VARIANTS OF EMBRYONIC
TESTICULAR DYSGENESIS: BILATERAL ANORCHIA AND
THE SYNDROME OF RUDIMENTARY TESTES

By
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ABSTRACT
Three groups of patients, all of whom had chromatin-negative buccal smears are reported. The chromosomes were XY in the 5 cases in which studies were made.
Group A («Syndrome of rudimentary testes») consisted of 4 patients with exceedingly small rudimentary testes who showed no abnormality of male sex differentiation except for a very minute penis. The testes were composed of scanty, small testicular tubules, containing pre-Sertoli cells and some spermatogonia. Foetal Leydig cells were present.
Group B consisted of 4 patients with incompletely masculinized external genitalia and normal male gonaducts but in addition there was persistence of Mullerian elements in all cases, with an infantile uterus in two cases. These findings were similar to those of male pseudohermaphrodites; but careful surgical exploration with extensive microscopic sections revealed no gonadal tissue. Small nodules were present consisting only of fibrous tissue and in three cases a small clump of cells resembling either aberrant

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adrenal cells or Leydig cells. It is possible that these patients were male pseudohermaphrodites who had had defective testes in early embryonic life which had degenerated later.

Group C («Bilateral Anorchia») consisted of 4 patients of adolescent or adult age whose sex organs were entirely male. Testes had never been palpated. They failed to develop secondary sexual characteristics at puberty and they grew tall with eunuchoid proportions. Careful surgical exploration revealed no gonads in either the inguinal canals or the abdomen. The vasa deferentia were traced to their ends and were found to end blindly or in rudimentary epididymes. According to the theory of Jost functioning testes must have been present in the stage of embryonic sex differentiation and degenerated later.

The selection of the sex of rearing is discussed and it is pointed out that the patients of Group A and B have a phallus so small that they can never function adequately as males. Accordingly it is better that they be assigned the female gender in early infancy. This opinion is confirmed by the fact that two patients of Group B who were raised as males and treated with testosterone were psychologically very badly maladjusted and in adult life decided to change to the female role.

In a recent report (Bergada et al. 1962) on 41 patients with abnormal gonadogenesis or with male pseudohermaphroditism who showed discordances between the type of gonad and the sex differentiation of the gonaduct and/or external genitalia, we purposely omitted a number of cases which did not fit these categories. We wish now to present the following 12 patients all of whom had chromatin negative buccal smear, and 46 chromosomes with XY sex chromosomes in the 5 cases in which these studies were done.

A – 4 patients with exceedingly small »rudimentary« testes who showed no abnormality of male sex differentiation except for a very minute penis (»Syndrome of rudimentary testes«).

B – 4 patients with incompletely masculinized external genitalia, normal male gonaducts and some development of the Mullerian ducts. The exploratory laparotomy revealed very small nodules bilaterally in the place of the gonads, but histologically no gonadal tissue was found.

C – 4 patients of adolescent or adult age who were anatomically normal males but failed to develop secondary sexual characteristics in whom no gonads were found (»bilateral anorchia«).

Group A. »Syndrome of rudimentary testes«

Wilkins (1957, 1958, 1960) has referred to these cases previously as »the syndrome of rudimentary testes« and has considered that they belonged to the spectrum of defective gonadal development which he referred to as »gonadal dysgenesis«.
Case 1 (C. W. No. B 87588). At the age of 12 days the external genitalia showed complete fusion of the labioscrotal folds, the phallus was very small, composed of a short corpus about 0.5 cm in length embedded in the subcutaneous tissue below the mons pubis. The urethra opened on the end of this very minute structure. No gonads were palpable in the scrotum. On rectal examination no internal sex organs could be felt. Buccal smear showed chromatin negative pattern. Chromosomal studies performed by Dr. Ferguson-Smith on bone marrow revealed 46 chromosomes with XY sex chromosomes. Because the child’s phallus was so small that it could never be expected to appear or function as a penis, it was decided to raise the patient as a female. At the age of 15 months an exploratory laparotomy was performed revealing normal development of the male genital ducts, and absence of Mullerian structures. Bilateral small white structures measuring no more than 0.7 by 0.5 cm which appeared to be testes were seen in the inguinal canals and removed. The urethra was slit open in the midline for a distance of about 3 cm proximal to the meatus so that its orifice was moved posteriorly to the mid-perineum. Subcutaneous tissues were dissected in such a way that a cleft was made in the perineum and the urethral mucosa was tacked to the edges of the skin. Microscopic examination of the gonads showed an area of tubular structures with a single layer of low cuboidal epithelium forming a cavernous structure resembling the rete testis. Adjoining it, there was a very small area containing a few small seminiferous tubules (Fig. 1). The tubules contained pre-Sertoli cells and a few spermatogonia. Interestingly, the scanty interstitial tissue revealed fairly well defined Leydig cells (Fig. 2). Epididymus and was deferens were also observed on microscopic examination.

