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The Endocrine Control of the Prostate

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FROM the turn of the present century until some five or six years ago, the prostate was an organ whose physiology was little discussed and even less investigated, and whose departures from the normal were events to be treated only by direct surgical methods. Within the past few years, facts about the endocrinology of this organ have multiplied so fast as to suggest a revision of present ideas on the treatment of one of the commoner of prostatic ailments—benign enlargement—and they have also achieved that measure of certainty which justifies their presentation to those whose interests in the organ are not purely scientific. Yet what is now recognized as an endocrinological approach to problems of the prostate is no new departure. Surgeons themselves had turned the physiological knowledge of the nineteenth century to account in the treatment of enlarged prostate by what to-day could well be described as one of the more drastic of endocrinological treatments —castration. This earlier phase in the endocrinological treatment of prostatic disorders, which came to a summary end about 1900, is no less interesting and instructive than that which has developed in recent years.

CASTRATION AS TREATMENT FOR PROSTATIC OBSTRUCTION

Enlargement of the prostate had been recognized as a clinical entity long before the dependence of prostatic growth on testicular function appears to have been appreciated. Samuel Collins, for example, described the ailment, somewhat vaguely it is true, as far back as 1685, attributing it to "indulgence in venery," and speaking of the presence of many "Hydatides—vesicles full of Liquor" in the "inward Penetrals" of the organ. Morgagni, during the earlier half of the eighteenth century, was also certainly aware of the disorder, and his extensive work on "The Seats and Causes of Diseases" (1769) contains numerous references to it, to observers other than himself who had described it, and to the part played by prostatic enlargement in obstructing the flow of urine. In 1786 John Hunter published his "Observations on the glands situated between the rectum and bladder, called vesiculæ seminales," in which he wrote that "the prostate and Cowper's glands, and those of the urethra, which in the perfect male are soft and bulky, with a secretion salt to the taste, in the castrated animal are small, flabby, tough and ligamentous, and have little secretion." Whether or not he was the first to make this observation I do not know. The practice of castration, both as it applies to man himself and to his domestic animals, goes back to time immemorial, and it seems possible that the fact which

Hunter recorded had not been entirely missed before he drew attention to it; it seems equally possible also that the cyclical variations in the internal reproductive organs of seasonal male mammals, and the obvious dependence of the accessory reproductive organs on testicular function, had not escaped notice until he remarked on them. This dependence was not established scientifically, however, until 1849, when Berthold showed that the effects of castration in cocks can be prevented by means of testicular grafts, and thus uncovered for the first time a specific hormonal mechanism.

When one considers the slender rational basis demanded by any form of treatment in the earlier phases of its history, it seems remarkable that the obvious implication of these facts, i.e. that enlargement of the prostate could perhaps be corrected by means of castration, was not realized. The implication, however, was not grasped, and further facts pointing in the same direction continued to multiply. In the thirty odd years which followed Berthold's announcement several papers appeared, recording the observation that the prostate of eunuchs, for example the Skoptzys of Russia, is smaller than that of normal men; even this additional evidence does not appear to have pointed to the obvious inference.

In 1877, and again in 1882, a surgeon named Tupper performed the operation of castration, and in doing so found that he had relieved prostatic obstruction. The primary purpose of both operations had been to effect a radical cure for testicular neuralgia, and at the time Tupper was in no way moved to publish the results of his treatment.

It was not knowledge of the gonadal control of prostatic growth that led to the next, and first deliberate, operation of castration for prostatic hypertrophy, but the fact that oöphorectomy was at that time being performed for the treatment of uterine fibromyomata, a form of treatment that seems to have been well established in the seventies of last century. In Galabin's "Students' Guide to the Diseases of Women," published in 1879, oöphorectomy is referred to as a reputable method of treatment for uterine fibroids, and its basis, as revealed in contemporary literature, is the fact that uterine fibromyomata are frequently resorbed after the cessation of ovarian function at the menopause—the purpose of the operation thus being to produce an artificial menopause. White, of Philadelphia (1893), who is usually credited as having been the first to suggest castration for the treatment of prostatic enlargement, was activated by the idea of the homological identity of the prostate and uterus. "It occurred to me some time ago," he writes, "that possibly if the analogy between uterine fibromyomata and prostatic overgrowth was a real one, castration might have the same effect upon the latter that oöphorectomy does upon the former, and cause a shrinkage or atrophy which would result in the practical disappearance of the obstruction." His suggestion had, however, the added strength of a clear realization of the part played by the testes in the growth and maintenance of the prostate. Ramm, of Christiania, was independently activated by the same idea, and was the first to castrate patients with the deliberate intention of relieving prostatic obstruction (1893).

