THE USE OF SEX HORMONES IN THERAPEUTICS*

BY

P. M. F. BISHOP, D.M.

*Endocrinologist to Guy's Hospital, Chelsea Hospital for Women, and the Department of Obstetrics and Gynaecology,
British Postgraduate Medical School*

Modern sex-hormone therapy is no more than fifteen years old, and, considering that progress was seriously retarded during the war, the rapidity with which this branch of therapeutics has expanded is remarkable. Few could have imagined that it would spread beyond the narrow confines of gynaecological endocrinology, and yet to-day sex hormones are beginning to play a prominent part in cancer treatment, general medicine, and such of its specialties as dermatology. It has therefore become the duty of every doctor to learn how to administer these substances.

Technique of Sex-hormone Administration

The sex-hormone compounds at present employed in this country, together with their routes of administration and dosage, are set out in the accompanying Table. The

Hormone	Route of Administration	Dosage		
		Low	Moderate	High
Oestrogens:				
Natural:				
Oestrone	Oral	3,000-10,000 i.u.	—	—
Oestradiol benzoate	Injection	—	10,000-50,000 i.b.u.	—
"Oestrone sulphate"	Oral	0.625 mg.	1.25-5 mg.	—
Synthetic:				
Stilboestrol	Oral	0.1-0.5 mg.	1-3 mg.	5-15 mg.
Dienoestrol	"	0.3-3 mg.	3-10 mg.	15-50 mg.
Hexoestrol	"	3-5 mg.	—	—
Ethinyl oestradiol	"	0.025-0.05 mg.	0.05-0.15 mg.	0.25 mg.
Progestogens:				
Progesterone	Injection	—	5-20 mg.	—
Ethisterone	Oral	—	20-50 mg.	—
Androgens:				
Testosterone propionate	Injection	—	10-25 mg.	50-100 mg.
Methyl testosterone	Oral	5-15 mg.	30-60 mg.	—

dose ranges are based not upon any universally agreed scale, for no such scale exists, but upon personal experience and opinion, except in the case of ethinyl oestradiol, which has only just been launched upon the British market and the figures for which are therefore taken from the American literature. Other routes of administration than by mouth and by injection are employed, but these will be specifically mentioned in discussing the conditions for which they are to be preferred. Nausea and other side-effects may accompany the use of any of the synthetic compounds, but fortunately the "toxicity" range usually lies well above the "low" and "moderate" therapeutic ranges, except perhaps in the case of stilboestrol, though even with this compound the high incidence of side-effects so often experienced is due

to lack of appreciation of its potency and the consequent tendency to use it in excessive doses.

Substitution Therapy in Gonadal Deficiency

The most logical use of sex hormones is to compensate for deficient gonadal secretion. To obtain the best results, however, it is well to distinguish between *congenital* and *acquired gonadal deficiency*. Ovarian agenesis and the failure of the testicles to develop or descend give rise to *objective signs*, such as infantile genitalia and scanty body-hair growth in both sexes, with amenorrhoea and lack of breast development in the female, and eunuchoidal lengthening of arms and legs and absence of beard and adolescent voice changes in the male. Embarrassment and introversion are understandable accompaniments of these serious physical defects in both sexes, but there is in addition a characteristic timidity which is especially noticeable in the eunuchoid youth and which, with androgen therapy, gives place to a more self-reliant, forceful, and aggressive personality. The aggressive properties of male hormone have been demonstrated in a fascinating study of the "peck order" in hens. Twelve hens from different broods when put together will quickly arrange themselves in a peck order, No. 1 hen pecking the rest and No. 12 being pecked by all. Administration of androgen to this last hen will, however, soon send her to the top of the peck order. Treatment of these mainly objective signs consists in intensive administration of sex hormones, preferably by pellet implantation. Breasts and the natural female curves may develop in the woman; beard and body-hair growth, deepening of the voice, erections, and emissions may appear in the man, in addition to the awakening of male aggressiveness.

