THE GENESIS OF EXSTROPHY OF THE BLADDER AND EPISPADIAS

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EIGHTEEN FIGURES

The manner of origin of exstrophy of the bladder, and more particularly the epispadias commonly associated with it, has long remained a subject of conjecture and controversy. This is due primarily to the lack of availability of stages in their genesis. No one, as far as we could ascertain from the literature, has ever seen epispadias or exstrophy in young embryos. That, after all, is not surprising because of the relative infrequency of these anomalies. Campbell, in his ''Clinical Pediatric Urology'' ('51), states that this combination of abnormalities occurs once in 40,000 to 50,000 births. Winsbury-White ('48) gives the same range of incidence. It is quite understandable, therefore, that as yet no embryos have been described which show exstrophy and epispadias in their developmental phases.

In the absence of material showing the crucial developmental steps involved, the condition as seen at birth has remained a constant invitation to theorizing. Since it is well known that the human embryo does not normally pass through any developmental stage comparable to either exstrophy or epispadias, the much overworked developmental arrest concept is obviously futile in interpreting these associated anomalies.

It would needlessly expand the present communication to attempt to discuss all the alternative theories that have been advanced. The papers of Connell ('01), von Geldern ('24), and Wyburn ('37) give excellent accounts of the work

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of the various investigators and their hypotheses. The interpretations suggested have been diverse. The advocates of the "Berstungs Theorie" hold that the ventral wall of the embryonic bladder is ruptured due to abnormal retention of fluids. This explanation is inadequate in that it offers no interpretation of the concomitant epispadias. Moreover one instinctively prefers a hypothesis which utilizes mechanisms such as are known to occur in the course of development and are already familiar as causative factors in other anomalies. Others have felt that the primary defect involves an abnormally formed umbilical cord or an atypically located yolkstalk. Still others have sought an explanation in intra-uterine disease. None of these hypotheses has seemed sufficiently plausible to gain general acceptance.

In 1869, Wood emphasized that exstrophy of the bladder was regularly accompanied by epispadias. Although this is not invariably the case, it is nearly always so, and furnishes the clue to what seems the most fruitful line of reasoning. Shattock (1887, p. 171) proposed that "the primitive cloacal invagination of the surface which normally lays open the lower end of the rectum and the lower end of the urogenital sinus, does in these cases, by an undue extension forwards and upwards, lay open the anterior wall of the urogenital sinus and the anterior wall of the bladder." He further stated (1894, p. 123) that "in the male it must be assumed that in the subsequent process of development, the halves of the penis (which would be completely double like the clitoris in the female) unite from below after the septum has descended between the urogenital sinus and the rectum to the perinaeum, i.e., the halves of the penis are united by the ingrowth of what would be the urethral floor whilst the cleft persists in the rest of the organ." As will be seen from the subsequent discussion, our own interpretation of these defects comes closer to that of Shattock than to any other previously suggested.

Johnston ('13), like Shattock, was of the opinion that exstrophy of the bladder is due to the rupture of the cloacal

membrane cephalic to the usual territory involved, and he emphasized that the departure from normal must have occurred early in development. He did not, however, suggest any explanation as to why the penis or clitoris is situated caudal to the site of rupture.

Von Geldern ('24) also believed that exstrophy is to be regarded as involving an abnormal rupturing of the cloacal membrane, although he felt that the explanations proposed by Shattock and by Johnston could not be accepted in their entirety, particularly with regard to the epispadias that accompanies exstrophy. Von Geldern's criticism was to the effect that both Shattock and Johnston had assumed "that the penis at one stage of its development is entirely split in half." He went on to say (p. 90) that "this, of course, may occur in some cases . . . but it is not the general procedure." The work of Keibel (1896), Spaulding ('21), Heuser ('32), Holmdahl ('35), and others has clarified the early stages in the normal development of the cloacal region of the young human embryo and shows that the primordia of the genital tubercle are at first paired. On this foundation it is possible to visualize a series of developmental stages that, starting early in the third week after fertilization, gives rise to the condition of exstrophy and epispadias. It is our conviction that the key to the understanding of the origin of this complex of anomalies lies in the correct interpretation of the epispadias. We believe that by starting with sufficiently young stages and placing the emphasis on relative positions of growing parts, and on the timing of their development, a hypothesis may be formulated which will account for the conditions seen in the definitive anomalies of epispadias and exstrophy without doing violence to any known embryological processes. It is such a thesis that constitutes the substance of this communication.