It is symptomatic of the development of the idea that castration would prove an effective treatment for enlargement of the prostate that, in its earlier phases, no one worker was aware of the activities of any other in this field. Tupper, whose work was first recorded by Walker in 1895, was, like Ramm, unknown to White, while according to Fremantle (1897), White's suggestion had already been put forward in 1885 by Launois. But the response to White's paper seems to have surprised even its author. Surgeons the whole world over took up the operation, and records of their successes and failures began to multiply in the medical literature. Some cures were undoubtedly obtained. Variations on the theme of castration were also suggested, and unilateral castration, ligation of the whole spermatic cord, and excision of the vas, were variously performed on patients suffering from enlargement

of the prostate. But opposition to all these procedures soon outstripped the enthusiasm of their protagonists, and they succumbed, within a few years of their institution as treatment for prostatic hypertrophy, to the arguments which raged about the question of their value.

It would be idle to attempt to evaluate the merits of the controversy.[1] White had originally claimed that the operation had a very low mortality. His opponents refused to accept this, or his insistence that the majority of deaths occurred in spite, not because, of the operation. Fremantle could write of this phase of the argument: "When two authorities from the same table of statistics give the rate of mortality for a given operation respectively as 7% (which is White's final estimate for castration), and 18·2% (which is Cabot's) or 31% (White's estimate of Moullin's tables of prostatectomy), and 20%, it is high time for the novice to turn his back on the controversy." Argument was no less intractable about the supposed insanity which castration caused, or about the amelioration of the symptoms for which the operation was designed. It is enough to say that White himself, reviewing the evidence in 1904, gave as his opinion "that castration and vasectomy are likely to occupy a more and more restricted field in the treatment of prostatic hypertrophy." But events proved that White was sanguine even in this modest view. Castration for the treatment of enlarged prostate disappeared entirely from human surgery. It survives to-day only in veterinary medicine, where dramatic success is still claimed for it (Hobday, 1924).

It is not difficult to understand why castration had such a brief vogue in the treatment of prostatic hypertrophy. In the first place, the treatment was suggested at a time when the technique of both perineal and suprapubic prostatectomy was being rapidly perfected, and a radical cure was obviously to be preferred to one which, if less severe surgically, was more questionable in its results. In the second place, there was no detailed rationale for the procedure, and little realization of the nature of the influence exercised upon the prostate by the testes. Fremantle, whose views are presumably representative of those of the period, doubted the existence of testicular hormones. "While admitting," he wrote, "that the general effect of sexual growth at puberty may prove in the future to be attributable to the influence of an internal secretion, we must still maintain that the connexion between the testes and the secondary sexual glands and especially the prostate, even if assisted by such a secretion, is primarily of a nervous character." To-day we know that his emphasis was misplaced. In so far as it is possible to characterize this earlier phase in the endocrinological treatment of the prostate, one might justifiably describe it as a phase in which practice far exceeded theory.

The Physiology of the Male Reproductive Organs

Accurate knowledge of the physiology of reproduction dates almost entirely from the beginning of the present century, and it was a strange accident of fate that the abandonment by surgeons of their interest in the endocrinology of the prostate should have coincided with an increase of interest on the part of biologists in the functions of the testes and in the physiology of the accessory reproductive organs. Studies of reproductive rhythms in every class of vertebrate established beyond doubt the relation of the functional phases of both the accessory reproductive organs and secondary sexual characters to the activities of the gonads. Removal and implantation of gonadal tissue in amphibia, birds, and mammals, showed further that the relation was a one-sided one, to the extent that testes and ovaries could continue to function in the absence of the accessory reproductive organs, whereas the activity of the latter was largely dependent on the well-being of the gonads.[2] In 1911 the story was carried still further by Pezard, who corrected the

[1] For data and references to the literature *see* Fremantle, 1897; White, 1904; Thomson-Walker, 1930.

