TESTES.*

By A. W. SPENCE, M.A., M.D. (Cantab.), M.R.C.P.

(Assistant Physician and Assistant Director of the Medical Unit, St. Bartholomew's Hospital, London.)

TESTES—THE MALE SEX HORMONE.

The functions of the testes so far known are the production of spermatozoa by the spermatogenic epithelium of the tubules, and the secretion by the interstitial tissue of a hormone, (or hormones), termed the male sex hormone, which is responsible for the male characteristics and the normal development of the accessory genital structures. The effects of castration are dependent on whether the operation is performed before or after puberty. After early castration there is a tendency to increased growth of the limbs, especially of the lower extremities, and delayed union of the epiphyses and occasionally of the sutures of the skull. Genu valgum and pes planus are frequent accompaniments. In some cases the configuration of the body approaches the feminine type and the subject may become obese, the excessive fat being confined mainly to the trunk. The distribution of the hair is feminine, and there is deficient growth of the larynx, so that the voice retains its boyish character. The penis, prostate and seminal vesicles remain small and ill-developed. Castration after puberty does not produce such well-marked changes. Libido may or may not be diminished. Although castration may have a psychological effect on the individual, eunuchs are known in history to have been able administrators and generals.

With the exception of sterility, the bulk of the changes which occur after castration is due to the absence of the male sex hormone. Our knowledge of its nature and properties has made remarkable progress during the last few years, the difficulty of advance in the past having been due to the absence of an adequate test for the hormone. Pézard in 1911 found that castrated cockerels were good objects for demonstrating its presence, the development of the comb being dependent upon it. This is known as the capon comb growth test. The male hormone is expressed in capon units, one capon unit being contained in the amount of material injected (daily) over a given period, which is required to cause a given increase in the size of the comb. Another method in common use for demonstrating the activity of male hormone preparations is their ability to bring about enlargement of the prostate and seminal vesicles of the castrated rat. Castration in the immature rat prevents the normal growth of the prostate and seminal vesicles, and in the adult rat is followed by atrophy of these organs.

Early extracts containing male hormone were obtained from bulls' testes. They proved capable of inducing growth of the capon's comb, and of preventing or repairing the changes produced in the prostate and seminal vesicles of rats by castration. In 1929 Funk and Harrow⁽¹⁾ obtained active extracts from human male urine, and in 1931 Butenandt⁽²⁾ prepared from urine a pure crystalline substance, which stimulated the growth of the capon's comb and acted on the prostate and seminal vesicles of castrated rats. Three years later Butenandt and Tscherning⁽³⁾ showed that the substance, which they called androsterone, had the formula $C_{19}H_{30}O_2$ and the structural formula:

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One tenth of a milligram (100 γ) of androsterone is equivalent to 1 capon unit (international unit). It is estimated that approximately two million gallons of urine contain about 1 gram of crystalline androsterone. This substance was subsequently prepared synthetically from cholesterol by Ruzicka and his co-workers.

The daily injection of androsterone into capons will bring about complete restoration of the comb within a few weeks (Callow and Parkes⁽⁴⁾). The isolation of androsterone, however, was not the solution of the problem, for it was found that (1) extracts of male urine caused very much less increase in the weight of the seminal vesicles of castrated rats than equivalent amounts in capon units of testicular extract⁽⁵⁾; (2) androsterone produced growth of the prostate more effectively than growth of the seminal vesicles⁽⁶⁾; (3) a given number of capon units of androsterone produced much less effect on the prostate and seminal vesicles of castrated rats than the same number of capon units of a urine concentrate⁽⁶⁾. From this it was concluded that androsterone was not the actual testis hormone in man.

In 1935 David and his co-workers⁽⁷⁾ in Amsterdam prepared from testicular extract a very active crystalline substance which they called testosterone. This substance has a capon unit value of 0.01 mg and the formula $C_{19}H_{28}O_2$ and the structural formula:

A few months later testosterone was prepared synthetically from cholesterol by Ruzicka and Wettstein, and by Butenandt and Hanisch independently. Testosterone is six to eight times more active on capons than androsterone, and produces a more normal weight relation between the prostate and seminal vesicles than androsterone. When testosterone, however, is compared with androsterone in capon units, it is little, if at all, more active on the prostate than androsterone, whereas testicular extracts per capon unit are many times more active (Deanesly and Parkes⁽⁸⁾). The effect of testosterone on castrated rats can be much increased

by the simultaneous injection of an extract of testes, which alone is completely inactive. This second activating substance in the testis is referred to by the Amsterdam workers as an x substance⁽⁷⁾. It may possibly account for the greater activity of testicular extracts on the prostate compared per capon unit with testosterone.

