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A SURVEY OF PROSTATIC ENLARGEMENT AND ITS TREATMENT *

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The fact that I propose to give a general survey of prostatic enlargement, and note any advances that have been made in our understanding of it and in our methods of treating it, is an indication that I have reached that time of life at which a man is prone to look back into the past and to contrast what he thought once with what he thinks now. And, in spite of the big gaps that still remain in our knowledge and of the imperfections of our treatment, this survey will give cause for satisfaction. The last ten years have witnessed a great activity not only in our surgery but also in our knowledge of the aetiology of prostatic enlargement. We have made definite progress and, unless I am mistaken, are on the threshold of still greater advances.

Some sixteen years ago I had the honour of delivering a Hunterian lecture before the Royal College of Surgeons on "The Nature and Causes of Old Age Enlargement of the Prostate." When I came to assess the result of my two years' work on this subject it amounted to little more than an assertion that every theory that had so far been advanced to explain the nature and causes of prostatic enlargement was inadequate. We were not only in ignorance of its aetiology; we did not even know what it was. The only positive statement in my lecture was the following, which I give verbatim:

"The close dependence of the prostate on the ductless glands, during its period of development, affords sufficient ground for considering carefully the possibility that enlargement may be associated with some change in the endocrine system. The menopause in the female is generally accompanied by a temporary loss of endocrine balance, and it is not improbable that a similar state of affairs may arise during the period of sexual decline in the male. . . . The condition of the endocrine glands in cases of prostatic enlargement offers a fruitful field for research."

This at the time was a new point of view. Up till then enlargement of the prostate had been considered to be an inflammatory lesion (Ciechanowsky and Rothschild, 1903), an adenoma (Cohnheim, Rindfleisch, and Velpeau), or a form of degeneration associated with arteriosclerosis (Launois, 1885). My suggestion that it might be the result of a disturbance of the endocrine balance was a blind shot that modern research has shown to have been very near the mark. I did not know at

the time that Paul (1910) of Liverpool had twelve years previously been struck by the resemblance between the enlarged prostate and involutionary cystic mastitis, and had suggested that enlargement was an involutionary lesion similar to that of the female breast at the time of the menopause.

It is difficult to say what particular subsequent research was responsible for establishing beyond doubt the endocrine factor in enlargement, but if emphasis is to be placed on the work of any one researcher it would have to be on that of Lacassagne, in 1933. While experimenting on the carcinogenetic powers of various sterols, Lacassagne found that if oestrone was administered over long periods to mice it produced an overgrowth of the dorsal prostatic lobes. This interesting discovery was confirmed independently by de Jongh (1933), by Burrows and Kennaway (1934), and by other workers.

Care must be exercised in applying these results to the problems of human enlargement. The dorsal prostatic lobe of a mouse is a specialized gland, secreting a semen coagulant. There is no true homologue of this in man. Zuckerman and Groome (1937) have, however, shown that prostatic enlargement can be produced in dogs by injections of oestrone, and that the histology of this artificially produced enlargement is similar to that which often occurs spontaneously in this animal. Parkes and Zuckerman (1935) have also studied the histology of the oestrone-stimulated prostates of monkeys, and found that they undergo a fibro-muscular overgrowth and a stratification of the uterus masculinus.

These experiments suggest that enlargement of the prostate in man may also be due to the action of an excess of oestrogenic substance. It has of course long been known that the male body forms oestrogenic as well as male hormones, and that both of these substances could be extracted from the testis. It is therefore not illogical to suppose that an upset in the normal balance between these two antagonistic principles may be the cause of prostatic enlargement. But so far no direct confirmation of this theory has been obtained from any quantitative estimate of the hormones formed by sufferers from prostatic enlargement. Hamilton and his co-workers (1936) failed to extract any oestrogenic substance from seven enlarged prostates, and Lower (1933) stated that the concentration of male hormone in the blood of prostatics was even higher than normal. Buehler (1933) has, however,

* A paper read to the Gloucestershire Branch of the British Medical Association.

asserted that this is only true of the blood of the younger prostatics, and does not apply to older patients. Direct evidence is therefore still lacking that artificially produced prostatic enlargement in animals is a true analogue of the condition found in man, and we shall have to wait for further evidence before we can feel fully satisfied that we have really found the key to the riddle. Our uncertainty need not, however, prevent us from attempting, in the light of these animal experiments, treatment along hormonal lines. This subject will now be considered.