[2] For reference to the literature, *see* Moore, 1932.

effects of castration in two capons by the intraperitoneal injection of a suspension of macerated hog testis. Sixteen years later, in 1927, McGee obtained for the first time potent extracts of "male hormone" from fresh bull testes.

The phase of research which I have so briefly reviewed showed clearly that the gross size of the male accessory reproductive organs is controlled by the secretions of the testis. For example, the Wolffian ducts undergo considerable involution when the testes of seasonal amphibia and birds pass into their inactive phase, or when they are removed by castration. Corresponding changes affect the accessory reproductive organs, including the prostate, of mammals. It was also definitely established during this period of investigation that the accessory reproductive organs can be restored to a functional size by replacement therapy, i.e. either by means of gonadal transplants or extracts, or by the administration of preparations of pure "male hormone." The bio-assay of male hormone depends upon this fact, and on the ability of preparations of the hormone to cause the comb of a capon, or the prostate and seminal vesicles of spayed rats and mice, to grow. The size of the epithelial cells in the rodent prostate and seminal vesicles has also been suggested as an index of male hormone action.

Crystalline male-hormone compounds have been both extracted from urine (Butenandt, 1931), and synthesized from cholesterol (Ruzicka, 1935). Some ten of these compounds have been prepared; they have varying potencies (Deanesly and Parkes, 1936a), the most active of the series apparently being testosterone and its esters, a substance first isolated by David and his co-workers (1935).

The Steinach II Operation

The newer knowledge of male reproductive physiology found its first clinical application by way of the operation of vasoligature, which had been widely advocated by Steinach for the purpose of "rejuvenation." According to Niehans (1936a) the immediate stimulus came from a report by Romeis to the effect that he had succeeded in reducing the size of the prostate in an elderly man by implanting into him the testis of a young man of 22. Steinach, as is well known, has for years claimed that the internal secretions of the testis can be increased by ligaturing the vasa deferentia. Niehans accordingly performed this operation in cases of prostatic enlargement, but with no success.[1] The basis for this treatment was apparently the general notion that a relation exists between the time of onset of benign prostatic enlargement and the beginning of a diminution in the secretion of male hormone, and the corollary belief—which Romeis' claim supported—that the enlargement can be arrested, and even corrected, if a high level of male hormone is maintained.

In order to secure this end, Niehans in 1927 resorted to the Steinach II operation, in the hope that occlusion of the vasa efferentia of the testis would lead to a higher secretion of male hormone, and a consequent relief of prostatic obstruction. Niehans claims to have succeeded in his aim in nearly 400 cases. Elliot-Smith (1936) has also been successful in the treatment of more than half of twenty patients by the same means, whereas Winsbury-White (1936) offers a warning about the possibility of acute retention and uræmia following the operation.

Until more surgeons have tested this method of treatment, it is obviously idle to pass any judgment on Niehans' claims. It is not, however, idle to examine the rationale by which he was guided, for here we are on surer ground.

When Niehans began his treatment in 1927, his approach was purely empirical, and considering the state of knowledge at the time, its theoretical basis could not have been more profound than that which I have already outlined. It is true that

[1] Niehans' description is ambiguous, and it does not indicate whether he or someone else first performed the operation for the specific purpose of relieving prostatic obstruction.

in the two papers published by him this year (1936a, 1936b), Niehans attempts to harmonize with his primary thesis many facts which have become available only during the past two or three years, and to construct an imposing, if not very convincing, scientific foundation for his procedure. These additions do not, however, alter the fundamental fact that Niehans claims to raise the male hormone-output of the testes by his treatment—and it is that issue alone which we have to consider. Needless to say, the merits of the Steinach II operation in the treatment of benign enlargement of the prostate will be decided, not on any theoretical basis, but on its practical value.