Case 2 (M. C. No. 94 06 95). This 26 days old infant had a congenital heart defect and muscular hypotonia. The external genitalia were completely male. The phallus was very small and was composed mainly of preputial skin with the urethra opening at the tip. However, a slender corpus measuring 1.5 × 0.3 cm was felt in the subcutaneous tissue. No gonads were palpable in the scrotum. A small structure approximately 0.5 cm in diameter was felt in the right inguinal canal. Nothing was felt on the left side. Urethrogram showed a normal urethra with no communicating vaginal pouch. Buccal smear revealed chromatin negative pattern and chromosomal studies showed 46 (XY) constitution. Exploratory laparotomy showed bilaterally vasa deferentia with very small testes at their ends – measuring 0.7 cm × 0.4 cm. No Mullerian structures were observed. The histologic examination of the gonads revealed only a small area of testicular tissue containing small seminiferous tubules (Fig. 3). These were made up of pre-Sertoli cells with only occasionally spermatogonia. (Fig. 4). The interstitial tissue was abundant and some Leydig cells were still present.

Case 3 (Sh. R. No. B 51832). This patient was seen at 1 month of age because of abnormal external genitalia. The labioscrotal folds were completely fused in the midline. The phallus was very small measuring no more than 1 cm in length. The tissue was soft and flabby and very little erectile tissue was palpable. The urethral meatus was situated at the tip of the phallus. No gonads were palpable either in the scrotum or in the inguinal canals. Buccal smear showed chromatin negative pattern. An urethrogram revealed absence of vagina. Exploratory laparotomy showed no Mullerian structures. The gonads were at the internal inguinal ring bilaterally resembling very small testes measuring only 0.3 × 0.5 cm. On each side extending from the testis there was a vas deferens. Labioscrotal separation was carried out from the tip of the urethra posteriorly for some distance so as to create a shallow vulval sulcus into which the urethra opened. Microscopic examination of the gonads showed only a small area of testicular tissue. However, examination of the seminiferous tubules under high magnification showed

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Fig. 1.
(Case 1, age 15 months).
Histology of the gonad showing rete tubules and on upper right a single small area of testicular tissue (× 38).

Fig. 2.
(Case 1, age 15 months).
High magnification of former figure showing some rudimentary seminiferous tubules with occasional spermatogonia and interstitial tissue containing some Leydig cells (× 300).
Fig. 3.
(Case 2, age 13 months).
Section of the gonad revealing rudimentary testicular tissue (×38).

Fig. 4.
(Case 2, age 13 months).
High magnification of previous section showing spermatogonia in seminiferous tubules (×75).
### Table 1.