Hormonic Treatment of the Enlarged Prostate

The fact that the testicle forms both male and female hormones supplies a rationale for the old treatment of prostatic enlargement by means of castration. No modern surgeon would care to revive this practice, even although in many cases it appears to have achieved its object—namely, the shrinkage of the prostate. He prefers rather to aim at restoring the normal balance between the two principles by injecting male hormone. De Jongh has shown experimentally that male hormone does possess the power to inhibit the action of oestrone on the prostate, and Parkes and Zuckerman (1935) have confirmed his findings in the case of monkeys. Incidentally, it would appear that progesterin is capable of exerting the same antagonistic action as male hormone, thus supplying another example of interchangeability of hormone in the two sexes.

There is plenty of experimental support, therefore, for the attempt to deal with human enlargement by means of endocrine therapy, either directly by injection of male hormone or else indirectly by the use of gonadotropic substances. Until recently these attempts have been handicapped by the difficulty of injecting enough hormone to produce an effect, but with improvements in methods of extraction and of manufacture this difficulty is being overcome. The Ciba Company have now prepared ampoules containing 50 mg. of testosterone propionate in sterile oil. A large supply of this has been put at the disposal of the Medical Research Council, and some half-dozen of us are testing it out on carefully investigated cases of prostatic enlargement. What will be the outcome of this trial remains to be seen. It must be remembered that second only in importance to the actual hormone preparation given is the method of giving it.

Important work, which may have a bearing on future lines of treatment, is at present being done by Parkes, Zondek, and others on the rate of absorption of hormone after injection. The ideal to be aimed at is to ensure a slow continuous absorption of small amounts over a long period, a result that has been obtained in animals by injecting compressed tablets of hormone into the muscle. It is possible, therefore, that new methods of administration will in the future play a part in the hormonal treatment of prostatic enlargement.

The Steinach Operation

Bilateral vasectomy was used as long ago as 1890 by Lennander of Upsala in the treatment of prostatic enlargement as a substitute for castration. Interest in this operation was revived by the writings of Steinach in 1918, and it has since been used extensively as a treatment of both premature senility and prostatic enlargement on the assumption that it increased the output of male hormone in the testicle. The original Steinach operation of ligature of the vas not having given satisfactory results, Niehans in 1927 substituted for it ligature of the efferent

ducts of the testicle. It is difficult to see why a ligature in this situation should prove more effective than a ligature placed higher up on the vas. It is even uncertain that a cutting off of the external secretion of the testicle is necessarily followed by an increased output of hormone. Nevertheless, Niehans and other operators have claimed many successes for this simple form of treatment.

The proof of the pudding lies in the eating; the value of Niehans's operation can only be assessed by the results that are obtained from it. The ingenious endocrinological arguments put forward by Niehans as a justification of his operation carry with them little conviction, for in the present state of endocrinology it is possible to bolster up almost any thesis by choosing those observations that happen to support it and rejecting those that are opposed to it. We would be wise, therefore, to judge the Niehans operation by the results that follow it rather than by the endocrinological arguments that support it. What, then, are the clinical results of the ligature operation that goes under the name of Steinach II? Niehans himself gives no actual statistics, but makes only the following general statement:

"Since 1927 I have operated on about six hundred prostatic patients in my clinic at Clarens and in the hospitals at Vevey and Montreux, and my experience for ten years empowers me to assert that Steinach's ligature II is particularly suitable for the soft adenoma of the prostate so often encountered, and equally suitable for myomata, whilst its influence is less apparent or *nil* on small hard fibromata. . . . In fact, the great majority of hundreds of patients with adenoma of the prostate who have undergone Steinach ligature II see their bladder troubles gradually disappear, often indeed very quickly. They pass urine more easily and in greater quantities, consequently less often. Strangury ceases and the bladder is completely emptied. The prostate decreases in size."