The evidence regarding the effects on the testis of vasoligature has been admirably summarized by Moore. On the one hand there are the followers of Steinach, mostly clinicians (*see* Steinach, 1936), who believe that ligature of the vas leads to degeneration of the germinal epithelium, and to an increase in the number of interstitial cells—by which it is believed male hormone is secreted. Almost all acceptable laboratory studies controvert this view. As Moore (1935) writes: "The facts are that closure of the outlet passages does not of itself lead to germinal epithelium destruction, that it is questionable whether hypertrophy of the interstitial cells occurs, and that there is no available evidence that more hormone is secreted." The same strictures apply to the view that the effect claimed by Steinach and Niehans is secured by ligature of the vasa efferentia. Van Wagenen (1924, 1925), Oslund (1926), and Cunningham (1928) have all found that after the operation the interstitial tissue either appears normal, or at most *relatively* increased owing to the degeneration of germinal tubules. Additional evidence in favour of these findings is, as Moore points out, the fact that spermatogenesis may occur in testicular grafts, and the fact that it is known to occur in testes whose vasa efferentia are congenitally missing.

Evidence provided by laboratory workers is thus significantly opposed to the theory with which Niehans backs his practice. In the circumstances it is unfortunate that, in spite of the large numbers of patients he has treated, he has so far failed to supply any data showing that his procedure does raise the level of male-hormone secretion. And it is equally unfortunate that the rationale for the treatment should be sufficiently vague for some workers (e.g. Landau, 1934) to believe that the relief of prostatic obstruction which follows the operation is due, not to any hormonic action, but to a reflex relaxation of the sphincter at the neck of the bladder, following stimulation, by the ligature, of a ganglion situated in relation to the vasa efferentia.

The Treatment of Benign Enlargement of the Prostate with Male Hormone

Niehans was not the only one to be struck by the idea that, since benign enlargement of the prostate usually begins during a phase of life that has been called "the male menopause," it should be possible to correct the condition by administering male hormone. The attentions of Lower (1933, 1936), and McCullagh (1936) were turned in the same direction, but for very different reasons. According to them, the enlargement is a consequence of the imbalance between two separate normal testicular hormones, the one secreted by the seminiferous tubules, and the other by the interstitial cells. It is the latter hormone which they believe is responsible for the growth of the prostate and the other accessory reproductive organs, whereas the hormone of the germinal epithelium ("inhibin") is restricted in function to preventing the anterior lobe of the pituitary from becoming gonadotropically hyperactive, and thus stimulating the secretion of too much interstitial testicular hormone, which in turn would cause prostatic hypertrophy. The basis

for their view is a number of experimental procedures that have the effect of enhancing one testicular function (promotion of growth of the accessory organs) and depressing another (inhibition of pituitary hyperactivity). It could hardly be said, however, that the existence of two testicular hormones, so opposed in function, is believed in by more than a few workers, and at the same time it should be pointed out that there are a number of observations which conflict with the experimental data adduced by Lower and McCullagh. McCullagh freely admits the necessity for repeating and confirming nearly all the work on which their views are based.

Whatever the answer to the question of the reliability of their experimental data may be, it is perfectly plain that the views of Lower and McCullagh conflict with the rationale of Niehans' treatment. According to Lower and McCullagh, enlargement of the prostate is caused by an excess of the "interstitial" male hormone, indirectly determined by a diminution in the presumed hormone "inhibin" following on degenerative changes in the germinal epithelium. This hypothesis is entirely speculative, but their treatment is either to decrease the secretion of the interstitial male hormone,[1] or to administer, in some way, the other presumed testicular hormone "inhibin." On the other hand, if any success Niehans' treatment may have achieved is due to an endocrine factor, the obvious possibility (for the moment disregarding the actual experimental evidence) is that it is due to an increased secretion of the interstitial male hormone. The disharmony between these opposing theories appears, however, to be of little consequence from the practical point of view. Lower claims to have relieved prostatic obstruction in 48 of 76 cases by the administration of "inhibin"—which, never having been isolated, had to be administered in the form of the equivalent of 60 grm. of fresh beef testicular material daily. It is quite clear from his description that this material may have contained at least as much male hormone proper as the problematical "inhibin," and it is likely that the improvement in the 48 cases, if not due to general management and suggestion, was due to its inclusion. It is necessary to remark, however, that the improvement was entirely symptomatic, for the size of the prostate had, as a rule, not altered, nor had any histological changes been induced (the method of obtaining histological material is not stated).