<table>
<thead>
<tr>
<th>Name</th>
<th>Age examined (years)</th>
<th>Age explored (years)</th>
<th>Present age (years)</th>
<th>Gonads (cm)</th>
<th>Phallus (cm)</th>
<th>Gonaducts</th>
<th>Sex of rearing</th>
<th>Height attained (cm)</th>
<th>U/L ratio</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. C. W.</td>
<td>12</td>
<td>$1^{1/4}$</td>
<td>$4^{1/2}$</td>
<td>$0.7 \times 0.5$</td>
<td>0.5 urethra</td>
<td>Vasa</td>
<td>$\varnothing$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. M. C.</td>
<td>26</td>
<td>$1^{1/2}$</td>
<td>$1^{1/2}$</td>
<td>$0.7 \times 0.4$</td>
<td>$1.5 \times 0.3$ urethra</td>
<td>Vasa</td>
<td>$\varnothing$</td>
<td></td>
<td></td>
<td>Ventricular septal defect</td>
</tr>
<tr>
<td>3. S. R.</td>
<td>24</td>
<td>$1/12$</td>
<td>$3^{1/4}$</td>
<td>$0.5 \times 0.3$</td>
<td>$1.0$ urethra</td>
<td>Vasa</td>
<td>$\varnothing$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. D. H.</td>
<td>11 months</td>
<td>$11/12$</td>
<td>$9^{1/2}$</td>
<td>$0.5 ?$ No biopsy</td>
<td>$1.5 \times 0.5$ urethra</td>
<td>Vasa</td>
<td>$\varnothing$</td>
<td></td>
<td></td>
<td>At 8½ years no growth of penis. Ht. av.</td>
</tr>
</tbody>
</table>

**Group A - Rudimentary testis syndrome**

**Group B - Male pseudohermaphrodites without gonads (?)**

<p>| 5. K. C. | 17 | 23 | 25 | None | $2.0 \times 1.0$ hypospad. | Comm. vagina + uterus | $\varnothing \rightarrow \varnothing \rightarrow \varnothing$ | 183 | 0.77 | Treated with test. 17–22 years. Oestrogen after 22 years. F. S. H. 26.4 M. U. |
| 6. P. C. | 11½ | 19 | 20 | None fibrous nodule | $1.0 \times 0.5$ hypospad. | urethrogram dem. vagina + uterus | $\varnothing \rightarrow \varnothing$ | 170 | 0.88 | F. S. H. 26.4 M. U. |</p>
<table>
<thead>
<tr>
<th>No.</th>
<th>Name</th>
<th>Age</th>
<th>Height</th>
<th>pub.</th>
<th>Genitalia</th>
<th>Genitalia</th>
<th>Age at pub.</th>
<th>Age at first pub.</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.</td>
<td>T. J.</td>
<td>13½ years</td>
<td>13½</td>
<td>15½</td>
<td>None fibrous nodules</td>
<td>1.5 × 1.5 hypospad.</td>
<td>rud. tubes no uterus vag. pouch Vasa</td>
<td>169 0.90 at 13 years</td>
</tr>
<tr>
<td>8.</td>
<td>E. A. B.</td>
<td>3 months</td>
<td>1/4</td>
<td>1½</td>
<td>nodules 1.0 × 0.3 fibrous no gonad. tissue</td>
<td>1.0 × 1.0 urethra at tip</td>
<td>rud. tubes Vasa + epididy.</td>
<td>169 0.90 at 13 years</td>
</tr>
<tr>
<td>9.</td>
<td>P. B.</td>
<td>9½ years</td>
<td>12½</td>
<td>23</td>
<td>None</td>
<td>5.0 × 2* Normal</td>
<td>Vasa</td>
<td>187 0.88 Treated with testosterone at 10½ years</td>
</tr>
<tr>
<td>10.</td>
<td>O. T.</td>
<td>17½ years</td>
<td>12½</td>
<td>25</td>
<td>None</td>
<td>4.5 × 2 Normal</td>
<td>Vasa</td>
<td>177 0.89 Treated with testosterone at 17½ years. Married at 20 years</td>
</tr>
<tr>
<td>11.</td>
<td>R. B.</td>
<td>21½ years</td>
<td>12</td>
<td>22</td>
<td>None</td>
<td>8.0 × 2 Normal</td>
<td>Vasa?</td>
<td>173 0.86 Married at 19½ years. Treated with testosterone at 21½ years</td>
</tr>
<tr>
<td>12.</td>
<td>C. O.</td>
<td>2½ years</td>
<td>6</td>
<td>8</td>
<td>None</td>
<td>4.0 × 1.7 Vasa?</td>
<td>168 0.97 Treated with testosterone at 12½ years</td>
<td></td>
</tr>
</tbody>
</table>

* Before treatment.

**Group C - Bilateral anorchia**
fairly well developed tubules with pre-Sertoli cells and spermatogonia (Fig. 5). The interstitial tissue revealed some Leydig cells.