Niehans's statements have found little favour either in Europe or in America, and few urologists of repute have even given his methods a trial. Personally I feel that, however incredulous one may be about any form of treatment, it should not be condemned offhand without any attempt having been made to assess its value. I have therefore during the last two years carried out Niehans's ligature operation on a number of patients who have come to me with the express wish that I should do so. Out of some thirty patients within my range of observation, three only would appear to have benefited from their operation and to have maintained their improvement. Three or four others have asserted that they were slightly better, and the remainder have either expressed doubt whether any change had occurred or else have been sure that it had not.

The only statistics bearing on the subject of the Steinach II operation that I can find are those published by Elliot-Smith (1936). He performed the operation on twenty patients, most of whom were admitted to hospital as emergency cases, with acute retention. Three died and seventeen left hospital with four ounces or less of residual urine. It was noticeable that several patients with complete retention passed urine on the same day as the operation. This makes it likely that the improvement was due to a reflex action on the sphincter mechanism at the neck of the bladder. It is inconceivable that in so short a time any change could have been effected through the influence of hormones.

The Surgery of Prostatic Obstruction

It is unnecessary in this paper to describe at length the work of Bellfield and Fuller in America and of McGill and Freyer in this country in laying the foundations of

prostatic surgery. Here we are not concerned with foundations, but with the building that is being erected on those foundations. What form is it now taking? Where have we failed in our building and where have we succeeded?

In the *British Medical Journal* of July 20, 1901, Freyer first advocated and described the technique of suprapubic enucleation of the prostate. It was a crude and blind proceeding, guided only by the sense of touch and entailing the insertion of a finger in the rectum. After enucleation no attempt was made to deal with haemorrhage by the usual method of ligature or suture, reliance being placed on the haemostatic processes of the body to bring bleeding to an end. Drainage was provided for by means of a large tube inserted not in the most dependent but in the highest part of the field of operation. Although the results were as a rule excellent, no conscientious surgeon could feel entirely satisfied with the operation described by Freyer, since it violated almost every surgical principle. Obviously it could only be regarded as a stepping-stone to a more finished operation.

We will now consider the efforts that have been made to get rid of the shortcomings of the Freyer technique and try to estimate what success, if any, has attended them.

The Perineal Operation

In this country these efforts have been mainly directed to a more finished toilet of the prostatic bed and to the adoption of better methods of arresting post-operative haemorrhage. We have hitherto never departed very far from the original technique, nor abandoned for long the suprapubic approach to the prostate. In America the suprapubic route has been seriously challenged by the perineal operation elaborated by Proust, and strongly advocated by H. H. Young of Baltimore. There are many points in its favour, notably the better drainage provided by a wound in the perineum, and for a time the protagonists of the suprapubic and of the perineal routes seemed evenly matched. Of late years, however, the protagonists of the suprapubic operation have steadily gained ground, and it is now chiefly through the influence of H. H. Young and of those trained in his clinic that perineal prostatectomy still remains the routine operation for the relief of prostatic obstruction in certain American clinics. In this country it has never gained any hold. A few of us have at one time or another been attracted by the advantages of the perineal operation and have provided ourselves with the necessary equipment for carrying it out, but at the end of a year or two this equipment has usually found its way into our surgical lumber-rooms.

Suprapubic Prostatectomy

The first serious effort to eliminate the more obvious shortcomings of the Freyer operation was made by the late Sir J. Thomson-Walker in 1928. By means of a larger suprapubic incision, introducing a suitable retractor, and placing the patient in the exaggerated Trendelenburg position after the prostate had been enucleated, the field of operation could be inspected, torn shreds of tissue cut away so as to reduce subsequent infection, and bleeding points ligatured. Haemostasis was completed by the insertion of a continuous suture along the posterior segment of the bladder outlet. The originator of this open operation hoped by these means to reduce post-operative haemorrhage and sepsis to a minimum, and to banish entirely that occasional sequel to operation, post-prostatectomy obstruction.