Niehans' treatment may safely be regarded as having been, at least in the earlier phases of its history, a purely empirical one. Equally empirical considerations inspired van Cappellen (1933, 1936) some years ago to treat patients suffering from enlargement of the prostate with such preparations of male hormone as were then available on the market. Since, as van Cappellen writes, "prostatic hypertrophy occurs at an age which is sometimes called the male climacterium and at which the sexual function begins to decrease, it was obviously desirable to try to find a connexion between these two conditions." The original suggestion apparently came from Professor Laqueur of Amsterdam; its rationale, like that of Niehans' treatment, is opposed to the view put forward by Lower and McCullagh. Van Cappellen has treated some fifty patients suffering from prostatic obstruction with a male hormone preparation, using doses of up to 20 capon units (equivalent to 0·66 mgm. androstanediol) daily. He claims that this treatment has given good results from the symptomatic point of view, but points out that he has only once observed a diminution in the size of the gland. He also states that he has achieved good results in the treatment of prostatic enlargement in dogs.

[1] The belief that male hormone proper (presumably some substance closely related to, if not identical with, testosterone) is secreted by the interstitial cells of the testis is a basis of Lower and McCullagh's theory. The evidence both in favour of, and against it, is amply summarized by Moore (1932), and in general it may be said that, so far as mammals are concerned, the view is strongly supported by the experimental data. A most important observation is that the accessory reproductive organs may be altogether normal when the germinal epithelium of the testes has completely degenerated (as in experimental cryptorchidism).

I do not wish to make any comment on van Cappellen's claims other than that the amounts of hormone he used would hardly have had much effect on the prostate of an immature monkey. A great deal more has to be done clinically before it can be decided whether the improvement reported with these small doses is due to actual physical changes in the prostate or to elements of suggestion and general management.

The Effect of Œstrogenic Substances on the Prostate

The questions I have so far considered in this paper have been arranged in their proper historical sequence. The matter which I propose discussing now is the effect that œstrogens have upon the growth of the prostate, and it concerns a phase of research which, in my opinion, is of the greatest clinical importance.

To my knowledge no experimentalist has ever succeeded in causing abnormal prostatic growth with a true male hormone. Such treatment may make the prostate grow bigger than normal, but histologically the prostate shows no pathological changes (Callow and Deanesly, 1935). In 1933 Lacassagne, while investigating the carcinogenetic powers of certain sterols, found that œstrone, the so-called female sex-hormone, administered to mice over relatively long periods (five months) produces considerable growth of the dorsal prostatic lobes, leading to retention of urine and hydronephrosis. These initial observations were independently confirmed by de Jongh (1933), and by Burrows and Kennaway (1934), and immediately received further confirmation in the work of David and his co-workers (1934), and of Korenchevsky and Dennison (1934).

The initial response of the prostate of the mouse to œstrin treatment is a reduction in the number of glands in the dorsal lobe, and an increase in the fibro-muscular stroma. The glandular epithelial cells then begin to multiply, and become metaplastic, the cuboidal cells being replaced by a stratified and rapidly desquamating epithelium. As the process continues the glandular alveoli become distended out of all recognition, and leucocytic infiltration occurs.

The epithelial and fibro-muscular changes are not restricted to the dorsal prostatic lobes (coagulating glands), but spread as treatment continues (*see* Burrows, 1935a). The response of the coagulating glands is followed by that of the seminal vesicles, and then in turn the ejaculatory ducts and vasa deferentia, the other lobes of the prostate, and the urethra and urethral glands become affected. As a rule, too, the epithelial changes begin in the glandular structures nearest the urethra.[1]

Within a very short time of the publication of Lacassagne's findings, the effects of œstrogenic substances on other male mammals were investigated. The first to be studied were the rhesus and Barbary macaques. I shall deal with these studies shortly. Then followed the dog (de Jongh and Kok, 1935), the ground squirrel (Wells, 1936), and the guinea-pig (van der Woerd, 1936), the prostates of which in general react like that of the mouse.