Acquired gonadal deficiency, on the other hand, leads to characteristic *subjective symptoms*, such as hot flushes, headaches, giddiness, lack of concentration, irritability, emotional instability, and easily induced fatigue, but to few or no objective signs. The severity of these symptoms varies from case to case. In most men and many women the climacteric is symptomless. At the worst the natural climacteric is a self-limiting condition readily controlled by judicious administration of the appropriate sex hormone. At the menopause the smallest daily dose of oestrogen which will appreciably diminish but not necessarily abolish the number and severity of the hot flushes should be determined by careful trial, and the aim should be to wean the patient as soon as possible from this dose. Overdosage leads, apart from the probability of annoying if not alarming uterine bleeding, to such symptoms as abdominal distension and headaches and not infrequently to return of the hot flushes.

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Sudden deprivation of actively secreting gonads by castration in the adult of either sex, or by destruction of ovarian function with radium or deep x-ray therapy, at whatever age it is performed, may lead to a stormy climacteric, difficult to control and certain to be prolonged. In the male this may be characterized by frequent drenching hot flushes and physical weakness which may seriously interfere with work. Implants of four 100-mg. pellets of testosterone repeated every six months will fortunately control nearly every case. In women, however, the results of treatment of the artificial menopause are often less satisfactory, and the dose of oestrogen may need to be increased until there is likelihood of troublesome uterine haemorrhage unless the uterus has been extirpated with the ovaries. Not only do hot flushes occur, but severe headaches and intense depressions are in some cases such prominent and distressing features that every gynaecologist should be reluctant to deprive his patient completely, by whatever means, of functionally active ovarian tissue whatever her age may be.

Certain post-climacteric conditions seem, from their specific response to gonadal hormones, to be manifestations of sex-hormone deficiency. In women the troublesome itching of kraurosis vulvae and senile vaginitis will be promptly relieved by a short course of moderate doses of oestrogen. A somewhat rare condition of hyperkeratosis of the palms of the hands and soles of the feet (keratoderma of Haxthausen), with sore and bleeding fissures, is seen in the post-climacteric period and responds well to similar treatment. In elderly men the skin tends to become thin and atrophic, and this is sometimes associated with intense irritation, which may be relieved by androgen therapy.

Sex Hormones in Gynaecology

The female sex hormones control the events of the endometrial cycle which culminate in "menstruation," or uterine bleeding resulting from complete shedding within a period of three to five days of the superficial layers of an endometrium stimulated first to grow under the influence of oestrogen and subsequently to secrete under the influence of progesterone. Uterine bleeding may occur, however, in association with a variety of endometrial patterns, and is not so much a reflection of endometrial histology as of the changes in calibre of the endometrial vessels. These changes may be induced by a number of factors, and bleeding may be produced by non-specific drugs such as "prostigmin" (neostigmine). Oestrogens and progesterone, however, exercise a specific influence on uterine haemorrhage. Two oestrogenic patterns may be identified — the scanty and always painless bleeding which results from oestrogen withdrawal, and the prolonged, irregular, and usually excessive bleeding from a "metropathic" endometrium which occurs when oestrogen secretion or administration is long-continued and unopposed. Not only is oestrogen capable of inducing bleeding either by

withdrawal or by continued administration or secretion, but it may also arrest it or prevent it from occurring when the oestrogen level is raised or kept high. These somewhat paradoxical effects may be explained by Fig. 1. Progesterone, on the other hand, can produce bleeding only from an endometrium which has previously been stimulated to grow or proliferate by oestrogen. Progesterone bleeding is characteristic of normal menstruation, and consists in complete shedding of the endometrium, or, as Fuller Albright describes it, a "medical curettage."

Probably the most dramatic result of the use of the sex hormones in gynaecology is the *haemostatic* effect produced by oestrogen in cases in which the bleeding has been prolonged and is alarmingly heavy. High doses given every four hours will arrest the haemorrhage in 24 to 36 hours. This treatment renders obsolete the scramble of a hurried curettage in an exsanguinated patient or the tragedy of a hysterectomy in a child with uncontrollable puberty bleeding. Eventual arrest of haemorrhage can also be achieved by opposing the action of oestrogen, and so lowering the bleeding level, by progesterone or androgen. Neither can be relied upon to stop the bleeding, however, in under four to five days, and they cannot be regarded, therefore, as effective emergency measures. Furthermore, progesterone in the process of performing a medical curettage will make the bleeding even heavier before it stops.