The characteristic conditions seen in an infant with exstrophy of the bladder and epispadias are illustrated in figure 1. The bladder is wide open all the way to the umbilicus. Where the bladder margins are continuous with the unclosed

belly wall there is a conspicuous mucocutaneous junction. The penis is broad and short as well as being deeply grooved on its dorsal surface. The impossibility of a normally closed pubic arch is self-evident (fig. 2). Instances have been reported of exstrophy without epispadias, or epispadias without exstrophy, but either of these conditions existing alone is exceedingly rare.

Fig. 1   Photograph of case of exstrophy and epispadias in an infant. (From University of Michigan Hospital, Urological Service, courtesy of Dr. Reed M. Nesbit.)

Closely related to typical cases such as that illustrated in figure 1 are cases in which the penis or the clitoris is completely divided medially. Such a condition in a male is illustrated in figure 3A and in a female in figure 3B. Cases of either of these types should be regarded as belonging in the same general category as the case illustrated in figure 1A. They are simply the maximal manifestations of the same basic disturbances in which there has been a failure of the paired primordia of the genital tubercle to make even a partial union.

Most of the previous attempts to interpret these defects have taken as their starting point relatively too advanced stages of development when the genital tubercle has already been established (fig. 6). The interpretation of epispadias

Fig. 2   Roentgenogram from case of exstrophy of the bladder showing open pubic arch. (From University of Michigan, Department of Radiology, courtesy of Dr. Fred J. Hodges.)

must be based on the conditions which exist in embryos young enough to show the genital tubercle primordia still in their initial paired condition. To understand the relations at this crucial stage it is desirable to review briefly, from its begin-

ning, the developmental history of the cloacal region. Going back to the primitive streak stage which human embryos go through at about the transition from the end of the second week to the beginning of the third week, fertilization age, it is possible to identify, in the mid-line just caudal to the primitive streak, a small area into which the mesoderm has not grown. This area where ectoderm and entoderm are in direct contact with each other may be designated as the prospective cloacal plate (fig. 4A). As the caudal end of the embryo grows, the cloacal plate is carried over the curve of the de-
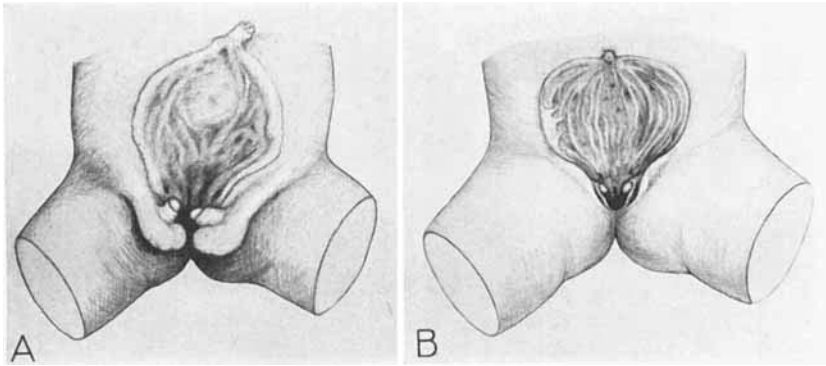
Fig. 3   Maximal extent of combined defects resulting in exstrophy and divided penis or clitoris. A. Male, drawn from case no. 5370 in the Rokitansky Museum, Vienna. B. Female, redrawn from Winsbury-White.

