diet No. 380 plus irradiated ergosterol (1 mg per 1,000 gms of diet). Two series were studied: Series I, in which the syrup of ferrous iodide, 1–350 dilution, was given daily, in doses of 3 or 5 drops, as a curative measure, after xerophthalmia had developed; and Series II, in which the iodide solution was given daily in the same dosage, as a preventive measure, from the beginning of the experimental period. The animals were compared with litter mates on the same diet, but without added iodide solution; and also with control rats receiving cod-liver oil as a source of vitamin A, with and without iodide solution. Since the control rats were consistently negative for xerophthalmia, terminal infections, or other pathology, they are not included in the results given here.

In Series I, 45 rats were given iodide treatment daily, when xerophthalmia appeared—usually at about 9 weeks, when constant weight was reached; and were compared with 21 litter mates on the same diet without added iodide solution. The dilute syrup of ferrous iodide was made up fresh each week, and given to the individual rats daily by pipette, calibrated to deliver drops of the solution containing 0.000098 grains of iodine, and 0.0000216 grains of iron. Treatment was continued until death, when autopsy was performed. Weights were taken once or twice a week, and observations made on the eyes three times a week. Three criteria of xerophthalmia were used: (1) swelling of the lids, (2) appearance of blood, first at the inner canthus, later generalized over the lid; and (3) exudate, first serous, later purulent. The degree of these symptoms was described from day to day by plus signs, grading from (+) to (+++).

In practically all the animals, bleeding about the eyes was the same in amount and character in the treated as in the untreated rats; and there was no detectable difference in the swelling or exudate. In a few cases, the iodide seemed to exert a temporary inhibiting effect on bleeding about the eye; but bleeding always reappeared, and xerophthalmia progressed through the usual stages. Since this same phenomenon appeared in a few of the untreated rats also, it can not be regarded as due to the iodide.

Iodide treatment had no effect whatever on the incidence of terminal infections of the glands about the mouth so characteristic of vitamin-A deficient rats. In 100 per cent. of the animals, both with and without iodide treatment, pus was found at death in one or more of the following loci: submaxillary gland, sublingual gland, thyroid, nasal sinuses, and frequently in the middle ear.

Death was hastened by ferrous iodide by an average of 12 days; although the weight at death was about the same for iodide treated as for untreated rats, the difference being 5 grams or less. Food consumption was decidedly less in the iodide treated rats, the average difference being 25 grams, and probably representing what might be expected from the shortened life of the rats treated with iodide.

In Series II, 18 rats were given daily doses of 3 or 5 drops of dilute syrup of ferrous iodide from the beginning of the experimental period, until their death. When so given, the iodide had no effect upon the incidence of terminal infections of the glands about the mouth, nor upon the incidence or course of xerophthalmia, although it did delay the onset of xerophthalmia, and the time of appearance of constant weight and death. It also increased the food consumption.

The results of these experiments, therefore, confirm the work of Mason,[4] who found syrup of ferrous iodide without effect on the xerophthalmia of vitamin-A deficient rats, and further show that ferrous iodide can not substitute for vitamin A in the cure or prevention of terminal infections characteristic of vitamin-A deficiency in rats.

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DUAL ENDOCRINE ACTIVITY OF THE TESTES

EXPERIMENTS, the results of which are now being prepared for publication, and a review of the literature, establish the following facts:

(1) The castration of male rats results in changes which can be placed in two distinct groups, namely, (a) those in which secondary sex characteristics are lost and the secondary sex glands (prostate and seminal vesicles) atrophy, and (b) those in which the pituitary gland undergoes hypertrophy and becomes hyperfunctional; the adrenals also hypertrophy.

(2) Testicular extracts prepared with fat solvents will prevent the atrophy of the secondary sex glands if administered immediately after castration. If the glands are permitted to atrophy the testicular extracts will cause regeneration.

(3) The comb-growth-promoting substance from male urine[1] has the same physiological properties as the hormone extracted from testes. The known chemical and physical characteristics of the hormone from testes and that from urine would indicate that they are identical.