Case 4 (D. H. No. B 241). This patient was first seen (1953) at the age of 11 months because of small genitalia. The penis was normally formed with the urethra opening at the end but measured only 1.5 × 0.5 cm. No gonads were palpable. The chromatin pattern in a buccal smear was negative. Exploratory laparotomy by Dr. W. W. Scott revealed no female organs. A vas deferens was seen on each side terminating just inside the internal inguinal ring where there was a very small whitish oval body thought to be a testis. No biopsy was made of these bodies. The patient continued to be raised as a male. When he was last seen at the age of 8½ years he was of slightly taller than average height; the penis had not grown and no sexual development had occurred.

Group B. Male pseudohermaphrodites without testes (?)

These patients were originally classified as male pseudohermaphrodites because they had chromatin negative buccal smears and it was considered that their partial masculinization must have depended upon the presence of a foetal testis.

Case 5 (K. C. No. B 1770). Patient was raised as a girl for the first 6 years and was then changed to a boy at the insistence of an urologist. At the age of 17 years because of lack of male development another surgeon suggested that the patient be changed back to a girl, and he was referred to our clinic. At that time his height was 169 cm and he had marked eunuchoid proportions with an U/L (upper/lower) ratio of 0.79. The
external genitalia consisted of 2 cm long preputial folds covering a small glans measuring 1 cm long. Immediately below the phallus was an orifice about 1 cm in length. No masses were palpable in the scrotal folds. Although the genitalia looked more female than male, since the patient was 17 years old, it was thought better to continue raising him as a boy. Later on he was treated with methyltestosterone in the hope of increasing the size of his penis and preventing markedly eunuchoid skeletal development. This therapy produced only preputial hypertrophy, more pubic hair, deepening of the voice and some breast development. The patient took treatment only intermittently and at the age of 20 years his height was 183 cm and he was exceedingly eunuchoid with U/L ratio of 0.77. As a consequence of the lack of improvement of the external genitalia which remained ambiguous with a very small phallus the patient decided at the age of 23 years to change to a female and started taking oestrogens. Buccal smear showed a chromatin negative pattern. Chromosomal study revealed a 46 XY chromosomal constitution. A vagina communicating with the urogenital sinus was seen by urethroscopy. At surgery an infantile uterus 2 cm in diameter supported bilaterally by round ligaments was found. Vasa deferentia were seen bilaterally. A small body, 1.5 cm in diameter which grossly was thought to be a testis was present in the right inguinal canal. A similar structure was reported removed on a previous exploration on the left side. The labioscrotal folds were divided in the midline and the edge of the urogenital sinus sutured to the skin. Microscopic examination of what was thought to be the gonad showed absence of testicular or ovarian tissue and revealed only connective tissue and a few tubular structures with a single layer of low epithelium resembling rete tubules. The nodule on the other side was not available for microscopic examination. The vasa deferentia, Fallopian tubes and uterus were identified in the microscopic sections.

Fig. 6.
(Case 6, age 19 years).
Clump of cells resembling adrenal cells or Leydig cells found in fibrous nodule in broad ligament (×225).
Case 6 (Ph. C. No. 1769). The brother of the patient K. C. showing the same syndrome was first seen at 11½ years. External genitalia revealed a small phallus consisting of preputial folds measuring 2 cm in length containing a small glans of about 1 cm length. A single orifice could be seen below the glans. Urethrogram revealed a vagina communicating with the urogenital sinus. At age 19, the U/L. ratio was 0.88, the phallus measured 1.0 × 0.5 cm and there were only 30 or 40 hairs over the pubic region. No gonads were palpable in the labioscrotal folds or in the inguinal canals. Buccal smear showed a chromatin negative pattern. Chromosomal studies revealed 46 XY chromosomal pattern. By that time, as a consequence of the uselessness of his genitalia, which failed to improve with androgenic therapy, and in view of the fairly good result of his new «sister», the patient decided to changes also to a female role. Exploratory laparotomy revealed findings identical to those of the other case: an infantile uterus, bilateral vasa deferentia and at their ends what appeared to be two small gonads. Microscopic examination of numerous serial sections made through the adnexa and including these bodies revealed no seminiferous tubules or other characteristic testicular or ovarian structures. Fallopian tubes and vasa deferentia were identified. In addition there were tubules thought to be rudimentary epididymus and others resembling rete tubules which were lined by characteristic flat epithelium. In the midst of these on the left side there was a clump of cells (50–75 cm diameter) which resembled either Leydig or adrenal cells. No crystals of Reinke could be identified (Fig. 6).