In a case of *metropathia* in which ovulation fails to take place the constant and unopposed oestrogen influence slowly builds up the typical hyperplastic, vascular, polypoid endometrium from which the flooding eventually takes place. The characteristic picture, therefore, is one of amenorrhoeic phases, variable in duration but seldom lasting less than five or six weeks, alternating with bouts of haemorrhage, which at times is heavy and may be prolonged. These metropathic floodings may be anticipated and prevented by giving progesterone to induce a medical curettage two to three weeks after cessation of the last bleeding episode and therefore before the haemorrhagic bout is due

FIG. 2.—Prevention of metropathic flooding by rhythmic induction of medical curettage by progesterone.

to begin. Subsequent progesterone-withdrawal bleedings may be induced at any convenient regular interval, such as every 28 days (Fig. 2).

Two other types of abnormal bleeding are commonly found—*intermenstrual bleeding* often associated with short cycles, and "*menorrhagia*," or excessive and sometimes prolonged bleeding occurring cyclically. Both are probably due to defective progesterone activity. Normally the appearance of progesterone in the second half of the cycle inactivates oestrogen, and the subsequent "menstrual" bleeding conforms to the characteristic progesterone pattern. Defective secretion of progesterone would therefore have two effects: (1) to fail to ensure the complete shedding which limits menstrual bleeding to four to five days, and (2) to permit active oestrogen to exert its characteristic influence on the bleeding pattern, leading to intermittent bleeding or heavy and relatively prolonged haemorrhage. One might therefore expect progesterone given in the premenstrual phase to prevent these types of functional bleeding from taking place. In practice, however, this is seldom the case, though the condition is often satisfactorily controlled by androgen given continuously in low doses for about two months. The intermenstrual bleeding may be treated by giving rather high doses of oestrogen daily up

FIG. 1.—Oestrogen bleeding levels.

to the immediate premenstrual phase, though this often tends to produce a heavier "period."

"*Premenstrual tension*" is a syndrome of nervous tension, irritability, and depression, accompanied by a bloated feeling of abdominal distension and sometimes severe headaches and mastalgia. It is probably also due to defective progesterone production with incomplete inactivation of oestrogen. The symptoms are sometimes relieved by administration of ethisterone or low doses of androgens in the second half of the cycle.

Amenorrhoea usually results from ovarian deficiency, whether primary or secondary to failure of pituitary gonadotrophin secretion, and leads to sub-threshold oestrogen levels or to endometrial resistance or atrophy. Oestrogens are unlikely to restore normal ovarian activity or to overcome endometrial resistance. If given in fortnightly courses they may produce withdrawal bleedings which will raise false hopes in the patient. If given continuously they may, by inhibiting the pituitary control of ovarian activity, render the chances of spontaneous recovery less likely. Amenorrhoea is almost always compatible with blooming health, though it is frequently, but not always, associated with non-ovulation and consequent infertility. Treatment should therefore be confined to attempts to induce ovulation in those women who are anxious to become pregnant immediately; or to cases in which the amenorrhoea is accompanied by distressing minimal symptoms or is secondary to other causes, such as malnutrition, obesity, or chronic disease, in which case it is the other causes rather than the amenorrhoea which should be treated.

As for the treatment of *non-ovular infertility*, it is claimed that oestrogen followed by oestrogen and progesterone may stimulate the pituitary to release its gonadotrophins in the correct proportions to induce ovulation. Three or four courses of low to moderate doses of oestrogen given daily for three weeks, and ethisterone in addition during the third week, with a week's interval between each course, may occasionally be followed by one or two ovular cycles during which it might be possible for conception to take place.