The experimental production of pathological growth of the prostate in mice soon suggested to its investigators that benign enlargement of the prostate in man may also be an effect of stimulation by an œstrogenic substance. Attention was drawn to the fact that both the experimental changes in the rodent and the spontaneous changes in man begin in the most cranial part of the prostate—probably a dangerous homology in view of the fact that the human prostate has no coagulating glands—and attempts were also made to homologize the experimental histological effects in

[1] It is interesting to note that these very pronounced effects were not observed by Moore and Price (1932), who conducted an extensive investigation into the effects of œstrin on normal and castrated male rats. Presumably their animals failed to show these changes because of too low dosage and too brief periods of injection. The fact is of importance, since Moore and Price were led to formulate the principle that "gonad hormones stimulate homologous accessories, but are without effect upon heterologous accessories." This hypothesis requires modification in view of the newer findings to which I have referred (*see* Zuckerman, 1936a, 1936b).

rodents with the usual pathological changes in man (e.g. Burrows, 1935b; de Jongh, 1935a). In general, however, it is impossible to see in the experimental changes in the rodent prostate an exact correspondence to the changes in the "simple" enlarged human prostate. Data yielded by studies of the dog on the other hand provide indisputable evidence that the prostate may "naturally" undergo a process of benign enlargement under the influence of an œstrogenic substance elaborated in the body.

The dog happens to be the only familiar mammal other than man known to suffer from spontaneous enlargement of the prostate. As a general rule the enlargement of the canine prostate, which may be considerable, takes a form of a simple glandular hyperplasia, but in one of a series of ten specimens studied, the histological appearances were identical with those of the œstrone-stimulated prostate (Zuckerman and Groome, 1936). In this case, therefore, there is every reason to suppose that the benign enlargement resulted from the action of an œstrogen, and this instance provides strong support for the view that "simple prostatic hypertrophy" in man may also sometimes be a result of œstrogenic stimulation.

Such a view naturally presupposes that the male organism elaborates an œstrogenic substance, and it is in fact the case that the vertebrate testis produces both "male" hormone and an œstrogenic hormone. In the case of birds this fact is revealed both in seasonal plumage changes, and in other characteristics of the feathers (Callow and Parkes, 1936). In the stallion the œstrogenic substance secreted by the testis appears to be a simple derivative of œstrone, but whether or not an œstrone derivative is also secreted by other mammals, including man, is not known. What is known is that some of the compounds of the androsterone-testosterone series are œstrogenic (Butenandt and Kudszuz, 1935; Deanesly and Parkes, 1936b), and the œstrogenic potency of these substances may therefore be responsible for benign enlargements of the human prostate.

The thesis I am advancing is that normally the male organism produces male hormone proper and an œstrogenic substance in a ratio so balanced to each other that the œstrogenic powers of the latter are inhibited, and so that its action, if any, is that of a synergist to the male hormone in the maintenance of the functional condition of the epithelial and fibro-muscular tissues of the reproductive organs (*see* Freud, 1933; Korenchevsky and Dennison, 1936). In middle or later life the balance becomes altered in certain individuals so that the œstrogenic substance becomes dominant. It then exercises its own power to produce changes in certain sensitive tissues, which result in enlargement of the prostate.

Since experimental work of the necessary kind is out of the question with human subjects, it is perfectly obvious that this hypothesis cannot be tested, so far as man is concerned, in the way that it has been in the case of the dog. Investigation of various species of monkeys has, however, yielded information which adds strength to the theory (Parkes and Zuckerman, 1935; Courrier and Gros, 1935; Zuckerman and Parkes, 1935; van Wagenen, 1935; Zuckerman and Parkes, 1936a). It has been found that apart from a general increase in size, the most pronounced prostatic changes occasioned in these animals by œstrone are fibro-muscular growth and, in all except one species thus far studied, stratification of the uterus masculinus. The prostatic tubules and acini are little affected in the rhesus monkey after as many as eighty-nine days' treatment (Zuckerman and Parkes, 1936a), and the available data thus suggest that these glandular elements are far less sensitive than those of the dog or small rodents. Whether or not the glands react after longer treatment remains to be seen; at present it is necessary to hold to the tentative view that the general glandular tissue of the Old-World primate prostate does not respond to œstrogens in a way which would make them resemble the glandular elements of human prostates affected with benign hyperplasia.

