorrhagia in consequence of a fibroid that she was unable to work. On December 29, 1939, 600 mg. of testosterone propionate were implanted. On the sixth day after this we tried to detect the tablets in the tissue by x rays. The tablets could not be detected with certainty, although it was thought that some crystal-like shadows could be observed. The period of observation is too short for account to be taken of the case here.

Case 9.—The patient was 40 years of age, with regular menstruation. Her mother had died of cancer of the breast. For the last five months she had had pains in the breast and a nodule the size of a bean could be felt in the right breast. Histological examination revealed chronic mastitis. The patient had had the same symptoms a year ago. On March 27, 1939, 300 mg. of testosterone were implanted. Ten days later the breast pains disappeared. There was amenorrhoea for six weeks, and after that the periods were normal again. The whole of the remaining tumour had disappeared. In July, 1939, however, it was again possible to feel a small nodule in another part of the right breast; but it had vanished in three weeks. So far no new tumour has appeared: there are no more pains. Time of observation after the implantation was ten months.

Case 10.—The patient was 40 years old and her menstruation was normal. During the last six years she had been operated on four times on both breasts for cystic tumours. Histological examination revealed a fibro-adenoma. For three months before implantation she had noticed a tumour in the right breast. It was the size of a walnut and gave rise to considerable pain. On September 9, 1939, 700 mg. of testosterone (fourteen tablets) were implanted. Amenorrhoea followed and has persisted till now (February 20, 1940). Examination carried out six months after the implantation shows that nearly the whole of the tumour has disappeared; there is no pain. (Another very remarkable coincidence is that the patient stated she was able to dispense with her glasses, which she was wearing for myopia. The same observation was made in another case in which 600 mg. of testosterone propionate were injected.)

Case 11.—The patient was 60 years of age, and had been treated for the last eight years with radium for carcinoma of the breast. Multiple recurrences were treated by operation. Metastasis now exists on both sides, supraclavicular and mediastinal. In the right axilla there is a diffuse infiltration; around the right nipple there is a suppurating ulcer the size of a half-crown. The radiologist called in recommended morphine for combating pain; on account of the disseminated carcinoma no other treatment was carried out. On July 1, July 14, and October 3, 1939, 1,650 mg. of testosterone propionate in all were implanted. On October 3 two of the tablets implanted on July 14 were removed in order to determine the degree of absorption. The temporary result was a superficial swelling around the right nipple, accompanied by considerable reduction of the ulcer, a softening of the hard infiltrations in the armpit, and also a superficial swelling and pigmentation of the healthy breast. Striking features were an increase in weight by 5 lb. and an obvious state of improved health; the patient also had a certain dark pigmentation of the face as if she had been given ultra-violet rays, and the pain along the right arm was considerably less. This improvement lasted only until the middle of November, when the patient's weight again fell off, and further decline could not be checked.

Case 12.—The patient was a woman 45 years of age, who after radical operation for cancer of the breast on the right side and much x-ray treatment over a period of one year showed two recurrences in the operation cicatrix. There is now a fresh acute recurrence in the armpit. On August 22, September 18, and November 8, 1939, 1,500 mg. in all of

testosterone were implanted. In the beginning the patient showed similar symptoms to those described in the case of the preceding patient, but up to January, 1940, no change in the size or consistency of the recurring tumour in the axilla could be found (although it did not reveal any growth), for which reason the patient was again given x-ray treatment.

Technique of Implantation and Absorptive Powers of the Tissues

Under a local anaesthetic an incision two to three inches in length is made through the skin of the right or left hypogastric region; the fatty tissue is drawn apart, and each tablet (which has been previously sterilized in boiling water for three to five minutes) is embedded separately in the subcutaneous tissue. The tablets should not be in contact with one another and should not lie directly beneath the skin, as otherwise they act too much as foreign bodies and are expelled again too easily. The deeper the tablet lies the better it will be retained; the larger the tablet the less certain the chances of healing up. A tablet one-third of an inch in diameter is most suitable for implantation, although the absorption proceeds more rapidly when the surface is larger. The skin, and on occasion the fatty tissue (when there is a thick layer of the latter), is closed with a few stitches of catgut. This technique has given me the best results.