Dysmenorrhoea is a condition of multiple aetiology, but one of the causes of spasmodic dysmenorrhoea may be powerful uterine contractions leading to ischaemia of the muscle. These contractions may be due to progesterone, and it has been asserted that spasmodic dysmenorrhoea occurs only in ovular cycles. Certainly it seems to be true that administration of progesterone increases the severity of the pain. In a condition in which results are notoriously difficult to assess it is not surprising that claims have been made for relief in a fair proportion of cases no matter which sex hormone or gonadotrophin is given. Androgens in high doses might be expected to suppress ovulation by pituitary inhibition and so render the subsequent bleeding painless, but it has been reported that equally successful results have been obtained with almost homoeopathic doses. Moderate doses of oestrogen will also suppress ovulation and result in a scanty withdrawal bleeding which is always painless. It would seem, therefore, that the best hope of relieving dysmenorrhoea by endocrine therapy is to suppress ovulation or produce an oestrogen-withdrawal bleeding, and there is no reason to believe that such treatment will have any effect on cycles subsequent to the ones in which it is given.

Sex Hormones in Pregnancy

Progesterone

Progesterone obviously plays an important part in the maintenance of pregnancy, especially in its early stages. Immediately embedding of the fertilized ovum begins,

chorionic gonadotrophin is secreted to prolong the life of the corpus luteum. Towards the end of the second month of pregnancy a "peak" excretion of very high concentrations of chorionic gonadotrophin can be observed—presumably ensuring the continued secretion of progesterone before the placenta itself takes over its elaboration. There has been some confusion concerning the functions of progesterone in pregnancy. Some years ago it was believed that it exerted a "sedative" effect on the uterine muscle and was essential, therefore, for the prevention of abortion, especially in the first third of pregnancy before the embryo was firmly embedded and the placenta fully formed. It is now known that progesterone induces contractions, at any rate in the non-pregnant uterus, which are forceful and of high amplitude, and it has for this reason been suggested that it should never be administered either prophylactically in cases of habitual abortion or therapeutically in threatened abortion. It would be understandable that, at a time when abortion is actually threatened, administration of a hormone which induces forceful uterine contractions, if indeed it does so in pregnancy, might be harmful.

The most important role of progesterone in pregnancy, however, is undoubtedly in relation to the development of the decidua and the formation of the placenta. Therefore a deficiency of the hormone, especially in early pregnancy, might lead to resorption of an embryo not yet securely embedded or adequately nourished. In such cases there would seem to be ample justification for progesterone therapy as early in pregnancy as possible, or indeed even before pregnancy is known to have taken place. Administration of ethisterone in the second half of each menstrual cycle, once pregnancy has been planned, with an immediate implantation of progesterone pellets once a period has been missed, should ensure the early prophylaxis which is required. Tendency to abortion, however, may be due to many and various factors, and this empirical use of progesterone without selecting the cases in which there is a progesterone deficiency will clearly result in many failures. Unfortunately, present methods of estimating pregnanediol do not always help in demonstrating such progesterone deficiency so early in pregnancy.

Oestrogens

It is the oestrogens rather than progesterone which are intimately concerned with the state of the uterine muscle. In the non-pregnant uterus they increase muscular tone and induce frequent contractions of low amplitude. In pregnancy they sensitize the muscle to the oxytocic effects of posterior pituitary extract. Since the concentration of oestrogens rises throughout pregnancy to a peak just before parturition one might well marvel that any pregnancy should reach term if the uterine muscle were to become increasingly sensitive to oxytocin. The fact is, however, that oestrogens are excreted in two forms, as "combined" or "conjugated" oestrogens (chiefly in the form of oestriol glucuronide), and as "free" or "unconjugated" oestrogens. Combined oestrogens have no effect on uterine muscle, whereas free oestrogens sensitize it to oxytocin. It is only immediately before parturition that free oestrogens appear in significant concentration. The conjugation of oestrogens is a characteristic step in their metabolism during pregnancy, and would apply equally to extraneously administered oestrogens as it does to the endogenous hormones.

In the light of these observations it becomes easier to rationalize some of the phenomena of oestrogen therapy in pregnancy. Oestrogens will be effective only when parturition has begun or the foetus is dead. They are therefore useless in the induction of premature labour, but may be helpful in the treatment of uterine inertia and in the evacuation of the uterus in missed abortion.