The changes that occur in the "uterus masculinus" are of great interest in this

connexion. In most monkeys this structure is a "vagina masculina," and reacts as such to œstrone by epithelial stratification and desquamation. In man, however, it is a distinctly glandular organ, and is presumably homologous with the uterus. If this were the case, its response to the unopposed action of an œstrogenic substance should be cystic hyperplasia, such as takes place in the female primate in similar circumstances (Zuckerman and Morse, 1935). "An extensive cystic hyperplasia of a true uterus masculinus would produce a histological appearance of the "middle lobe" not unlike that of the enlarged glandular prostate of clinical medicine" (Zuckerman and Parkes, 1935). The only experiment that has so far been possible on a monkey with a glandular uterus masculinus has provided support for this view.

I am advancing this idea of the ætiology of benign enlargement of the prostate very tentatively, not as an established theory, but as a basis for further work. There are, however, certain facts which suggest that it is not as empty as its novelty might at first suggest. For example, there are numbers of observations in the surgical literature to the effect that benign enlargement in man is usually confined mainly to the prespermatic lobe and the upper parts of the lateral lobes, and that it starts in the middle lobe—the lobe that contains the uterus masculinus. There is also the widely-held belief that when a prostatic adenoma is carefully shelled out, it leaves behind a capsule of true prostatic tissue in which lie the ejaculatory ducts, whose normal relations have been distorted by the adenoma which has developed in the region between them and the urethra—again the bed of the uterus masculinus. And, finally, there is the difficulty of distinguishing utricular from true prostatic glands in cases of prostatic enlargement. But here I am on uncertain ground, and supported only by some hasty observations; in mentioning this matter I simply wish to suggest it as a subject for further investigation.

It is not my aim to suggest that only the utricular glands may be concerned in the development of benign enlargements of the human prostate. It is, however, likely that these glands are more sensitive than the general prostatic epithelium, which begins to react, when it does, only after the uterus masculinus has become hyperplastic. Such a view would fit in with the widely-expressed opinion, to which I have already referred, that the condition usually begins in the middle lobe.

The occurrence of fibro-muscular growth in benign enlargement of the human prostate is readily understandable on the view that the condition is determined by an œstrogenic agent, for one of the effects which œstrogens have been shown to have is to stimulate growth in mesodermal tissues derived from the genital cord. Many species of monkey experience rapid growth and desquamation of the urethral epithelium when under treatment with œstrin, and it might be asked why it is, if benign enlargement of the prostate is determined by an œstrogen, that the condition is not associated with hyperplasia of the urethral epithelium? The problem is answered by comparative study of the responses of different species of monkeys (Zuckerman 1936a), and the lack of this change in man is in no way incompatible with the ætiological view which I am discussing.

Before considering the bearing which this view has on treatment, there are three further points that I should like to raise. The first, the evidence for which has been fully summarized both by Burrows (1935b) and by Owen and Cutler (1936). is the fact that the prostate of the newborn child is often greatly enlarged, and that it presents characteristic signs of stimulation by an œstrogen. The second is the fact that evidence in other fields suggests that many benign growths are a consequence of similar stimulation (*see* Lacassagne, 1936; Witherspoon, 1935; Ingleby, 1935; Geschickter and Lewis, 1935). It may, however, be noted in this connexion that Hamilton and his co-workers (1936) failed to extract any œstrogenic substance from seven enlarged prostates. And the third point is the suggestion that, in their levels of hormone excretion, sufferers from enlargement of the prostate fulfil the conditions demanded by the view that they are primarily suffering from an imbalance

of male hormone and œstrogenic substance. The evidence on this question is, however, very conflicting. Lower (1933), for example, states that the concentration of male hormone in the urine and blood of these patients is higher than normal. Buehler (1933), on the other hand, writes that only the urine of young and middle-aged men contains large quantities of male hormone. According to Oesterreicher (1934), the urine of aged men, in contradistinction to elderly women, always contains some œstrogenic substance. Owen and Cutler (1936), who provide a useful summary of the literature of the problem, were themselves unable to find "much variation" from the normal in the levels of excretion of either œstrogenic substance or prolans in cases of prostatic enlargement. It is obvious that much remains to be done before this question can be answered.