As with oestrone, the effectiveness of testosterone can be enormously increased by esterification, the acetate and propionate being many times more active than the free hormone. This is probably because the hormone becomes slowly but continuously available to the animal. The action of testosterone acetate and testosterone propionate is so prolonged that injections may be given twice a week instead of daily without loss of effectiveness. The propionate has a more intense and more prolonged action than the acetate, and is the most active male hormone compound so far known (Parkes⁽⁹⁾).

Clinical Uses.

Although we now have an extremely potent preparation of male sex hormone in testosterone propionate, because of the paucity of our knowledge its clinical uses are limited. It is indicated in testicular insufficiency and impotence, and to correct if possible any somatic or psychological disturbances in eunuchoidism and genital hypoplasia. Although it sounds paradoxical the theories of benign prostatic enlargement lead one to suppose that male hormone may be effective in the treatment of this condition. Parkes and Zuckerman⁽¹⁰⁾ have shown that daily injections of oestrone cause prostatic enlargement in monkeys, and the suggestion has been made that an oestrogenic substance is responsible for the condition in man. The experimental production of prostatic enlargement by oestrone is prevented by testosterone propionate and other male hormone compounds (Zuckerman⁽¹¹⁾).

TESTES AND ANTERIOR PITUITARY⁽¹²⁾.

The normal development and function of the testes are dependent on an adequate secretion of the anterior pituitary. After the removal of the pituitary in the adult male rat there is a general atrophy of the testes; daily transplants of the anterior lobe, or injections of anterior lobe extracts, cause an increase of all the components of the testes and induce spermatogenesis. Daily transplants of anterior lobe into normal immature rats result in an increase of all the tissues of the testes and increased growth of the penis and accessory genital glands, but there is no acceleration of spermatogenesis. The hormone which is responsible for these changes is known as the gonadotropic hormone. The action of the hormone on the accessory genital glands is indirect, through stimulation of the interstitial cells of the testes. Similar results have been obtained in immature animals by means of extracts of pregnancy urine, which is rich in gonadotropic hormone. The gonadotropic hormone of pregnancy urine is not identical with that of the pituitary. Its predominant action in the male is to cause hypertrophy of the interstitial tissue of the testes, and it is doubtful whether it induces spermatogenesis.

In immature monkeys the testes are situated at the upper end of the inguinal canal. Injections of extracts of anterior pituitary or of pregnancy urine cause descent of the testes into the scrotum by the fourteenth day.

Treatment of Undescended Testes in Man⁽¹²⁾.

In the vast majority of undescended testes spermatogenesis does not occur; occasional exceptions, however, have been reported. Until puberty many of the tubular cells of the undescended testis are normal in appearance; after puberty degenerative changes take place, consisting of fibrosis, and later disappearance of the tubules, with consequent aspermatogenesis. A bilateral cryptorchid, therefore, is usually sterile, but as secondary sexual characteristics develop normally, it must be concluded that the interstitial tissue is still functional. It appears from experimental work that spermatogenesis is connected with the temperature of the scrotum, which is several degrees lower than that of the inguinal canal or abdominal cavity, and that the degenerative changes take place because of the higher temperature to which it is subjected.

Gonadotropic hormone is now used in the treatment of undescended testes⁽¹³⁾. Before considering such treatment care should be exercised in determining (1) the situation of the testis—if it be ectopic, i.e. lying outside the inguinal canal, descent of the organ cannot be brought about by hormone therapy. (2) whether the testis be anchored in the canal by adhesions: here again hormone therapy will be unsuccessful: the diagnosis, however, of this condition may be very difficult, and (3) whether the testis can be brought into the scrotum by manual pressure; if it can, it is extremely likely that the testis will descend spontaneously before or at puberty, though the administration of hormone will speed its descent.

The best age to begin treatment is between 10 and 13 years. If treatment be started before this period, precocious sexual development may occur; on the other hand, if it be delayed till late in puberty in the hope of spontaneous descent, degenerative changes may take place in the testis.

The mode of action of gonadotropic hormone in bringing about testicular descent is unknown; it may be purely mechanical due to the increasing size of the testis. It has been suggested that the hormone may be involved in the intra-uterine descent of the testes, as it is present in the maternal circulation throughout the period of gestation. It is postulated that mal-descent may be due to inability of the testes at that time to respond to the stimulus.

Treatment of Azoospermia.

As mentioned previously, the injection of gonadotropic hormone from the anterior pituitary will stimulate spermatogenesis in the adult hypophysectomized animal, but it is controversial whether pregnancy urine extract will bring about the same effect. Although there are one or two reports of cases of azoospermia in man successfully treated with urinary gonadotropic hormone, the hormone from the anterior pituitary is more likely to prove successful in this condition.

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