Sex Hormones and the Breasts

The very considerable species variation in hormonal control of the mammary glands makes it difficult to analyse the role of individual hormones in this complex mechanism. In some animals, such as cows and goats, oestrogens alone are capable of stimulating the various stages of breast development up to and including normal lactation, so that it may be possible with a stilboestrol implant to obtain copious quantities of milk from a virgin heifer or barren cow. In other species oestrogens are required for duct development, progesterone for subsequent acinar development, prolactin for lactation, and posterior pituitary hormone for expression of previously secreted milk.

In the human species breast development may be abnormally induced in the male (gynaecomastia) either by oestrogens or simply by testicular deficiency. Oestrogens may induce satisfactory mammary development in women with congenital gonadal deficiency, though attempts to increase the size of the breasts in women with normally developed but nevertheless small breasts usually lead to disappointing results. Furthermore, prolonged application of oestrogens to the breasts, conveniently given by injection, in such cases may increase the tendency to develop generalized nodularity or fibro-adenosis ("chronic mastitis"). Whatever part the oestrogens may play in the aetiology of this condition, the symptoms of pain and tenderness experienced, particularly in the premenstrual week, are usually considerably relieved by small doses of androgen.

Though it is generally agreed that oestrogens exert a direct effect on breast development both in the non-pregnant and in the pregnant woman, it is also clear that through their action on the pituitary they may lead to inhibition of mammary function. Thus in the goat or in the cow it is possible for a relatively moderate dose of oestrogen to stimulate and initiate lactation, while a larger dose will inhibit the pituitary and suppress lactation. This pituitary inhibition is utilized in the case of the parturient woman who for one reason or another is not going to feed her baby. Relatively large doses given for about ten days, and started if possible before lactation has actually begun, will suppress the formation of milk and the painful engorgement of the breasts which accompanies it in the non-nursing mother.

Sex Hormones and Cancer

Evidence continues to accumulate concerning the intimate relationship between the sex hormones and tumours of the breast and uterus and of the prostate. In mice, mammary cancer can be induced by oestrogen administration in the males of a strain in which the females are cancer-susceptible. Women with carcinoma of the breast are five times more likely to have had a delayed menopause than women without breast cancer. If a woman with carcinoma of the breast becomes pregnant the tumour may grow at an alarming rate. Fibromyomas of the uterus and other structures have been produced in guinea-pigs, but not in other species, by administration of oestrogen. Carcinoma of the cervix has been produced in mice by giving oestrogens, and it has been suggested that the relatively high incidence of cervical cancer in multiparae is due to the fact that they have been submitted to the prolonged effect of their own oestrogens during pregnancy. Carcinoma of the prostate never occurs in eunuchs or eunuchoids: acid phosphatase appears in prostatic tissue only after puberty, but can be made to appear before this age by androgen administration. In patients with prostatic cancer and bone metastases it may be present in high concentration.

Nevertheless, despite these and many other suggestive observations, it is quite remarkable how few reports have

appeared of cancer of these organs following administration of the ipse-sexual sex hormone in human patients, and it would seem to be true of the human species that, though the influence of endogenous sex hormones may be an important factor in the development of certain neoplasms, administration of the ipse-sexual sex hormones does not lead to the development of such neoplasms.

On the other hand, administration of the contrasexual hormones may have profound effects on the progress of certain neoplasms, and in particular carcinoma of the prostate and breast. Oestrogens were first employed for this purpose in the treatment of carcinoma of the prostate. It had been observed that orchidectomy arrested the progress of the condition, and it was hoped that oestrogens might produce a "medical castration" by inhibiting the secretion of pituitary gonadotrophins, thereby leading to testicular atrophy. The arrest of the primary growth, the disappearance of the bone metastases, and the dramatic amelioration of the symptoms are now a familiar experience to anyone who has treated such cases with oestrogens.

More recently, isolated reports have appeared indicating that administration of androgens in high doses and over long periods leads to a regression of breast cancers, with relief of symptoms and disappearance of radiological evidence of bone metastases in the younger group—i.e., of patients under 60—whereas oestrogens are reported to produce similar results in the older age group. It should be emphasized that there is no evidence of cure in any of these cases, and that after a period of anything from a few months to as long as five years there is a recurrence of symptoms with renewed activity of the primary growth and reappearance of metastases.