veloping tail bud until it presents caudally for a brief time (fig. 4B). Slightly later, when the tail has extended out over the subcaudal fold, the cloacal plate swings in beneath the developing caudal region (fig. 4C). By the 4th week the tail of the embryo has elongated and its tip is beginning to be recurved so that it points toward the yolk-sac. At this stage the cloacal plate is readily recognizable just caudal to the point where the belly-stalk joins the body (fig. 5). In this position the cloacal membrane forms the ventral wall of the urogenital sinus at the root of the allantois. This relationship is of importance and will be further emphasized later.
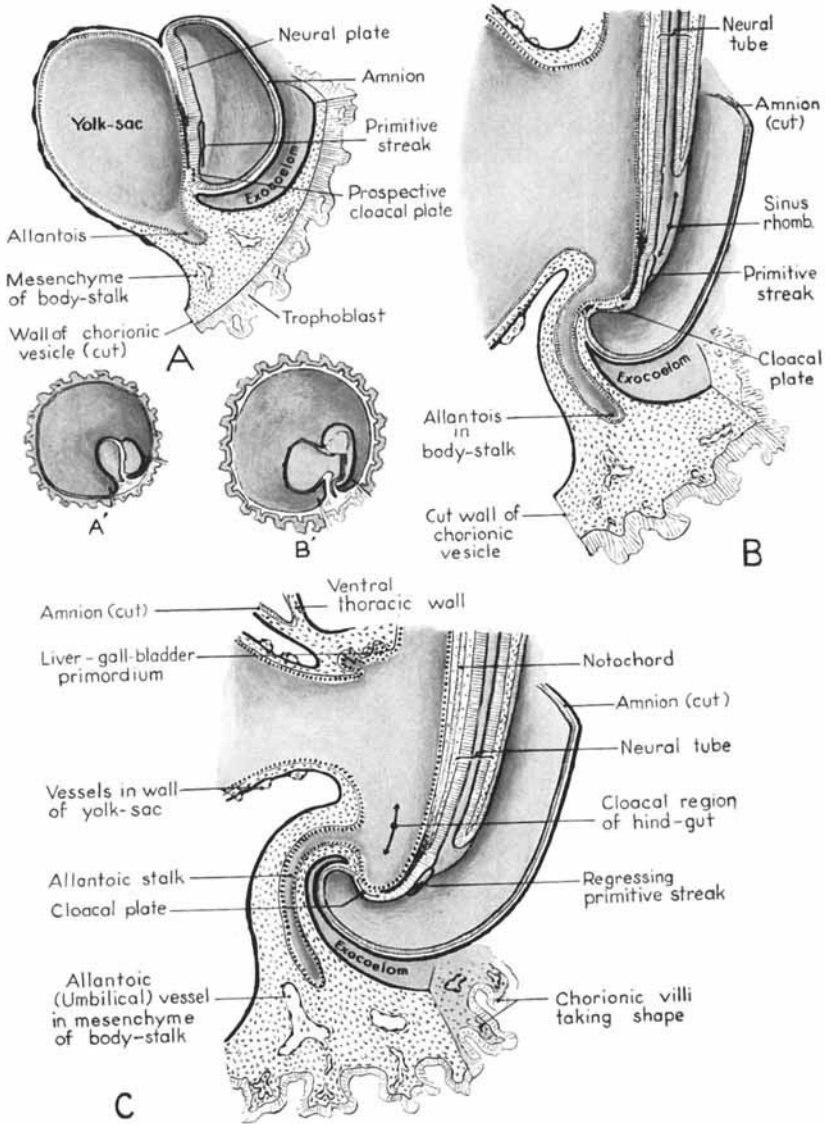
Fig. 4   Schematic sagittal diagrams showing early stages in the establishing of the cloacal membrane in human embryos. A, primitive streak stage; fertilization age approximately two weeks. A′, orienting sketch to show relations of body-stalk to chorionic vesicle. B, caudal part of embryo at early stage of delimiting of tail fold; fertilization age 17–18 days. B′, orienting sketch. C, caudal portion of embryo with tail bud well marked; fertilization age about three weeks.

