ENDOCRINES IN THEORY AND PRACTICE

This article is one of a series on Endocrinology contributed by invitation

HORMONE DEFICIENCIES IN THE MALE

BY

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The Male Hormone

The testicle was the first organ in the body in which the existence of an internal secretion was demonstrated. Bertholdt's transplantation studies in the capon, as long ago as 1849, might indeed be considered the pioneer experiments in endocrinology. In spite of this early start it is only within the last few years that the testicular hormone has actually been isolated. That this should have happened long after other organs of internal secretion have yielded their active principle to the biochemists' methods of extraction is due in great part to the fact that, whereas such glands as the thyroid store large amounts of hormone in concentrated form, the quantity of internal secretion within the testis at any given moment is very small. F. C. Koch has estimated that to obtain one capon dose of testicular hormone anything from 50 to 100 grammes of testicular tissue are required. Yet in human therapy the amount of effect produced by one capon dose is negligible, and it would be necessary in order to produce an effect to measure the amount of secretion given not in capon doses but in milligrammes of pure secretion. When it is realized that according to Koch a whole ton of bull's testicle contains only 100 to 150 milligrammes of pure hormone it will not seem surprising that the therapy of the testis lags woefully behind that of the thyroid.

To Butenandt must be given the credit of first having isolated in pure crystalline form the male sex hormone. This he achieved in 1931, not, as others had attempted, from the testicle itself, but from human urine, obtaining 15 milligrammes of a substance he called androsterone from 25 litres of urine. Eventually sufficient of this pure product was extracted to permit of analysis; it yielded the formula $C_{19}H_{30}O_2$. Later E. Laqueur and his associates succeeded in isolating the hormone from the testis itself (testosterone), and Ruzicka, in preparing what was apparently an identical substance, from cholesterol (androsterone and dehydro-androsterone).

The chemistry of these various products is still debated, as is also the question whether the testis may not form more than one hormone. Moore, writing last year, says that, in spite of the fact that different methods of extraction yield what is apparently the same product, there are reasons for believing that the testis secretes more than one active principle. Should this turn out to be the case it may explain the confusion that has long existed on the subject of the source of the internal secretion of the testis. Of late years Ancel and Bouin's conclusions that the interstitial cells of Leydig were alone responsible for the formation of internal secretion have been widely criticized, many authorities believing that the cells of the seminiferous tubules furnish an internal as well as an external secretion. This subject, although of great interest, is, however, outside the scope of a paper that aims only at giving a general survey of male hormone therapy.

Of the male hormone deficiencies with which medical men may be called upon to deal the commonest are the various deficiencies that are grouped under the heading of eunuchoidism, arrest of the normal descent of the testis (undescended testicle), and failures in spermatogenesis (azoospermia, oligozoospermia, and necrozoospermia). These conditions will now be considered.

Eunuchoidism

From the outset it must be confessed that attempts to treat eunuchoidism either by the administration of hormones or by means of testicular grafts have met with but little success. This is due partly to the fact that in the majority of cases eunuchoidism is not a pure condition but is associated with deficiencies in other members of the endocrine circle, and especially in the pituitary. Its treatment therefore calls for multiple organotherapy and for the administration of active principles which we do not at present possess in sufficient quantity for the purposes of medicine. It is also explained by the practical difficulty of obtaining enough testicular hormone to exert a therapeutic action on the human body. Professor Koch once confided to the writer that with all the abattoirs of Chicago at his disposal he could only obtain enough male hormone for laboratory experiments, and that he saw little hope of sufficient quantities ever being available for human therapeutics. Since this remark was made other sources of male hormone have been discovered, but unfortunately all the methods of extraction are so expensive that many years are likely to pass before testicular hormone therapy becomes practicable. It is probable that when eventually this is the case the source of supply will be from sterol by means of synthetic degradation methods.

In the meantime various commercial preparations, labelled "testicular extract," will be administered by the medical profession to their patients in a spirit of optimism that may sometimes help the patients psychologically and can certainly never harm them. Even when the brand of male hormone selected for injection contains the active principle of the testicle the amount given is so small as to exert no appreciable influence on the body. But as often as not the testicular extract, as well as being inert, is administered orally, by which route at least ten times as much hormone would be required in order to produce an effect.

Undescended Testicle

Of the hormonal treatment of undescended testis it is possible to speak with greater optimism. The experimental work of Evans, Smith, Engel, Aschheim, and many others has shown that a gonad-stimulating principle is present in the anterior lobe of the pituitary, controlling the activities of the ovaries and testis. Other experiments suggest that this principle is twofold: one acting chiefly on the germ cell and the other on the thecal cells of the ovaries and the interstitial cells of the testis. Aschheim and Zondek's subsequent discovery that a gonadotropic hormone similar in action to that produced by the pituitary could be extracted from pregnancy urine has much facilitated work on this subject. By providing a source from which gonadotropic hormone can with less difficulty be obtained they have indeed brought what was previously

an interesting scientific observation within the realms of practical therapy. Engel in 1932 led the way by proving that injections of extracts of anterior pituitary or of pregnancy urine into immature monkeys brought about the descent of the testis into the scrotum by the fourteenth day. Since then a large number of writers have published the results of this treatment in human beings. In a paper appearing in the *Lancet* of last year A. W. Spence and E. F. Scowen recorded the results of treating thirty-three patients suffering from imperfectly descended testis with 500 rat units of pregnyl twice weekly. In eleven out of the nineteen unilateral cases the testis descended, and in six of the bilateral cases both testes reached the scrotum: in four only one did so. E. McLellan later published similar results, and at the same time commented on the type of case that was more likely to respond to hormonal treatment. His conclusions were that hormonal therapy had a better chance where the undescended testicle was small and undeveloped, but that when the testicle approximated to the normal orchidopexy was the treatment of choice.