Treatment on the Basis of the View that Benign Enlargement of the Prostate is due to the Action of an Œstrogenic Substance

The belief that benign enlargement of the prostate is a response to stimulation by œstrogens, following an imbalance between male hormone and some œstrogenic substance, has obvious therapeutic bearings. If, as many believe, both sets of substances are secreted by the testes, a radical treatment would be castration. Because of several secondary considerations, such treatment could not, however, be expected to recommend itself; neither is it likely that surgeons would be prepared to reopen a chapter which was closed more than thirty years ago in an atmosphere of heated controversy. What the effect of castration would be in suitable cases will probably never be known with certainty, but fortunately other measures are available which make it an unessential question.

It is unessential because the primary aim of treatment—the restoration of a normal balance between male-hormone and œstrogenic hormone—can be achieved more simply by the injection of male hormone compounds. De Jongh (1935b) has experimentally shown that male hormone can inhibit the effects which œstrone has on the prostate of mice. The same observation has been made, perhaps more convincingly, on rhesus monkeys (Zuckerman and Parkes, 1936b), and there can be no doubt about the efficacy of male hormone in correcting the abnormal histological changes which œstrogenic substances bring about in the prostate.[1]

There are other ways of giving male hormone than by direct injection, e.g. by means of testicular grafts. De Jongh and Kok (1936) have also tried to stimulate the production of male hormone in the testis by giving a gonadotropic extract of the anterior lobe of the pituitary, and they claim that this method of treatment has proved useful in the case of dogs suffering from enlargement of the prostate. Male hormone does not even appear to be specific in its action as a protective agent against stimulation by œstrogenic substances, for there is every indication that progestin, the hormone of the corpus luteum, as well perhaps as other sterol substances, will prove equally useful (Zuckerman and Parkes, 1936b).

The mechanism of protection is not as yet clear, but there is some evidence that progestin, and presumably male hormone too, lowers the renal threshold to œstrogens. The maintenance of an effect of an œstrogen demands the continuous application of the œstrogenic substance responsible for it, for changes produced by œstrogens are reversible. Consequently if such œstrogenic compounds as are being elaborated in the male organism were readily excreted—as is perhaps the case when male hormone or progestin is administered—the changes produced by them in the prostate would gradually become less pronounced, as can be shown experimentally in the case of the monkey. These ideas are, I need hardly say, largely speculative, and it is possible to suggest other equally plausible pictures of steps in the process of cure.

[1] The substance that was found effective in this respect is androstanediol; there is, however, no reason to suppose that other members of the androsterone-testosterone series would fail to be effective if given in adequate amounts.

It is necessary to point out, in conclusion, that benign enlargement of the prostate may represent a class of abnormalities, each member of which may have a different ætiology. At least two types of enlargement, for example, appear to afflict the dog, and only one is obviously a response to the action of an œstrogenic substance. It is even possible that the other type is determined by an excess of male hormone, and the possibility has therefore to be borne in mind that male hormone itself may cause excessive enlargement of the prostate in man. Fortunately, as I have already remarked, male hormone is not known to cause any abnormal histological changes, but only a uniform development of all the true prostatic tissue. To my knowledge, preparations of male hormone sufficiently concentrated to be of value in the treatment of enlargement of the prostate have not been marketed in England as yet[1]; I am making this observation on the basis of knowledge of the amounts necessary to secure adequate changes in rhesus monkeys. When such preparations do become available, great care will be necessary in evaluating their efficacy in the treatment of enlarged prostates, for to a large extent the treatment is empirical so far as man is concerned. It will be necessary to remember that improvement in the symptoms of prostatic obstruction are known to follow suggestion and general treatment. Above all, it will be necessary to keep in mind the fact that the enlarged prostate which comes before the notice of the clinician is in all likelihood the end-result of a prolonged pathological process. If the process is as I have suggested, stimulation by œstrogenic substances, prolonged treatment with male hormone may be necessary to remove its morphological effects.

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[1] While this paper was passing through the press, solutions of crystalline testosterone and testosterone propionate in oil, in concentrations of 5 mgm. per c.c., have been made available for clinical use. Experimental study of the reactions of laboratory mammals shows that the propionate is the more effective preparation.

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