Case 7 (T. J. B76559). The patient had ambiguous external genitalia at birth and was raised as a girl. At 12 years she was explored elsewhere and it was reported that no sex organs were found. At 13 years the height was 169 cm, with an upper lower ratio of 0.90 which represents eunuchoid proportions. She did not show breast development and there were only 10 or 15 short hairs over the pubic region. The phallus measured 1.5 × 1 cm consisting mainly of preputial folds. Labioscrotal folds were fused in the midline except at the base of the phallus where a funnel shaped orifice 1 cm in diameter was observed. No gonads were felt. Urethroscopy showed an urogenital sinus with a communicating vaginal pouch measuring no more than 2 cm in depth and ending blindly. Buccal smear revealed a chromatin negative pattern. At surgery no uterus was seen, but rudimentary Fallopian tubes were present bilaterally. Vasa deferentia were also present on both sides. Two small nodules with the gross appearance of testes were seen at the ends of the genital ducts. Microscopic examination revealed absence of testicular or ovarian tissue; only connective tissue and blood vessels were observed. Sections of epididymis, vas deferens and Fallopian tube were seen on both sides. Treatment with oestrogens was started and some breast development was immediately induced.

Case 8 (E. A. B. No. 912768). This patient was seen at the age of 3 months because of small external genitalia which, however, were of entirely male type. The phallus was very small measuring 1 × 1 cm and consisted almost entirely of preputial skin. The urethral meatus was at the tip of the phallus. No palpable gonads were felt in the scrotal sac or in the inguinal areas. Buccal smear showed a chromatin negative pattern. Exploratory laparotomy revealed no uterus, but rudimentary Fallopian tubes and vasa deferentia were seen bilaterally. In the location where one would expect to find ovaries there were bilateral structures measuring 1.0 × 0.3 × 0.3 cm. Microscopic examination of these structures showed no gonadal tissue and not even fibrous stroma resembling ovarian-stroma was found. However, rudimentary Fallopian tubes, vasa deferentia and epididymes were identified microscopically. A small nodule of cells resembling aberrant adrenal rest cells was present on the right side. The structures which had been thought to represent gonads were removed and separation of the labioscrotal folds was carried out.
Group C. »Bilateral anorchia«

These patients were thought originally to be normal males except for bilateral cryptorchidism. On operation to correct the undescended testes, however, diligent search failed to reveal any gonad on either side. In previous writings (Rea 1938; Wilkins 1957) such cases have been reported as »bilateral anorchia«.

Case 9 (P. B. A 61553). This patient was thought to be a cryptorchid male whose testes had never been felt. At the age of 3 years he had been treated unsuccessfully with weekly injections of chorionic gonadotrophin for a period of one year. When he was seen at 9½ years his height of 150 cm was 17 cm taller than the average for his age but his skeletal ratio was normal (U/L 1.03). The penis was normally formed and measured 5 × 2 cm. No gonads were felt in the scrotum or canals. There was no secondary sexual development. The 17-KS output was 3–4 mg per day. He was given daily injections of 1000 IU chorionic gonadotrophin for a month without any effect upon the 17-KS excretion or the nitrogen balance. At the age of 12½ years his height was 163 cm and his proportions had become somewhat eunuchoid with a U/L ratio of 0.92. A few pubic hairs had appeared but otherwise there was no sexual development. The 17-KS excretion was 9.7 mg per day. The urinary gonadotrophins were elevated to 192 M. U. per day. Chromatin pattern negative in buccal smears. Surgical exploration of the abdomen and inguinal canals carried out by Dr. W. W. Scott revealed no gonads although the vasa deferentia were identified on both sides and traced along the lateral pelvic walls to their ends near the internal rings. No female organs were seen. Treatment was not begun until he was 13½ years when his height had reached 168 cm and the U/L ratio was 0.89. At this time there was still no secondary sexual development except that about a dozen long dark pubic hairs had appeared. The penis measured 5.5 × 1.5 cm and the prostate was not felt. Treatment with monthly injections of testosterone oenanthate was begun and six months later artificial testes were implanted in the scrotum. The response in sexual development was excellent including heavy growth of both body and facial hair. The penis developed to the size of 13.5 × 3.5 cm. He continued to grow until he was 18½ years old at which time his height was 187 cm, lower segment 99 cm with U/L ratio 0.88. Under treatment he had normal libido and was very well adjusted psychologically.

