CLINICAL ASPECTS OF THE ENDOCRINE FUNCTIONS OF THE TESTES IN MAN*

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That the principal and accessory sex organs as well as many secondary sex characteristics of male animals are dependent upon the endocrine function of the testes has been conclusively shown by experiments in many research laboratories. Recent scientific clinical observations in human castrates have attested to the same fact. The spermatogenic elements of the testes may be destroyed by roentgen irradiation or by cryptorchidism without alteration in the sexual characteristics. It is believed that the interstitial cells of the testes produce one or more substances which act as pituitary depressants and sex stimulants. Such substances, whether natural or synthetic, are collectively known as androgens. The clinical problems which must be considered in the light of these findings have been approached from several different angles by various workers. At the Cleveland Clinic we have attempted to obtain as complete and consolidated a picture of testicular physiology and physiopathology as possible. We have therefore attacked the problem from several points, some of which are discussed in this paper. Particular attention has been directed to bio-assays and their results, the problem of prostatic hypertrophy, the question of the diagnosis and treatment of hypogonadism, the endocrinological aspects of spermatogenesis, and the results of experiments with testicular transplants.

BIO-ASSAYS IN THE STUDY OF TESTICULAR DISORDERS

In recent years it has become increasingly obvious that the clinical diagnosis of endocrine disorders can sometimes be considerably facilitated by a proper study of the hormone content of the body fluids. By proper methods of assay it is sometimes possible to determine the state of activity of an endocrine organ when all other known procedures are inadequate. This is particularly true in disorders of the pituitary gland and of the gonads. A review of the many papers on this subject is impossible here, but a summary of the methods now employed for clinical studies at the Cleveland Clinic is included.

THE EXTRACTION AND ASSAY OF ANDROGENS FROM BLOOD AND URINE

The methods employed were devised and described by McCullagh and McLin[1] and McCullagh and Osborn[2]. When working with blood it is diluted with 10 volumes of water and treated in the same fashion as urine. The urine or blood is hydrolyzed by boiling for 15 minutes with 5 per cent sulphuric acid and extracted twice with dibutyl ether. The ether is washed with alkali and water and evaporated to dryness by steam

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distillation in partial vacuum. The residue contains the hormone and is dissolved in sesame oil.

The quantity of hormone in the sesame oil is assayed by a modification of the method of Gallagher and Koch[3]. The details of the procedure for assay have been published by McCullagh and Cuyler[4].

The principle of the Gallagher and Koch method is that of producing growth in the comb of a capon. Several capons must be used for each assay. In dealing with moderate amounts of hormone, (e.g. the amount found in a 24 hour specimen of urine) the sample being tested can be injected into the pectoral muscles of the birds. When working with smaller quantities of hormone the test can be made about 35 times more sensitive by inuncting the hormone into the combs of the birds instead of injecting it into their muscles. The inunction method must be used for the quantitative measurement of the amount of androgenic material in blood.

The excretion of urinary androgens has received extensive consideration here[5] and in several other laboratories[6]. In normal men, approximately 20 to 80 international units are excreted daily. If testosterone propionate is injected into normal individuals, there ensues a prompt increase in the excretion of androgenic material. This is followed by a period of subnormal androgenic excretion and then a return to normal. The period of subnormal excretion probably represents a period of pituitary depression caused by the injection of the testosterone propionate. When testosterone propionate is injected into hypogonadal individuals, the urinary androgens increase in proportion to the dose. Following a single moderate dose the increased excretion lasts for only about 24 hours; larger doses effect an increase for several days.

The gonadotropic hormone: It is well known that the pituitary gland and the testes are closely interrelated. In the absence of pituitary hormone the testes produce no hormone, and except when proper hormonal therapy is instituted the spermatogenic function of the testes disappears following ablation or removal of the pituitary. Following castration there is an increase in activity of the pituitary gland. The histological picture changes, the gland increases in size, and an increased amount of gonad-stimulating hormone appears. Therefore, in studying prostate-pituitary-testes interrelationship it has seemed advisable to make quantitative measurements of the amount of pituitary gonadotropic hormone appearing in the urine. These studies have been made by a modification of the method of Heller[7].