Lateral to the cephalic border of the cloacal membrane the mesoderm of the body-wall heaps up to form a pair of low mounds, the paired primordia of the genital tubercle. These primordia are clearly visible by the 4th week (fig. 5). They rapidly become higher and migrate toward each other along the cephalolateral edge of the cloacal membrane. By the 5th week (fig. 6) they have fused in the mid-line to form the genital tubercle, which thus reinforces the cephalic boundary of the cloacal membrane.
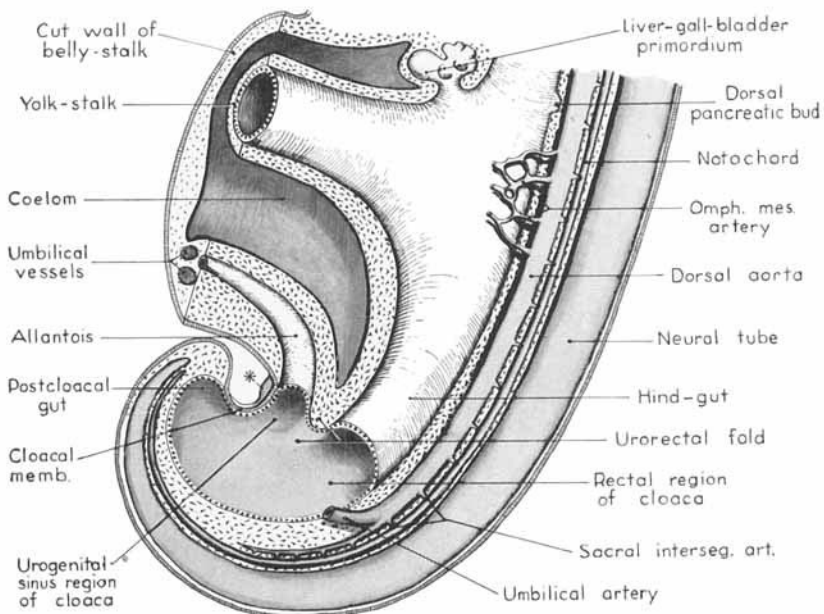

Fig. 5 Primary relations of the cloacal membrane to the unfused primordia of the genital tubercle and to the belly-stalk during the 4th week. The right tubercle primordium is indicated by an asterisk.

Figure 7 presents a series of diagrammatic plots of the genital region in ventral aspect. As a matter of convenience in presentation they are based on conditions in the male, which is appropriate enough in view of the fact that the anomalies under consideration are about 7 times more frequent in males than in females. On the left side are three

stages in the normal process of development. The paired primordia of the genital tubercle are shown first in their primary location flanking the cephalic part of the cloacal membrane (fig. 7A). Their subsequent fusion to form a single, medially located genital tubercle is shown in figure 7C. The same convergent growth process also involves the mesoderm of the infra-umbilical portion of the ventral body-
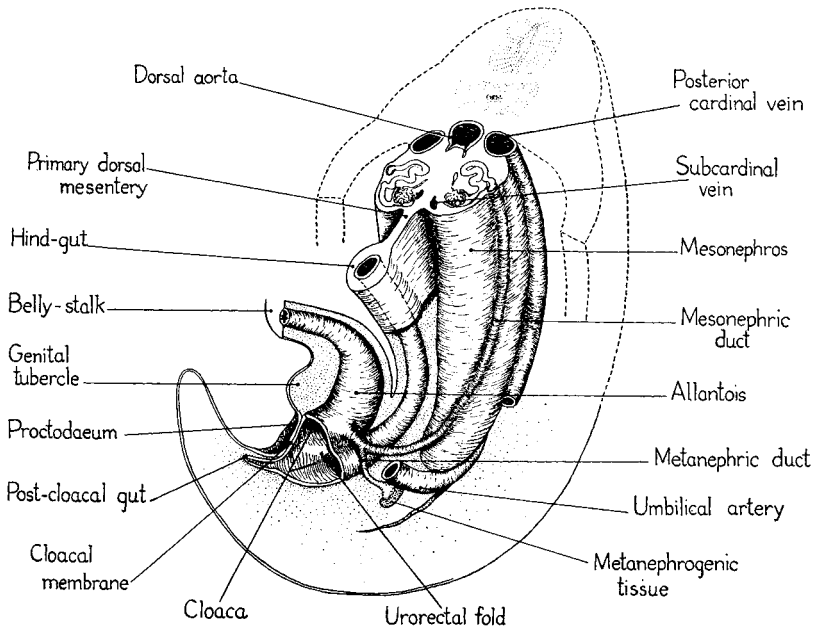

