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AN ORALLY-ACTIVE SEX-MATURATION FRACTION
 FROM THE ADRENAL GLAND

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Cryptorchism, following the report of Bevan (1) was formerly looked upon in America as a condition which only the surgeon could correct. Shapiro (2) in 1930 showed that the anterior pituitary-like hormone of pregnancy urine, in certain cases of undescended testicles, brought about rapid descent. Engelbach (3) noted that patients with thyroid deficiency and cryptorchism often obtained a descent of the testicles from the administration of thyroid extract. Drake (4) reported a series of boys whose testes responded to the stimulation of puberty. The gonadotropic hormone of the anterior pituitary has been used successfully by Werner (5) and his associates.

This report is based on the observation of boys who, with one exception, have come under my care for a condition that is rarely looked upon as a developmental disease, namely allergy, particularly asthma. In studying these children we were early impressed by the frequency of undescended testicles and also the apparent smallness of the testes in others who presented no signs of cryptorchism. These facts coupled with similar observations of the sexual development in girls, as well as other clinical and experimental data, led the authors to suspect that childhood allergy, at least in the severe form, may be associated with a failure of factors which are responsible for maturation. In our series of patients we also found, in about 30 per cent of cases studied, a hypothyroid condition as evidenced by delayed bone growth. We obtained a history of thyroid, or so-called 'ovarian trouble' in well over 50 per cent of the mothers of these children.

These observations have extended over a period of 3 years, and each of the children discussed was subjected to a thorough physical examination. Precautions were taken to make sure that neither cold nor psychic factors were responsible for their apparent cryptorchism. This report includes no cases in which testicles could be brought into the scrotum by manual traction at first examination.

The adrenal gland possesses powerful growth-stimulating factors. These factors are not all cortin, although cortin is one of them. There seem to be several sex fractions in the adrenal that may be chemically different. The fractions herein discussed not only affect migration of the organ, but also its size.

The extract used in this work is produced by taking whole adrenal glands through the 2 alcohol extractions, and the benzene extractions of the original Swingle and Pfiffner method (6, 7). The residue resulting, when the benzene is evaporated, is taken up in alcohol or glycerine. Whole glands are used ex-

clusively. The whole gland equivalent given to children varies with their ages. Children from 1 to 3 years of age usually receive 1.25 gm. equivalent 3 times a day by mouth; 3 to 6 years of age 2.5 gm. equivalent 3 times a day; 6 to 10 years of age 5 gm. equivalent 3 times a day; and over 10 years of age, 10 gm. equivalent 3 times a day.

Inasmuch as most of these patients were under treatment for their allergic condition, the descent of the testes was a secondary matter, and the observations were probably not always made as soon as the testicles actually completed their descent. As noted, the earliest descent occurred in 2 months, the latest in 17 months, although the latter observations were undoubtedly delayed. The average time was about 9 months.

The boys ranged in age from 2 to 13 years. In all, 9 boys were observed. Three presented bilateral intra-abdominal testes, one presented a unilateral intra-abdominal testicle. In all instances of intra-abdominal testes full descent was obtained. Three boys presented both testes in the inguinal canal, and complete descent of these inguinal testes was observed. Two boys had but one testicle in the canal. In one instance, in which the testicle descended into the scrotum, testicular and penis growth was still retarded after 17 months. In the other case, the testicle grew to normal size, although it did not fully enter the scrotum, and, as the patient says, "It usually rides just below my abdomen if I push it out in the morning." At night there is a tendency for it to remain just inside the external ring. Consequently, this patient cannot be listed as a complete success. Something apparently draws this testicle back into the inguinal canal.

Only a brief history of the pertinent facts relating to the condition of the testes will be given. No attempt will be made to classify the endocrinopathies which these boys show. However, as stated above, they were all sexually underdeveloped and highly allergic.

CASES

Bilateral, intra-abdominal testes. Case 10670. J. E. B., aged 2 years. At the beginning of treatment, Oct. 7, 1935, neither testicle could be made out on examination. On Oct. 15, 1936, both testes had fully descended in one year, and were about normal in size. Extract equivalent to 1.25 gm. of fresh gland was given orally 3 times a day.

Case 10656. J. A., aged 3 years. At the beginning of treatment on Sept. 17, 1935, neither testicle could be palpated, and the penis was small. On July 2, 1936, the right testicle had fully descended; the left was in the canal. On March 1, 1937, both testes had fully descended, and their size was about normal for the age. The descent occurred in 17 months. Extract equivalent to 1.25 gm. of fresh gland was given orally 3 times a day.

Case 10806. R. D., aged 9½ years. At the beginning of treatment on June 29, 1936, neither testicle was palpable. On Sept. 17, 1936, both testes had entered the scrotum. On Nov. 24, 1936, both testes were still in the canal but could be pushed into the scrotum. On March 4, 1937, the testes were still small and in the scrotum. The descent occurred in 8 months. Extract equivalent to 5 gm. of fresh gland was given orally 3 times a day.

Unilateral intra-abdominal testicle. Case 10850. J. G., aged 2 years, 3 months. At the beginning of treatment on Sept. 17, 1936, there was a large accumulation of

fat over the mons. The left testicle was well developed, but not quite in the scrotum. The right testicle could not be made out. On May 17, 1937, the scrotum was well developed, with no excess fat. Both testes were in the scrotum, and about the same size, 1.3 x 0.8 cm. The penis measured about 4 cm. Descent occurred in 8 months. Extract equivalent to 2.5 gm. was given orally 3 times a day.