Ten years have elapsed since Thomson-Walker introduced his open operation, and experience has shown that it affords no certain guarantee against the occurrence of any of the accidents that its originator hoped to prevent. Severe haemorrhage, sepsis, and post-prostatectomy obstruction have all occurred after an open operation. Their incidence may be less frequent, but none of these accidents has been entirely eliminated, and many of us have come to the conclusion that the extra half-hour required for the open operation is not justified by the benefits it confers. Where speed is necessary the old Freyer operation still remains preferable. A glance at the last annual surgical report of St. Peter's Hospital, in which the results of the various operations performed there during the year are admirably set out, serves to confirm this view. There it will be seen that the highest mortality rate is that which follows the performance of the Thomson-Walker operation. Undoubtedly its originator was right in attempting to eliminate the defects of the Freyer operation, but unfortunately his efforts to do so have not met with the success that he hoped for.

The Harris Technique

To a worker in Australia—namely, the late S. H. Harris (1933, 1935) of Melbourne—must be accredited the next serious effort to get rid of the glaring defects of the Freyer technique. Dissatisfied with the half-measures of Thomson-Walker, he aimed by means of carefully placed sutures to arrest haemorrhage so completely that the bladder could be closed by primary suture. Young's boomerang needle, a clever invention that had been originally devised to aid in the difficult task of closing fistulae left by the perineal operation, provided him with the instrument necessary to his purpose. With the boomerang needle it was possible to take a big bite of the tissues round the prostatic cavity, to underpin all bleeding-points, and to reconstitute the neck of the bladder. The suture on which Harris placed most emphasis was a median posterior suture so inserted as to carry a tongue of mucous membrane and muscle deep down into the prostatic cavity. This "trigonization suture," as he termed it, served to re-form the floor of the urethra. Lateral stitches were then inserted in such a manner as to draw together the walls of the cavity and to help to obliterate it. Drainage was provided for by an indwelling urethral catheter anchored in position by means of a stitch passed through its eye and brought out through the abdominal wall. The bladder was then closed by primary suture. Harris claimed excellent results from his operation, and published a remarkably low mortality rate. That ugly trio of the Freyer operation—haemorrhage, sepsis, and post-prostatectomy obstruction—had apparently been conquered, and the author of the new operation waited confidently for his colleagues' blessing on the new technique.

The urological world was slow to take note of his writings. In opening a discussion on prostatectomy at the Centenary Meeting of the B.M.A., held in London in July, 1932, Mr. Swift Joly commented unfavourably on the Harris operation. He expressed the opinion that attempts to perform plastic operations on the prostatic cavity resulted only in an increase of sepsis. Other speakers were inclined to agree with him. Harris was bitterly disappointed.

Soon afterwards the tide began to turn. Clifford Morson and Ogier Ward gave his method a trial, and later published good results from the new technique. Other British urologists followed suit, and at the annual meeting

of the Urological Section of the Royal Society of Medicine a complete reversal of opinion was found to have taken place. It was the majority of speakers who now upheld the Harris operation, the minority who opposed it. But it was very noticeable that everyone who was using the new operation had considerably modified Harris's technique, one having eliminated the posterior trigonization suture, another the postero-lateral, and a third the antero-lateral. Moreover, only a few had dared to follow Harris's lead in carrying out primary closure of the bladder as a routine measure. Usually a small suprapubic drainage-tube was inserted and retained during the first few days of convalescence.

Present Position of the Harris Operation

Operations are subject to the same laws as those that control other human inventions; at first a new operation meets with a certain resistance, and then if it has any merit it is acclaimed as a great advance that will supersede all other methods. Finally it reaches the period of equilibrium or of decline: it either takes a permanent place in the repertoire of the surgeon or else sinks into oblivion. This I believe will be the history of the Harris technique, but at the present moment I am not prepared to say what the final stage will be. I am sure, however, that in the exact form in which Harris planned it his operation will not survive, for it suffers from a great defect, a defect from which the Freyer operation is altogether free. In inserting some of the sutures the boomerang needle passes well outside the limits of the urinary tract, and is therefore capable of carrying with it infection—if infection there be—into the cellular tissues of the pelvis. That this is not merely a theoretical objection but a very real danger is shown by the fact that practically every operator who has used the Harris technique at all extensively has met with cases of pelvic cellulitis. It can of course be urged that pelvic cellulitis may occur after every type of prostatectomy, but the consensus of opinion favours the view that it is more frequent after the employment of the Harris technique. This is a very serious objection, and Harris's insistence on the necessity for the careful pre-operative treatment of infection does not remove it. However carefully we prepare our patients we cannot guarantee that we have rendered the bladder aseptic.