The mechanism by which this amelioration is produced is quite unknown. It may well be due to inhibition of the gonadotrophic influence of the pituitary on the gonad, and in this connexion it is interesting to observe that similar results have been claimed for surgical castration both in the male with carcinoma of the prostate and in the female with cancer of the breast. Some intrepid surgeons have even gone to the length of suggesting partial extirpation of adrenal cortical tissue in order to deprive the patient as completely as possible of the ipse-sexual sex hormone. It has also been suggested that carcinoma of these secondary sex tissues can flourish only in an environment of normal or unduly prolonged sex-hormone secretion, and that by flooding the system with the contrasexual sex hormone this normal sex hormone pattern is disturbed, with arrest of the progress of the malignant condition.

The Protein-anabolic Effect of Androgens

Of the multiple excretion products of adrenal cortical activity (54 have so far been identified) three main groups have been classified. The first, which is exemplified by deoxycortone, controls water and electrolyte metabolism, and lack of this factor is mainly responsible for the symptoms of Addison's disease. A second group, the glyconic corticoids or 11-oxysteroids, is responsible for the conversion of protein precursors to glycogen, and is referred to as the S-hormone ("sugar" hormone) by Fuller Albright. There is evidence of excessive secretion of this hormone in Cushing's syndrome, which is usually accompanied by excretion of high concentrations of 11-oxysteroids in the urine. Albright seeks to explain the osteoporosis so characteristic of this condition on the theory that the conversion of protein to glycogen is selective and denudes the protein matrix of the bone on which subsequent calcification normally occurs. Other tissues selectively affected by this protein deficiency in Cushing's syndrome are, according to Albright, the skin, which becomes thin and atrophic as seen

typically in the legs and distal portions of the arms, and the peripheral blood vessels, which rupture easily and account for the bruises, ecchymoses, and "petechial haemorrhages." The third group consists of substances identified in the urine as the neutral 17-ketosteroids, which include all the adrenal androgens. According to Albright these are the substances responsible for nitrogen retention, and he refers to the group as the N-hormone ("nitrogen" hormone). S-hormone and N-hormone are mutually antagonistic, in so far as the latter is protein-anabolic and the former "anti-anabolic." Thus the effects of excessive S-hormone production, which depletes protein storage and leads to muscle wasting and weakness (as seen typically in Cushing's syndrome in the atrophy of the muscles of the buttocks and thighs), are similar to those due to deficiency of N-hormone, as indicated by lowered 17-ketosteroid excretion. The conditions associated with lowered or absent 17-ketosteroid excretion are pan-hypopituitarism (true pituitary infantilism and Simmonds's disease), eunuchoidism, Addison's disease—especially in women, though in men testicular androgens account for some degree of 17-ketosteroid excretion—and myxoedema. In all these disorders therapeutic administration of androgens leads to beneficial effects, though to a varying degree. Perhaps the most remarkable changes are seen in Simmonds's disease, in either sex, where an implantation of four to six 100-mg. pellets of testosterone overcomes the characteristic muscular weakness and is followed by an appreciable gain in weight, with increased muscular development and a positive nitrogen balance. In eunuchoidism there is also an increase in weight and muscular strength. In Cushing's syndrome the administration of androgens has been reported to have cured the osteoporosis. The therapeutic applications of this concept of the protein-anabolic action of androgens are still largely in the experimental stage, but it seems to be true in a general way that where the 17-ketosteroid excretion is low there is a tendency to muscular atrophy and weakness, and where it is high there is nitrogen retention and increased muscular strength. For instance, the "infant Hercules" with a prepubertal adrenal cortical tumour is not only bulging with muscle but is also abnormally strong.

Conclusion

The object of this paper has been to provide a brief account of the modern trends in sex-hormone therapy, with an attempt to rationalize the principles involved. It has not been possible to do more than wipe the dust off the cover of this rapidly expanding loose-leaf volume in the encyclopaedia of modern therapeutics. No references to original work have been cited, for such writings have not been consciously referred to. In holding myself responsible, therefore, for the views herein expressed I must run the risk of perpetrating such errors, both of omission and commission, as commonly accompany the necessarily dogmatic oversimplification to which a postgraduate lecture lends itself.