(4) The hormone from urine or blood is derived from the testes since it is not found in the body fluids of castrated men, although it is readily demonstrable in normal men.

[4] Karl E. Mason, *Anat. Record* 51, No. 1, Supplement, 57 (1931) Abstract.

[1] Formula $C_{9}H_{26}O_{2}$—A. Butenandt, *Zeit. für Angewandte Chemie*, 1931, 46, S. 905.

(5) Such a hormonal preparation from urine, when given in doses sufficiently large to cause regeneration of the atrophic secondary sex glands of castrated rats, will neither prevent nor correct the hypertrophy of the pituitary gland and adrenals after castration.

(6) Aqueous testicular extracts, which could have contained no more than an insignificant amount of the prostate-regenerating hormone, prevent the cellular changes from appearing in the pituitary gland after castration of rats and also completely inhibit the hyperfunction of the pituitary gland.

(7) Destruction of the germinal epithelium of the testes will cause pituitary hyperfunction without causing atrophy of the secondary sex glands.

The apparent and only obvious conclusion is that the testicle secretes a hitherto unrecognized water soluble hormone, one function of which is a control of the pituitary gland.

To facilitate discussion, it is essential that the two testicular hormones be differentiated. Using the Greek root "andros" the name "androtin" has been suggested for the benzene soluble substance which is responsible for the development and maintenance of the secondary sex glands and other secondary sex characteristics. This name corresponds in derivation to the name "theelin" suggested by Doisy for the ovarian hormone. The water soluble testicular factor, which is characterized by its action on the pituitary gland, has been called "inhibin" from the Latin verb "inhibere."

The arguments in favor of the presence of two testicular hormones are almost but not absolutely conclusive. It has been demonstrated that "inhibin" in doses which do not influence the secondary sex glands will prevent the hyperfunction of the pituitary gland of castrated animals. Also, as mentioned above, "androtin" in doses sufficient to cause regeneration of the atrophic prostate of castrated rats will not prevent the hypertrophy and hyperplasia of the pituitary gland. It remains to be shown whether or not hyperfunction accompanies hyperplasia and hypertrophy. Fortunately this point can readily be established by available experimental procedures.

There is but the remotest possibility that the established facts can be explained on a basis of hormonal dosage.

The hypothesis of the duality of testicular endocrine function has been developed to explain well-controlled animal experiments. In addition to this experimental evidence there are certain general considerations which lead to the belief that there might be two hormones secreted by the male gonads. The testicle is the male analogue of the ovary. "Androtin" is comparable physiologically and chemically to theelin. Until now there has been no suggestion of a testicular hormone comparable to ovarian progestin. The idea that the testicle produces two hormones is compatible with the histology of the gland.

Prostatic hypertrophy as observed clinically in many adults beyond middle age has had no satisfactory explanation. It is now a well-recognized fact that the pituitary gland can stimulate the testes to the production of sufficient "androtin" to cause prostatic hypertrophy in rats. If the testicular cells producing "inhibin" were to fail, previous to the failure of those structures which produce "androtin," the hypertrophic phenomenon could easily be explained. The absence of "inhibin" would result in hyperfunction of the pituitary gland which, as pointed out above, is a known cause of prostatic hypertrophy in rats. The brilliant researches of Martins and Rocha[2] indicate that there is every possibility that "inhibin" is not produced when the germinal epithelium is destroyed. The destruction of the germinal epithelium does not change the secondary sex characteristics which are maintained by "androtin."

In closing I should like to point out that although nearly all of the experimental facts presented have been established or confirmed in this laboratory, this hypothesis could not have been established had it not been for years of careful investigation in many other laboratories. In particular I wish to thank Professor E. C. Dodds for much assistance received from personal communications concerning the researches on "androtin."

A more intensive study of "inhibin" and "androtin" is now in progress in this laboratory.

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[2] *Endocrinology,* 1931, Vol. 15, p. 421.