The method consists essentially of removing certain toxic substances from the urine with 50 per cent alcohol and then precipitating the hormone by increasing the alcoholic concentration to 80 per cent. The amount of hormone present is ascertained by injecting it into immature

female rats and measuring the extent of the stimulation of the ovaries and uteri.

Normal young men excrete only traces of this hormone. Patients suffering from hypogonadism of testicular origin excrete large quantities. In numerous elderly men with decreased testicular function, large quantities of the pituitary gonadotropic hormone have been found. This has been observed in several individuals with prostatic hypertrophy. It is not, however, by any means indicative of that disease only.

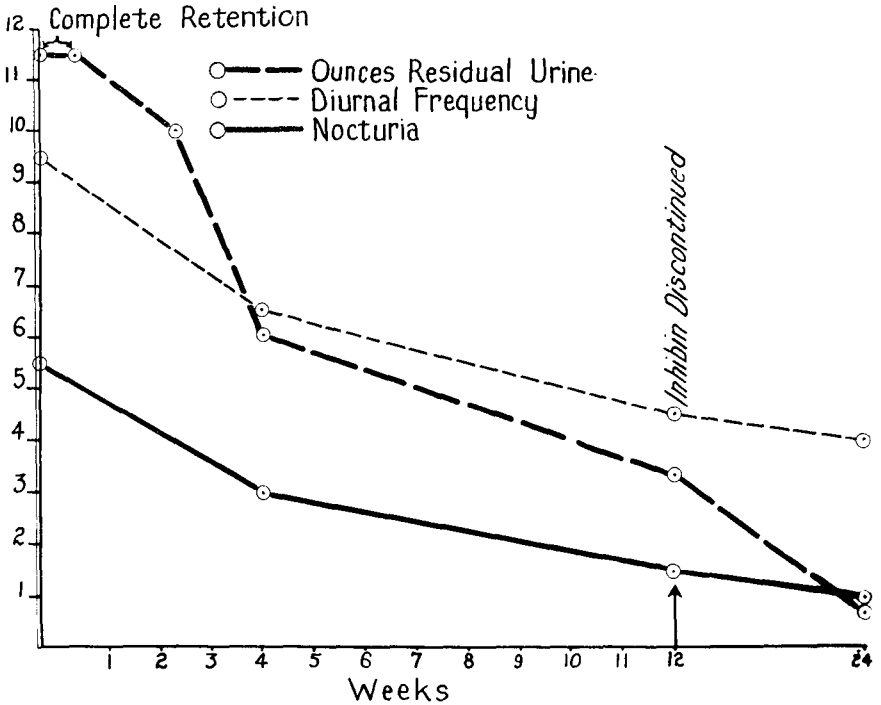
Prostatic Hypertrophy

A general discussion of the question of obstruction of the neck of the bladder is beyond the scope of this paper. One aspect of this problem, however, must receive our consideration. It has been my contention[8] that certain types of prostatic enlargement are the results of an endocrine disorder involving the testes and pituitary gland. For reasons which have received extensive consideration in earlier publications, we thought it probable that some hormone other than testosterone might be elaborated in the testes. The possibility that a deficiency of this second hormone which was tentatively termed "inhibin" could be a factor in the production of prostatic changes led to the administration to patients of a desiccated preparation made from whole bovine testes. We have now had the opportunity of observing the results of this therapy over a number of years. The hormone has been prescribed largely for patients having the clinical picture of benign enlargement of the prostate, that is, the large, soft, boggy glands. We asked a number of colleagues in other cities to cooperate with us in treatment along these lines and a certain number of them reported that in some cases they seemed to get rather striking results, characterized by relief from symptoms and urinary retention, with less residual urine, nocturia and diurnal frequency, usually less hesitancy and increased force of the urinary stream. McComb and Pearse[9] reported results by this method of treatment. It is obvious that as we have not fractionated the product and obtained the active principle, general application is not practical.

We appreciate that, following catheterization, a group of patients with urinary retention due to prostatic hypertrophy will improve and be relieved temporarily but, in our experience, no such percentage as shown here obtained the same amount of relief as the patients treated with the testicular preparation.

Chart I shows some of the results obtained in most of the cases that were benefited by the treatment.