Case 10 (O. T. 69 28 87). This patient had been thought to have bilateral cryptorchidism and at the age of one year had been given three injections of chorionic gonadotrophin at weekly intervals without effect. At the age of 12½ years no sexual development had occurred and the 17-KS were 1.5 mg per day. Abdominal and inguinal exploration was carried out at the Lynchburg General Hospital and no testes were found. The operative note reads: »The right inguinal canal was opened and the vas and its accompanying vessels were identified and followed into the scrotum. The vas ended in a blind pouch, and the fascia covering it thinned out and was connected to the tissue in the floor of the scrotum. This was followed up and the peritoneal cavity opened and the pelvis explored. There was a rudimentary shelf resembling a broad ligament, but there was no structure resembling uterus, tubes or gonads. The left side was then explored and a similar condition found.«

At the age of 17½ years he was referred to our clinic because of lack of sexual development. His height was 166 cm with a U/L ratio of 0.88. The penis was normally formed of preadolescent size, measuring 4.5 × 2.0 cm. The prostate was not felt. The voice was high pitched. There were about two dozen pubic hairs and some sparse axillary hairs but no facial hair. The urinary 17-KS were 5.0 to 8.0 mg per day.

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Urinary gonadotrophins 106 M. U./day. The buccal smear showed chromatin negative nuclei. Treatment with monthly injections of testosterone oenanthate was begun and eight months later artificial testes were implanted in his scrotum. He responded to treatment with excellent secondary sexual development including growth of beard. The penis reached the size of 11.0 × 3.0. He continued to grow and at the age of 22 years had attained a height of 177 cm with a U/L ratio of 0.89. At the age of 20 years he was married. He is now 25 years old, living a normal marital life with satisfactory sexual activity.

Case 11 (R. B. 79 45 77). This patient was referred to us at the age of 21½ years. Testes had never been palpated. At the age of 12 years an exploratory laparotomy at the Baltimore City Hospital failed to reveal any gonads. No female organs were found. In spite of this he married at the age of 19½ years. Both he and his wife claimed that they had mutually satisfactory intercourse three or four times a week, although he had orgasms without ejaculations. When examined at the age of 21½ years his height was 173 cm with eunuchoid proportions (U/L ratio 0.86). The epiphyseal development was between 12 and 14 years, no fusions having occurred. His sexual development was decidedly immature. The penis which was normally formed measured 8 × 2 cm. No prostate was felt. His voice was high pitched. Pubic and axillary hair were scanty and facial hair was absent. Buccal smear showed chromatin negative nuclei. Urinary 17-KS were 3.3 mg per day. Urinary gonadotrophins 105 M. U./day. Treatment with monthly injections of testosterone oenanthate was begun and has resulted in marked improvement in his sexual development. There has been increased libido and normal ejaculations now occur. Both he and his wife now recognize improvement in their sexual relations. During the past year his height has increased to 176 cm.

Case 12 (C. O. No. 70 95 76). The patient was referred at the age of 2½ years because neither testis had been palpable. The external genitalia were normal and the penis measured 4 × 1.3 cm. At the age of 6½ years Dr. W. W. Scott explored the right inguinal canal, identified the vas deferens and followed it into the scrotal sac in the depth of which it »splayed out and disappeared«. It was traced proximally along its normal course along the pelvic peritoneum and normal spermatic vessels were traced. No structure resembling a testis was encountered. The end and the entire length of the vas was excised and serial sections were made. Microscopic examinations of these showed the vas and smooth muscle fibers but no structures resembling a gonad. At the age of 8 years an exploration of the left side was made with identical findings. At this time his height age was 11½ years with normal skeletal proportions (U/L ratio of 0.99). Buccal smear showed chromatin negative pattern. At the age of 12 years his height of 168 cm was 23 cm greater than average but the skeletal ratio was normal (0.97). The epiphyseal development was 11½ years. The penis measured 4 × 1.7 cm. Three or four dozen coarse pubic hairs were present but there were no other evidences of secondary sexual development. At this time artificial testes were implanted in the scrotum and treatment with testosterone oenanthate was begun.