A second shortcoming of the operation is that while the lateral sutures certainly diminish bleeding they do not obliterate the prostatic cavity. All that they do is to draw the bladder together over the hole left by the prostate, unless, of course, the boomerang needle is inserted so wide that it goes well outside the prostatic capsule. Such a big excursion of the needle not only increases the risk of pelvic cellulitis but also, when the stitches are tied, turns in a great part of the base of the bladder and causes a marked deformity of that viscus. Although Harris himself showed no hesitation in inserting these widely placed sutures, I cannot feel that so gross a deformity of the bladder is desirable.

Because of these weak points in the Harris operation some of those who had previously adopted it have given it up, while others have so greatly modified the method that it can no longer be called a Harris operation. My own position is that I still employ a modified Harris technique, but only in those favourable cases in which I am fully satisfied that the patient is able to support a longer operation. When a two-stage operation is advisable, or when I feel any doubt about the patient's capacity

to withstand a more formidable procedure, I have fallen back again on an operation that in its essentials resembles the old defective method of Freyer. For me the technique of Harris, which at one time I hailed as a great advance in prostatic surgery, appears to be a method of definite but of limited utility. I look upon it as a portent of things to come rather than as a method that has already arrived. It indicates the lines along which we must continue to work—a direction and not a goal.

On the Continent and across the Atlantic the Harris method has met with no favour. Efforts to advance in prostatic surgery have in the United States taken another direction, more particularly the development of perurethral methods of treatment. This important branch of prostatic surgery will now be discussed.

Perurethral Operations on the Prostate

Again it will be unnecessary to deal with the foundation of perurethral surgery laid by Bottini, Civeale, Young, Caulk, and Luys, for we are mainly concerned with modern developments. After the usual period of resistance this method of dealing with prostatic obstruction received widespread recognition rather suddenly. By some enthusiasts it was even proclaimed to be a method that within a decade would entirely replace all others. Prostatectomy would then retain merely a historic interest. This has only proved to be approximately true in the case of the Mayo Clinic, at which about 98 per cent. of prostates are now being dealt with by perurethral methods. Elsewhere it has been felt, first, that resection is not a universal substitute for prostatectomy but a valuable alternative to be used in certain cases; and, secondly, that it is not a minor proceeding immune from all dangers. At a very early stage after the spread of perurethral methods disturbing reports of deaths from haemorrhage and sepsis destroyed the illusion that the resectoscope was an instrument that could be used by all and sundry with light-hearted enthusiasm. Even to the experienced urologist a perurethral resection often proves to be a difficult operation. In the hands of the inexpert the resectoscope can be an instrument that is more deadly than the knife. Years of practice are necessary in order to become master of it.

As in the case of prostatectomy, the chief dangers of perurethral resection have proved to be haemorrhage and sepsis; and it has been to eliminate these, and at the same time to increase the facility with which prostatic tissue is removed, that our efforts have in the main been directed. All techniques that entailed the leaving behind of a large area of coagulated tissue have now been abandoned on account of the sepsis that they encouraged. Of the many instruments that have been devised two have now definitely gained the ascendancy; these are the McCarthy resectome and the Thompson punch. In this country we prefer a modification of the former instrument, not necessarily because it is the better weapon, but because we find the direct-vision ocular system of the Thompson punch more difficult to use. From the point of view of sepsis, however, the Thompson punch, which employs a cold knife for cutting and only uses a coagulating current for stopping haemorrhage, is probably the better instrument.

On the whole it may be said that in this country urologists have reached an agreement not only as to the best method of carrying out perurethral resection, but also as to the indications for doing so. Only in America do we find discrepancies of opinion so wide as to result in the perurethral method being used only

exceptionally at one clinic and as a routine procedure in another. Here we regard it as a treatment that is suited to certain prostates and to certain circumstances. Perurethral resection is no longer on its trial, but has established for itself a definite place in the surgery of the prostate.