In Cases 2, 4, 7, and 11 it was possible to ascertain the loss in weight undergone by the implanted tablets during their retention in the body. When the tablets were removed it was found that some were still lying free in the fatty tissue, some were attached to the fatty tissue by light fibrous bands, and one tablet was surrounded by a tough fibrous layer. It will be seen from this that the absorption need not proceed uniformly when the implanted tablets are not lying quite free.

In Case 2 five tablets of oestradiol had been implanted, each tablet weighing 15 mg. On removal they weighed 3.8 mg., 5 mg., 2.8 mg., 6.4 mg., and 6.5 mg. respectively. Within 249 days, therefore, there had been a total absorption of 50.5 mg. of oestradiol. In Case 4 there had been, within 101 days, an absorption of 376 mg. of testosterone propionate out of the 948 mg. implanted; in Case 7 (likewise in a period of 101 days) 368 mg. of testosterone out of a total of 386 mg. had been lost. In Case 11 (of carcinoma), finally, within a period of eighty-one days, 34.5 mg. had been absorbed from one of the two tablets (each of which had weighed 48 mg.) and 34 mg. from the other. At the beginning, when the tablet presents a large surface, more is absorbed than later on, when the surface of the tablet has already been considerably reduced in size.

Results of Oestradiol Implantation

As regards Case 2, in which the female hormone was implanted, the patient reacted in the same way as the experimental animal. The large quantity of oestradiol depressed the function of the anterior lobe of the pituitary gland; gonadotrophic hormones were not emitted from the anterior lobe. Consequently maturation of ovum and menstruation did not occur. Just as in a normal pregnancy the function of the anterior lobe of the pituitary gland is depressed by the oestrogenic substances produced in the placenta, and the ovary forced into a kind of hibernation, so in this case the same effect was produced by the implant. Nevertheless local action of oestradiol on the uterine muscle and mucous membrane of the uterus became plainly visible. The uterus grew, and the mucous membrane became converted into cystically proliferated endometrium and was cast off gradually by haemorrhages.

After removal of the hormone tablets the anterior lobe gradually recovered, the hibernating ovary was stimulated by fresh gonadotrophic hormone produced in the anterior lobe, ripening of the ovum occurred again, and hence there was normal menstruation. The muscular apparatus of the uterus had been substantially strengthened and was now able to draw up the semen, which it had previously been unable to do because of muscular deficiency. The patient became pregnant.

Rationale of Male Hormone Therapy

French authors (Mocquot and Moricard, 1936; Capitan and Desmarest, 1937; Turpault, 1937) were the first to use the male hormone in gynaecological affections, but only after the experimental investigations of Zuckermann (1937) and my proof (1938) that a sufficiently large amount of male hormone produces in women a temporary atrophy of the endometrium (maintainable for a lengthy period) and a temporary sterilization could a sure enough basis of a quantitative character for therapy be established. Foss (1938) in this country and, in particular, American authors (Gaines, Geist, and Salmon, 1938) have later confirmed this.

The endometrium is the mirror in which are reflected the hormonal processes taking place in the ovaries. The growth and the ripening of the follicle are reflected in this mirror, as are the birth and the death of the corpus luteum. In the same way the endometrium reflects all the processes which occur after absorption of the implanted artificial ovary and of the artificial testicle in tablet form, although, of course, the artificial ovary is incomplete, as is the artificial testicle, for each yields only a single hormone. Both artificial glands, however, have a common feature in that they depress the function of the anterior lobe of the pituitary gland and reduce the secretion of the gonadotrophic hormones, or even suppress it entirely when the implantate is sufficiently large. In Cases 3 and 5 the gonadotrophic hormones were examined before and after the implantation (Dr. Wiesner), and in the first case they disappeared entirely from the urine after the implantation, while in the other case they were reduced by one-half. If atrophy of the endometrium ensues, as in the unsuccessfully treated Case 7, but bleeding nevertheless persists, the amount of testosterone (less than 400 mg.) may have been too small to depress the anterior lobe. In fifty-five cases in which injections of testosterone propionate have been given—reports on which will be published later—an average of 700 mg. of testosterone propionate had been necessary in cases of hyperfolliculinaemia in order to obtain the desired results. It might perhaps be suggested that this dosage, which might be called "hormone atrophy dose" for the endometrium (H.A.D.), should be designated as a basic value and only a portion of it be given, depending on the case. It is approximately twenty times the dose of follicular hormone necessary to attain a normal proliferation of the endometrium in cases of absent ovaries or of primary amenorrhoea (35 mg. oestradiol benzoate). This might be called the "hormone proliferation dose" for the endometrium (H.P.D.) (1933, 1934). For antagonizing this proliferation dose the atrophy dose of testosterone would be necessary.