Use of this non-surgical approach to the treatment of prostatic hypertrophy involved the usual difficulties encountered in endocrine replacement therapy. Even in those cases where there was a favorable reaction,



continued medication was required to prevent probable relapse. In some cases, even though the immediate effect of administration of hormone was most salutary, continued treatment failed to maintain satisfactory urinary function.

The failure of this type of treatment in a large percentage of cases is probably due to numerous causes. In a few cases in which we did not see improvement the condition may have been other than prostatic hypertrophy of endocrinological origin. In some instances it is probable that irreversible anatomical changes had occurred which could be corrected only by surgical measures.

The whole problem of the endocrinology of prostatic hypertrophy continues to be most perplexing. There is no agreement concerning the details of the nature of the disease. Parkes[10] feels that the disease is due to an imbalance between estrogenic and androgenic hormones and for this reason advocates the use of testosterone. Van Capellen[11] was probably the first to attempt this form of treatment. His success was comparable to that which we observed when feeding an amount of testicular material which contained only traces of testosterone. Several other workers have since had similar results[12]. Further researches concerning the functional condition of the endocrine system will be necessary before an adequate explanation of this disease will be forthcoming.

The Diagnosis and Treatment of Hypogonadism in the Male

E. P. McCullagh[13] has reviewed some of the literature on hypogonadism in males and has reported cases of testicular deficiency which have been treated with testosterone propionate in this institution.

In prepuberal hypogonadism, i.e., patients who have never shown signs of adequate testicular function—the growth of facial, axillary, and pubic hair is retarded, penile and scrotal development is poor, epiphyseal closures do not occur at the usual ages, and laryngeal maturation is interfered with. These individuals excrete only small quantities of androgenic material in the urine. Treatment with testosterone propionate results in penile growth accompanied by nocturnal emissions and increased production of semen. There is scrotal growth and prostatic enlargement, the latter change showing some lag. There is an increase in pubic and axillary hair and maturation of the larynx.

When gonadal failure occurs after puberty, the anatomical differences between the normal and deficient individual are not as marked as in prepuberal hypogonadism. The deficiency usually manifests itself by decreased libido and potency, which is frequently accompanied by nervous and vasomotor symptoms and decrease in the size of the prostate. The urinary excretion of androgens is decreased. Even in castrates, however, there is usually some androgenic material in the urine. This indicates obviously that there is some source of urinary androgens in addition to the gonads.

Observations made in this institution and the studies of others have shown the symptoms of gonadal failure in the adult can be completely relieved by adequate treatment with testosterone propionate.

The Endocrine Control of Spermatogenesis

Moore[14] has shown that under certain circumstances androgenic materials are injurious to the spermatogenic elements of the testes. Moore and Price[15] have demonstrated by the use of normal rats the fact that over a fairly wide range of dosage of testosterone propionate the testicular damage shows an inverse relationship to the dose, i.e., the greater the dosage the less the damage. Hypophysectomy causes rapid cessation of both the endocrine and spermatogenic functions of the testes.

In our laboratories it has been demonstrated that normal spermatogenesis can be maintained by the injection of androgens into hypophysectomized rats. Nelson and his co-workers[16] have confirmed this and have demonstrated that such treated animals could sire normal litters. If, under these circumstances, the testes are permitted to become atrophic, the pituitary hormones will cause their restoration but the androgens are ineffective.

Cutuly, McCullagh and Cutuly[17] studied the efficacy of various androgens in the maintenance of spermatogenesis and found that testosterone and testosterone propionate are among the least efficient. McCullagh[18] suggests that other androgens are normally formed in the testes and that the existence of these other substances accounts for the normal maintenance of spermatogenesis.

We have also demonstrated that testosterone propionate has a very potent influence as a depressor of the gonadotropic function of the pituitary gland. This no doubt accounts for the fact that small doses cause profound damage to the spermatogenic elements of the testes. Dr. E. P. McCullagh in the Department of Endocrinology is at present studying these effects in the human, and there is every reason to believe that the results will parallel those seen in experimental animals. This means that in partially hypogonadal men the treatment with testosterone propionate may have a deleterious influence over whatever spermatogenic function they have. This would suggest that when attempting to stimulate the sex functions by the use of androgens, some substance other than testosterone propionate should be employed if one desires to maintain spermatogenesis.