Selection of sex of rearing and treatment
In all 8 patients of Groups A and B the phallus was so exceedingly small that it could never be expected to look like or function as a normal penis. In addition the four patients of Group B had incomplete labioscrotal fusion with the orifice of the urogenital sinus opening on the perineum necessitating that they sit to urinate. The reasons why it is preferable to raise such individuals
as females have been discussed in detail elsewhere (Money et al. 1955; Wilkins 1959, 1960). Of the 5 patients (cases 1, 2, 3, 4 and 8) whose sex of rearing we were permitted to select during the first months of life, the female gender was chosen in four but the fifth (No. 4) was raised as a boy in the hope that the penis, which was only 1.5 cm long might grow. No growth had occurred when he was last seen at 8½ years. Both the patient and his parents are considerably disturbed. Patient No. 5 (K.C.) had been raised first as a girl and was changed to a boy at the age of 7 years. The younger brother (No. 6 P.C.) was accepted as a boy from the beginning. When we were consulted at the ages of 17 years and 11½ years respectively, it was thought that it might be psychologically hazardous to change their gender roles. Attempts to increase the masculinility of K.C. by the administration of methyltestosterone were relatively unsuccessful resulting only in deepening of the voice, increased pubic hair and muscular development. There was hypertrophy of the preputial folds but no real growth of the tiny hypospadic phallus. This boy and also his younger brother became progressively more maladjusted and insecure psychologically. Eventually at the ages of 23 years and 19 years respectively they insisted that they wished to change to the female role. After complete surgical explorations were carried out demonstrating the absence of gonads, they assumed female clothes and coiffeurs. Administration of oestrogens resulted in moderately good breast development and vaginoplastics were undertaken. They are still psychologically unstable individuals but claim to be more content in the female than male role.

The inability of these patients who have an exceedingly small phallus to adapt to the male role even when treated with androgen strengthens our conviction that they should be raised as females. It would be preferable that after thorough studies and exploratory laparotomy the decision be made in the earliest months of life. At the time of surgery separation of the labioscrotal folds should be carried out, if necessary splitting the urethra with a ventral midline incision (Jones & Wilkins 1961). We consider it also better to remove rudimentary testes if they are present although it is improbable that they would cause masculinization at puberty. It should be planned to institute oestrogenic therapy at puberty and to perform a plastic construction of a vagina in the late teens or twenties.

Changes of sex after the first two years of life may be accompanied by serious psychologic problems of adjustment but even then should be considered in some of the cases of Group A and B. This should be preceded by extensive psychologic study and preparation and the decision should probably be left to the patient after the adolescent years, as was done in cases 5 and 6.

The patients with bilateral anorchia described as Group C present entirely different diagnostic and therapeutic problems. The male sex organs are normally developed and of average preadolescent size and the patients are mis-
taken for cryptorchid boys. If untreated they remain sexually immature at puberty and develop eunuchoid proportions. However, they have a small amount of sexual hair and the 17-ketosteroids, probably of adrenal origin, are usually less depressed than in hypopituitary patients. Likewise the response to testosterone therapy, particularly in growth of the beard, seems to us much better than in hypopituitary infantilism. The diagnosis of bilateral anorchia is usually made only when surgical exploration is carried out for the purpose of orchidopexy. Urinary gonadotrophins become elevated after the age of puberty. Perhaps an earlier preoperative diagnosis could be made by studying the response to chorionic gonadotrophin (Cullen et al. 1957; Huis in't Veld et al. 1961). Its failure to induce early sexual changes or a rise of 17-KS might suggest that the testes are absent. The institution of androgenic therapy in moderate doses somewhat before the usual age of puberty might prevent the development of eunuchoid proportions.