The West of England Child Health Group was formed in March, 1948, to foster co-operation between doctors and others who are concerned in the various aspects of child health. At the first meeting Professor A. V. Neale and Professor R. H. Parry opened a discussion on "The Integration of the Preventive and Curative Aspects of Child Health." At subsequent meetings, which are held at monthly intervals, discussions have taken place on a wide range of subjects, including gastro-enteritis, thoracic surgery, and upper respiratory disease. During the present session, 1948-9, the group has held a discussion on orthodontics and a clinico-pathological conference on mongolism. Dr. William Hobson (professor-elect of social and industrial medicine, University of Sheffield) gave an address on "Social Medicine."

ALTERNATING ORTHOSTATIC HYPOTENSION AND HYPERTHYROIDISM OF PROBABLE HYPOPHYSIAL- HYPOTHALAMIC ORIGIN

BY

F. VEGA DIAZ, M.D.

(From the Cardiological Department, Madrid General Hospital)

No final conclusions can be drawn from the following report, since considerations based on a single case lack sufficient foundation and must always be hypothetical.

Case Report

The patient, a married woman aged 24, was sent for examination of her circulatory system. Her father died at the age of 57 from a liver disease, her mother is alive and well, aged 57, and three brothers are also alive and well. One brother died at the age of 9 months, from an unknown cause.

Personal History.—Birth and early development were normal. She had measles and whooping-cough in early childhood, without complications, and very frequent attacks of sore throat, and has always suffered from constipation, anorexia, and asthenia. Menarche was normal, at the age of 14, with a normal menstrual cycle. From the age of puberty onwards, and for several years, she has suffered from dizziness. Perspiration has always been scanty. Immediately after menarche she found that on getting up after lying down for some time she always had a sensation of mistiness and progressive loss of vision, and a feeling that she was going to faint; she had to take hold of something quickly and sit or lie down again. These phenomena sometimes progressed to actual fainting, and appeared at odd times totally unconnected with the taking of meals or fasting.

These symptoms persisted until soon after her marriage at 22 and improved immediately afterwards, though at this time she was very nervous, suffered from palpitations, became thinner, and developed a slight swelling in the neck. She became pregnant six months after marriage. At that time the dizziness had disappeared; but, simultaneously with pregnancy and when the attacks of dizziness were becoming less frequent, there appeared other phenomena of endocrine origin: loss of weight—progressive though not excessive and less marked than before—trembling, and bad temper (she always had a certain tendency to depressive neurosis). The slight goitre persisted, and there was some fever, with attacks of palpitation and paroxysmal tachycardia. Her usual pulse rate was 90-100, and she sweated at night.

This syndrome was considered to be due to focal sepsis in the tonsils, and in the third month of pregnancy they were removed. In spite of this the neurosis persisted and the paroxysms of tachycardia continued. At this time the slight thyroid enlargement was noted and the basal metabolism was found to be +28, and a month later +37.

A corrected diagnosis of gestation hyperthyroidism was made, and treatment with methyl thiouracil was prescribed, but the patient did not notably improve, the B.M.R. remaining unaltered. She then had a normal confinement but did not nurse her baby. The slight hyperthyroidism continued. Treatment with methyl thiouracil, alternating with Lugol's solution, was now instituted and the signs and symptoms of hyperthyroidism disappeared. She put on weight, though not enough to compensate for the previous loss; the thyroid became normal in size and the attacks of tachycardia gradually disappeared. Surprisingly enough, however, just as she was recovering from the hyperthyroidism and was getting well again, she noticed a return of the postural dizziness—i.e., the orthostatic hypotension syndrome reappeared after having been latent, or having disappeared, during the phase of hyperthyroidism.

Clinical Examination.—The patient was of asthenic constitution, with dry skin, waxen pallor, and prominent superficial veins. The mouth was healthy, without dental sepsis. The lungs were normal. The heart was normal on palpation and percussion. Cardiac sounds were lively but normal, and the pulse