Conclusions

Having surveyed the work that has been carried out by innumerable researchers in the laboratory and in the operating theatre during the last twenty years, I feel that we have no reason to be dissatisfied with the results. We have made definite progress, both in our understanding of the aetiology of enlargement and in our methods of dealing with it. The investigations of the biologist and of the biochemist are now leading us in a direction which may well mean that within a few years we shall be able to prevent its occurrence, and possibly cure the condition once it has arisen. In the meantime, close co-operation between the clinicians and the designers of instruments has provided us with a valuable alternative method of surgical intervention in the shape of perurethral resection. Finally it may be said that even if the efforts of prostatectomists to rid the original Freyer operation of its shortcomings have not so far met with success, there is no reason to disbelieve that in the end this also will be achieved.

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The fourth annual meeting of French radio-electrologists will be held in the physics theatre of the Paris Faculty of Medicine from October 5 to 8. Professor Joliot-Curie will deliver an opening address on the biological applications of the neutrons and the artificial radio-elements, including the therapeutical hypotheses concerned. Professor Didier will speak on the radiological methods of examination of sections of organisms, Professor Baudouin and Dr. Fischgold will present a communication on the bio-electrical phenomena of the nervous system and their possible applications in practice, Dr. Gaston Daniel of Marseilles will discuss radiotherapy as an antidote to inflammation. Lectures on various aspects of biophysiology will be given by Professors Lamarque, Soula, Marques, and Strohl ry Djourno. Visits will be paid to institutes and hospitals, and there will be entertainments and excursions. Full information may be obtained from Dr. Delherm, 1, Rue Las Cases, Paris, 7e.

ANAEMIA AND THE GASTRO-INTESTINAL TRACT*

BY

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It is recognized to-day that the commonest cause of anaemia is a lack of one or other of the essential haemopoietic principles. The known haemopoietic principles are: (1) iron; (2) the P.A. substance in liver effective in Addisonian pernicious anaemia; (3) vitamin C. Minute quantities of other minerals, such as copper, cobalt, and manganese, may be required for normal haemopoiesis, but are usually present in sufficient quantities even in poor diets, since only extremely small amounts are needed. Thyroxine is often included, but its effect is probably an indirect one (Bomford, 1938). The body is dependent for its supplies of these haemopoietic principles upon the food ingested, and subsequently digested and absorbed in the intestinal canal. It is therefore not surprising that there is a close relationship between anaemia and disturbances of gastro-intestinal function, since abnormalities in food intake, digestion, and absorption must result in a deficiency of these principles. It is essential in treating a patient with a deficiency anaemia to recognize not only the type of anaemia—that is, whether it is due to lack of iron, liver, or vitamin C—but also to determine how the deficiency is brought about, so that an attempt may be made to correct the disordered mechanism. It must also be remembered that an adequate supply of haemopoietic principles may be converted into an inadequate supply if the demands are increased. Thus iron-deficiency anaemias are extremely rare in men unless there is some source of chronic haemorrhage. On the other hand, iron-deficiency anaemias are common in women of the working classes because the iron content of the diet is not sufficient to make good the continuous iron drain of normal menstruation (Davidson and Fullerton, 1938).

For purposes of discussion the disturbances of gastro-intestinal function that may convert an adequate into an inadequate diet, so causing what Castle has called a conditioned deficiency, may be grouped as follows: (1) haemorrhage; (2) deficiency of gastric digestion; (3) deficiency of intestinal absorption; (4) production of toxic substances. So far as is known such factors influence only the utilization of iron and the P.A. principle. There is no evidence that intestinal abnormalities affect the utilization of vitamin C.

Haemorrhage

The commonest sources of gastro-intestinal haemorrhage are bleeding gastric and duodenal ulcers and haemorrhoids. The latter, especially in men, are an important cause of severe iron-deficiency anaemia. It should always be remembered that in tropical countries bleeding from hookworm infestation associated with a poor diet is a possible cause of hypochromic anaemia. An analysis of the stools for occult blood is an essential investigation in all cases of anaemia of unknown aetiology.

Deficiency of Gastric Digestion

Deficiency of gastric digestion may be due to: (a) organic lesions; (b) diminished secretion of hydrochloric acid; (c) diminished secretion of the intrinsic factor of Castle.

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