If pronounced hyperfolliculinaemia and hyperproliferation exist this atrophy dose would have to be increased. Even the largest doses of male hormone, such as were injected in earlier attempts, do not act on the fibroids themselves, which, according to our present-day concepts, are considered to be the result of hyperfolliculinaemia. In the case of one patient who had been treated with such

large doses by injection, and on whom I subsequently performed a supravaginal amputation of the uterus, the histological examination of the fibroid (performed by Dr. Oliver) revealed no change.

In the five women with haemorrhages treatment was successful in three, of only limited success in one—a younger woman (Case 4) in whom after an accident the tablets were expelled—and unsuccessful in one (Case 7), in whom the amount of the implanted hormone was too small. Improvement was obtained in the two women with chronic mastitis. It is known, and has been established particularly by French authors, that even small doses when injected give good results in this condition—a view also supported by workers in this country (Spence, 1939). But in this connexion it must be observed that results are also to be obtained with follicular hormone and other methods of treatment, such as diathermy. Treatment with male hormone is based on the fact that excess of follicular hormone produced in the body causes the proliferative processes in the breast, and that this excess cannot be antagonized for a long period by small doses of male hormone, but only by really large ones.

Testosterone and Cancer

If it is assumed that excess of follicular hormone can produce not only proliferative processes in the mammary gland but perhaps even precancerous processes, treatment with male hormone as an antagonist would be justified in cases of cancer of the breast. Experimental investigations with testosterone in mice with high incidence of cancer of the breast are available (Lacassagne, 1937; Flacks and Isser, 1938). Testosterone propionate acted in a prophylactic manner. I have had under observation two patients whose breasts were removed for cancer and who suffered from recurrences at frequent intervals. The recurrences had disappeared after irradiation when I saw them. I treated them for menorrhagia with injections of testosterone propionate, and up to date there has been no further recurrence for two and a half years; this suggests that testosterone had an inhibiting effect (1939).

In my two cases of cancer (11 and 12) testosterone had no effect on the growth itself.

General Effects of Testosterone Therapy

All patients who have been treated show throughout the following general effects: (a) Enlargement of the clitoris so long as the male hormone was acting. No patient found this to be unpleasant. (b) Increased sexual drive even in older women. The fact that this can be found without a single exception, even when the male hormone is given by injections in sufficient amounts, shows that testosterone can be designated as an infallible aphrodisiac, although of course only doses over 300 mg. have effect. (c) Deepening of the voice without anatomic alteration of the vocal cords. This disappears after three or four months. (d) Temporary occurrence of lanugo on the face, which also disappears again after some time.

As regards the psychic side of the patients treated in this manner, they all acknowledge a great feeling of well-being, more balanced moods, and clearer thinking; and some profess also a greater determination. We might therefore speak of a "chemistry of the emotions" in order to express that the temperament is influenced by the chemical substance so long as the hormone is active. It would be interesting to go further into this side of hormone therapy, and to study how the feelings might be chemically controlled. Some of Freud's theses would perhaps have to be modified. Such discussions, however, would lead too far from the original theme.

Summary

1. Female and male hormone can be implanted in tablet form in as large amounts as desired without injury.
2. Female hormone was implanted to allow a small infantile uterus to develop and to make it ready for conception, and this was done successfully.
3. Male hormone was implanted to control serious menorrhagia caused by fibroids. Good results were obtained in the case of women near the menopause.
4. Male hormone was unable to influence successfully existing recurrences of carcinoma of the breast following an operation or x-ray treatment. To what extent male hormone can have a prophylactic action against such recurrence is not yet determined.
5. The general effect of implants of male hormone on women is discussed.