**DISCUSSION**

The dependence of masculinization of the gonaducts upon «male organizing substances» of a foetal testis has been emphasized repeatedly in our previous writings (Wilkins 1957, 1958; Bergada et al. 1962). Since in all the patients reported here vasa deferentia were present, one must presume that during the critical period of gonaduct differentiation foetal testes were present and functioning.

In the 3 patients of Group A in whom gonadal biopsies were made testes were present bilaterally but were exceedingly small compared to those of normal boys of similar age. Histologically they showed small seminiferous tubules which in Cases 1 and 3 were very scanty. They contained pre-Sertoli cells and also spermatogonia in a large number of tubules. The interstitial tissue revealed fibroblasts and some Leydig cells considered remnants of the foetal Leydig cells since patients 2 and 3 were only 1 month old. However, it was considered unusual to find them in patient 1, an infant who was 15 months old. It should be pointed out that a unilateral «rudimentary testis» was present also in 2 cases of asymmetric gonadal development reported in the previous paper (Bergada et al. 1962). Male sex differentiation of both gonaducts and external genitalia was complete except that the genital tubercle had developed into an exceedingly small penis containing a normal urethra. Androgen must have been produced in adequate amounts at the critical time to cause labioscrotal fusion and the formation of the corpus spongiosum. Whether it was quantitatively insufficient for the growth of the penis or whether it decreased during the stage when such growth occurs cannot be determined. Whether the small penis was due to lack of response of a target organ as happened in the two patients to whom we gave testosterone we do
not know. Whether such testes if they persist to the age of puberty would bring about satisfactory development of the penis and male secondary characteristics is also not known. It was felt that this was so unlikely that it was better psychologically to raise these patients as females, gonadectomy them and feminize their genitalia surgically.

In patients of Group B, Mullerian suppression was not complete so that Fallopian tubes and a rudimentary uterus were found in addition to vasa deferentia. Likewise, there was incomplete masculinization of the external genitalia. In these respects they resembled a number of the male pseudo-hermaphrodites reported previously (Bergada et al. 1962). On surgical exploration, in the adnexa small nodules were seen which grossly were thought to be testes. On careful microscopic examination of serial sections of this tissue no true testicular or ovarian structures were found. There were tubular structures of various types which resembled epididymis and also rete tubules but nothing resembling seminiferous tubules. In three of the cases (No. 5, 6 and 8), however, in the vicinity of the tubules there were distinct clumps of cells which appeared to be either aberrant adrenal cells or Leydig cells. It is impossible to say whether more completely developed testes had functioned at the stage of gonaduct differentiation sufficiently to cause development of the Wolffian ducts but not enough to suppress Mullerian duct development. Possibly they degenerated slightly later during the stage of masculinization of the external genitalia. The role of the adrenal or Leydig cells is not known. Similar cells were found in the primitive genital streak in patients with atypical gonadal aplasia who had completely feminized gonaducts and only phallic enlargement without labioscrotal fusion (Bergada et al. 1962).

In patients reported to have complete bilateral anorchia, there is always a possibility that a surgeon may have failed to find a testis located in some unusual position. In the four cases reported here a thorough search was made of the pelvic cavity and the inguinal canals. The vasa deferentia were traced to their ends and were found to end blindly or in rudimentary epididymes. Unfortunately in only one case a biopsy was made of the ends of these structures. The absence of secondary sexual development confirmed the fact that there were no functioning gonads. Cases of unilateral anorchia (monorchia) have been reported frequently. In 1938 Rea could find reports of only 11 bilateral cases. In all cases there was complete masculinization of both the genital ducts and external genitalia but absence of secondary adolescent development. If the present theories of sex differentiation are correct one must presume that functioning foetal testes were present throughout the stage of differentiation and degenerated subsequently. The cause of such degenerations is not known. There is no history of any trauma or inflammatory condition occurring post-natally. The probability that torsion of the spermatic cord impairing the circulation might occur during descent of the testis prenatally must be considered.
Haemorrhagic infarction of the testis has been described in the newborn (*Fernicola* 1954) and conceivably might fail to be recognized. The probability of these accidents occurring bilaterally seems unlikely.

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