Treatment of Aspermatogenesis

Laboratory work on the gonadotropic hormone of the anterior pituitary strongly suggests that these consist of two factors: one of these, prolactin A, in the female brings about maturation of the Graafian follicle and the production of oestrin; the other, prolactin B, converts the follicles into the corpora lutea, inhibits the production of oestrin, and stimulates that of progesterone. In the male prolactin A acts on the tubules and stimulates spermatogenesis, whilst prolactin B works on the interstitial tissue of the testis, causing it to hypertrophy. Pregnancy urine, from which gonadotropic hormone for clinical purposes is usually obtained (pregnyn), contains much larger quantities of prolactin B than of prolactin A. Consequently the action of pregnyn on the development and descent of the testis is far more marked than any action on its tubules. Indeed it is controversial whether pregnancy urine extracts have any effect on spermatogenesis, and it is quite likely that we may have to wait until sufficient quantities of prolactin A can be obtained from animal pituitary glands before we can hope to influence materially cases of aspermatogenesis. This at any rate is the lesson to be derived from experiments in hypophysectomized animals, in the case of which anterior pituitary extracts have proved far more effective than urinary extracts in re-establishing the activity of the tubules. In the meantime we are compelled to treat these cases with the extracts that are at present available. In this connexion it should be remembered that some cases of male sterility are due not to a deficiency of prolactin A but of thyroid. These will rapidly respond to the use of small doses of that gland.

Endocrine Therapy in Prostatic Enlargement

Recently attention has been directed once again to the question of the relations of the male hormone to enlargement of the prostate, and attempts are being made to treat this condition by testicular extracts. This therapy is based on the assumption that enlargement is the result of a disturbance in the normal balance existing between the secretions of the testis and those of the pituitary. Niehans, in the endocrinological survey preceding his paper on the treatment of prostatic enlargement by operation Steinach II, has gone so far as to state categorically that enlargement of the prostate is due to a preponderance of the internal secretion of the Leydig's cells over that of the cells of Sertoli, with secondary reactions on the pituitary, and that if the balance between these secretions

can be restored the prostate shrinks. On the shifting foundations of as yet unconfirmed experiments he has built up a complicated structure in order to support his practical findings, that ligature operation brings about a shrinkage of the enlarged prostate. Unfortunately our present endocrinological knowledge is so limited that logical arguments for or against Niehans's operation have little value. Not only is the pathology of prostatic enlargement itself a matter of doubt, but the endocrinological foundations on which he builds cannot support the weight he places on them.

The only recent positive finding on the subject of the pathology of prostatic enlargement on which we can put reliance is Lacassagne's observation that if oestrin be injected into mice certain changes occur in the prostate. These changes consist of the conversion of the single layer of cells lining the prostatic tubules into stratified epithelium and distension of the alveoli by masses of keratin. These modifications in the prostate are often followed by retention of urine, hydronephrosis, and suppuration in the contents of the distended prostate. H. Burrows and N. M. Kennaway have noted the same phenomena after applying oestrin to the skin of mice, and Parkes and Zuckerman proved that similar changes may be produced in the prostates of monkeys. Laqueur has thrown further light on the subject by showing that these changes are more likely to occur in the absence of male hormone, being more readily produced in young castrated mice and rats. He has also shown that mice can be protected from the increase in size of the prostate by simultaneous injections of male hormone. He therefore suggests that in prostatic enlargement there exists an improper balance between the male and oestrogenic hormones in the body. Acting on this suggestion, he and a number of other investigators have attempted to treat enlargement in human beings by means of repeated injections of male hormone. Laqueur himself reports favourably on 133 cases so treated, but other workers have obtained less definite results.

At the present moment this matter is being investigated under the auspices of the Medical Research Council. These experiments are still in progress, and it would be rash on the part of one who is engaged in this work to foretell the future. I cannot, however, avoid expressing the opinion that when the results of these experiments are eventually published they will not reveal that any dramatic step forward has been taken in the hormonal treatment of prostatic enlargement.

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A. J. Ballantyne and I. C. Michaelson (*Brit. J. Ophthalm.*, January, 1937, p. 22) record a case of perivasculitis retinae in a man of 30. The clinical and pathological details, aetiology, and diagnosis are carefully discussed, and an analysis of sixty-eight similar cases is given. This condition occurring in young adults is usually confined to the veins, may be shared by the cerebral vessels, and may well be the basis of recurrent vitreous haemorrhages in adolescence (Eales's disease). Though usually stated to be tuberculous, perivasculitis may be associated with thrombo-angiitis obliterans. The case reported appeared to be toxic in origin.