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SULPHONAMIDE TREATMENT OF BACTERIAL AND TRACHOMATOUS CONJUNCTIVITIS

BY

A. F. MacCALLAN, C.B.E., F.R.C.S.

President of the International Organization against Trachoma

The idea of developing specific chemical substances for the treatment of bacterial infections is as old as bacteriology itself. In 1881 Koch failed to cure anthrax with mercurial salts; however, in 1904, with Ehrlich's success in protozoan infections the search for drugs of chemotherapeutic value began again. It has been only within the last few years, by haphazard trial and error, that the value of the sulphonamide group of synthetic compounds has been discovered. In 1908 Gelmo described the preparation of sulphanilamide in a purely scientific paper; by the substitution of various molecules he produced different compounds, including dyes. In 1932 Domagk, using a compound patented for dyeing, cured streptococcal infections in mice; this was then sold as prontosil.

The term "sulphonamide" is a generic one and embraces the following compounds: prontosil rubrum, prontosil soluble, rubiazol, uleron, sulphanilamide, proseptasine, soluseptasine, and M & B 693 (sulphapyridine). It appears that there is little difference in the effect of these drugs, the trade names of which have been given. It is said that they do not stimulate leucocytic activity, are not simple germicides, and do not affect the rate of production of specific immunizing bodies, either in quantity or in quality. Probably they act by neutralizing a metabolic function or

an enzymatic activity. The balance of evidence indicates that the sulphonamides affect the invading organism in the sense of producing a bacteriostatic action which in many cases is not sufficient to effect sterilization without the co-operation of the defensive mechanism of the host. The foregoing preface consists of extracts from various recent publications.

In the case of trachoma, however, Julianelle has shown that blood from trachomatous persons contains no demonstrable substance capable of inactivating or neutralizing the infective agent, as measured by the development of experimental trachoma in monkeys. The drug diffuses readily to all tissues and fluids of the body; experimentally it may be found in the eye within fifteen minutes of ingestion. This is the reason why it has been proved to be such a successful chemotherapeutic agent in certain bacterial diseases.

Preliminary Procedures

When its influence on trachoma is being investigated some attempt at scientific observation should be made. After the clinical condition of the conjunctiva has been diagnosed as a veritable trachoma a detailed description of the observations on which the diagnosis has been based should be noted before treatment is begun. This should include:

1. Cultural examination of the conjunctival flora. The conjunctival sac should be filled with sterile broth, which should be allowed to remain for a few minutes before being removed with a pipette for sowing on blood-agar and other media.

2. A slit-lamp examination of the tarsal conjunctiva of the everted upper lid. In the case of trachoma some or all of the following signs may be present: (a) papillary hypertrophy consisting of polygonal areas separated by interstices, forming a mosaic or marquetry; (b) on each of the polygons a congeries of plume-like capillaries; (c) bleb-like excrescences or follicles; (d) cicatricial lines in the epithelium and subepithelial tissue. Signs *a* and *b* are found in most forms of chronic conjunctivitis.

3. A slit-lamp examination of the corneal periphery in its upper fifth to note: (a) subepithelial grey infiltration; (b) corneal rosettes or limbal follicles; (c) Herbert's peripheral pits; (d) neo-vascularization of the normally clear corneal tissue, especially by reflected light.

4. A momentary application of Graddy's or Knapp's forceps may be made in some cases to the conjunctiva to see if gelatinous material is expressed from the bleb-like excrescences.

5. Epithelial scrapings from the upper tarsal conjunctiva should be made and stained with Giemsa for the detection of the epithelial inclusions which are characteristic of any virus disease.

These procedures should be carried out after there has been a cessation of all forms of treatment for about ten days; this, of course, should be maintained while the drug is being given.

Technique of Treatment

The derivative of sulphonamide which I have used has been M & B 693 (sulphapyridine), and the adult dosage has been 3 grammes the first day, divided into six doses and given with an equal quantity of sodium bicarbonate at intervals during the patient's waking hours; after this the daily dosage was 2 grammes, given similarly for nine days. It is not necessary to employ larger doses or to wake the patient up at night so that treatment may extend throughout the twenty-four hours, as is advised in acute bacterial diseases. During the treatment all articles of diet likely to contain sulphur are forbidden, including