Testicular Transplants

When patients suffering from hypogonadism are treated with testicular hormone, their functional response is usually largely lost if replacement therapy is discontinued. This of course is usual in endocrine replacement therapy. It would seem that the successful glandular transplantation would be more to be desired than the continuous administration of endocrine products. Therefore, in spite of the well known difficulties involved in the transplantation of human tissues, we have undertaken a reinvestigation of the subject of testicular grafts.

The study of the physiological effects of transplantation of the testes extends back many years. John Hunter is credited with first transplanting testes from one animal to another. This was about the middle of the eighteenth century. Foa[19] attempted to transplant the testes into the scrotum but had negative results. The first to attempt to transplant the testes of young rats into the scrotums of older castrated animals were Castle and Phillips[20]; negative results were obtained. C. R. Moore[21] first obtained perfectly differentiated spermatozoa in testes grafts residing in the scrotum. In no other location did this occur. Moore's work revealed that testes grafts residing in the scrotum gave a very poor percentage of takes because of poor vascularization. Furthermore, his grafts which were recovered from subcutaneous, intramuscular, or intraperitoneal positions revealed good interstitial cell development but relatively poor tubule development.

The research department of the Cleveland Clinic Foundation has been

investigating the factors involved in successful testes transplantation as well as their physiological effects. This experimental work has been done chiefly upon rats. Under our direction, Dr. Eugene Cutuly, formerly of this laboratory, selected the ear of the rat as a possible favorable location for testicular transplants, first, because the rat's ear might offer adequate vascularization and, second, the ear might supply the temperature necessary for the development of the spermatozoa.

The experimental results obtained in studying the organs of rats with transplants are given in table 1. The organ weights are expressed in

TABLE 1

MAINTENANCE OF NORMAL ORGAN WEIGHTS BY A SMALL TESTICULAR TRANSPLANT

	Average Body Weight	*Average Weight of Organs Expressed as Mgm. per 100 grams of Body Weight*			
		Pituitary	*Testes*	*Seminal Vesicles*	*Ventral Prostate*
10 Normals	226	2.1	1370	240	68
6 Castrates with testicular transplants	295	2.7	54 (Transplant)	274	120
6 Castrates	207	4.6		4.1	5.5

milligrams per 100 cc. of body weight, which we believe makes the comparisons more valid than a direct comparison of organ weights when the animals are not all of the same size. The pituitary glands of castrated rats with transplants in the ear are almost normal in size and do not show the marked hypertrophy which occurs in the glands of castrated rats which have no transplants. The efficacy of transplanted testicular tissue in maintaining the secondary sexual organs is very evident. The transplants are only about 4 per cent of the size of the normal testes. The secondary sex glands, however, of the castrated animals with transplants are larger than the same organs in normal animals, whereas those which had no transplants had infantile secondary sex glands.

These researches are an extension of earlier investigations in other laboratories. Fischera[22] concluded that the pituitary gland enlarges to about twice the normal size after castration. Our results show that the increase in the pituitary weight in the castrated rats is slightly above this 100 per cent increase. Libschütz et al[23] revealed that only ten per cent of the normal testicular tissue is necessary to maintain the secondary sex characteristics. This is comparable to our findings that a trans-

plant weighing 4 per cent of the weight of normal testes will maintain the secondary sex glands.

Summary

1. Animal experiments demonstrate that the pituitary, the testes, and the prostate are closely interrelated. Clinical investigations have demonstrated that this is also the case in man.

2. Clinical prostatic hypertrophy is frequently a disease of endocrine origin. The symptoms have been relieved in some instances by the use of testicular preparations.

3. The pituitary gonadotropic hormone and the androgens both play a rôle in spermatogenesis.

4. Useful laboratory methods have been developed to aid in the diagnosis of endocrine disorders of the testes.

5. When the production of androgens is deficient, the urinary androgens can be brought back to normal by the administration of substances such as testosterone propionate; symptoms of hypogonadism are relieved by this treatment.

6. New laboratory experiments concerning testicular grafts are reported.

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The annual meeting of the American College of Physicians will be held in Cleveland, April 1-5, 1940. The Bunts Course, usually given in the spring, will not be offered this year to avoid a conflict in meetings.