Bilateral inguinal testes. Case 10635. S. V. D., aged 3 years. At the beginning of treatment on July 26, 1935, both testes were still in the canal. On Dec. 18, 1936, both testes had fully descended. They were smaller than normal. Descent occurred in 17 months. Extract equivalent to 3.3 gm. was given orally 3 times a day.

Case 10797. D. O., aged 7 years. At the beginning of treatment on June 9, 1936, both testes were above the external ring and very small. On July 22, 1936, both testes were high in the scrotum. On Nov. 25, 1936, both testes were well in the scrotum, but apparently not increased in size. Descent occurred in 5 months. Extract equivalent to 5 gm. of fresh gland was given orally 3 times a day.

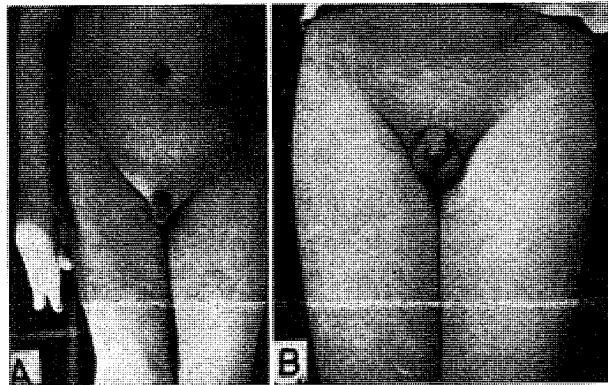


Fig. 1. A. Photograph of genitals of patient, case 10913, March 5, 1937. Taken at a distance of 42 inches. B. Same patient, April 9, 1937. Taken at a distance of 30 inches.

Case 10856. C. W. H., aged 13 years. At the beginning of treatment on Oct. 12, 1936, both testicles (small) were in the inguinal canal. There was little pubic hair. On Dec. 14, 1936, both testes were high in the scrotum. On April 1, 1937, both testes were well in the scrotum, the voice had changed, pubic hair was well developed, and the testes measured about 3 x 2 cm. Descent occurred in 2 months into the scrotum. Extract equivalent to 10 gm. fresh gland was given orally 3 times a day.

Unilateral inguinal testes. Case 10708. G. S. C., aged 11 years. At the beginning of treatment, Dec. 11, 1935, the right testicle was in the scrotum, the left in the canal just below the internal inguinal ring, the testicles were small. On July 7, 1936, both testes were in the scrotum and had greatly increased in relative size, although still small. On Sept. 22, 1936, both testes had fully descended and had possibly increased in size. On Dec. 17, 1936, the testes measured about 1.5 x 1 cm. The penis was still small, being 3 cm. in length. Descent occurred in 17 months. Extract equivalent to 6.7 gm. of fresh gland was given orally 3 times a day.

Case 10658. C. M., aged 12 years. At the beginning of treatment on Sept. 20, 1935, the right testicle was in the scrotum, the left one was above the ring and could not be brought into the canal. The testes were very small. On Jan. 5, 1936, the right testicle was in the scrotum, while the left testicle at the external ring could be pushed into the scrotum; the testes had increased in size; the pubic hair

had begun to develop. On Feb. 28, 1936, the left testicle could be pushed entirely through the ring. On Feb. 2, 1937, the size of the testicles was about normal for a boy of his age; the left testicle could be brought completely into the scrotum, but seemed to have some tissue ahead of it. It had not descended after 17 months. Treatment had been given only one third of this time. Extract equivalent to 6.7 gm. of fresh gland was given orally 3 times a day.

Figure 1 shows a case of a mentally retarded Jewish child who from birth had almost no external genital development. In fact, the Rabbi told the parents he could not circumcise the infant. In the case of this boy, who at the age of 16 had testicles that measured 0.8 x 1 cm., treatment with extract representing 10 gm. equivalent of whole gland 3 times daily for a period of 30 days increased the size of the testicles to 2 x 3 cm. His intellectual improvement was remarkable during the same period.

This extract seems to stimulate growth of testicular size of boys under 4 years of age and those at the age of puberty. Boys between the ages of 4 and 12 years do not seem to experience the same stimulation of testicular growth, although migration of the organs is apparently initiated at any time. To date we have not observed a case of cryptorchism after puberty. Nor have we noted any stimulating sex effects in boys with normal genital development.

There seems to be a very definite relationship between the adrenals, skeletal size and maturation. Maturation seems to be influenced in severe allergy. Changes in the rate and degree of maturation and the recovery from allergy also seem to be related. Even though the adrenal extract is unable to restore a normal maturation balance, the severity of the allergy is usually lessened, if not entirely abated.

SUMMARY

The residue from the benzene fraction obtained by the Swingle and Pfiffner method of extracting adrenal glands contains a factor which is gonadotropic and effective in restoring the physiologic balance of allergic children. It may or may not be cortin.

Of 9 boys with cryptorchism the testes of 3 were both located in the abdomen; 1 boy had but one in the abdomen; 3 had both testes located in the inguinal canal; and 2 had but one testicle in the canal. Complete descent was obtained with 8 boys. One boy presented a single testicle in the inguinal canal which failed to descend completely.

In this group a general enlargement of the testes was noted, although normal size was not attained in all cases. Stimulation of the size of the testes seems to vary with the age of the boy.

A case of definitely arrested development of the external genitalia is presented in which marked stimulation was obtained by 30 days' treatment with the cortical adrenal extract.

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