Fig. 6 Sagittal section of embryo of the 5th week showing the primordia of the genital tubercle fused in the mid-line. (After Kelly and Burnam, slightly modified, from Patten, "Human Embryology," courtesy of The Blakiston Company.)

wall. As is suggested by the series of arrows in these figures, the mesodermal component of the ventral body-wall closes in toward the mid-line as the belly-stalk is progressively restricted, and the distance between it and the cloacal membrane becomes greater. In the lengthening of this supra-pubic region, of course, the allantoic stalk is elongated and, together with the newly partitioned off part of the cloaca which remains

directly continuous with it, is involved in the formation of the urinary bladder. At the same time the urorectal fold has come to the surface dividing the originally single cloacal membrane into a urogenital membrane and an anal plate. With the rupture of these membranes and the subsequent formation and convergence of the scrotal folds in the perineal region, the normal adult relationships are established. (fig. 7E).
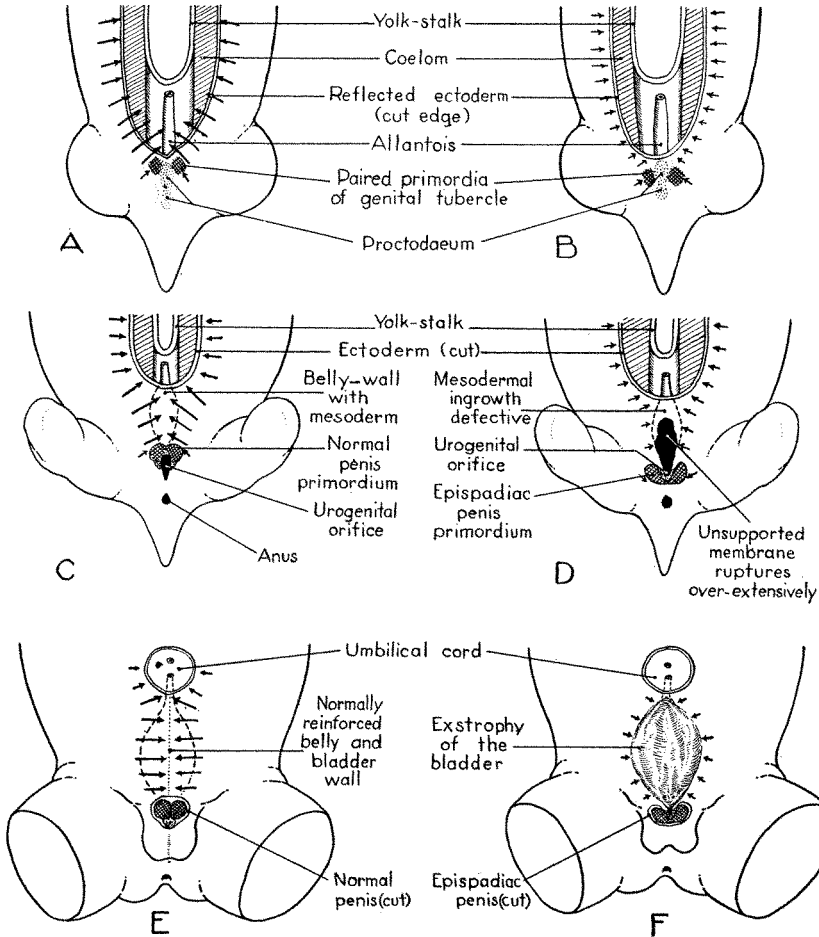

Fig. 7 Schematic diagrams contrasting normal with hypothetical abnormal positional changes of the primordia of the genital tubercle with relation to the cloacal membrane and the urogenital orifice. A, C, and E represent normal stages; B, D, and F, stages in the genesis of exstrophy and epispadias.

Now, in contrast with the normal conditions just briefly outlined, let us suppose that the paired primordia of the genital tubercles might, in certain cases, arise just a little caudal to their normal position, as indicated in figure 7B. If the paired primordia should arise in this position they would lie approximately opposite the point at which the urorectal fold comes to the surface. Under such circumstances, when they met each other in the mid-line the urogenital orifice would be cephalic to them and the anal orifice would be caudal to them as shown in figure 7D. The fact that the paired primordia of the genital tubercle fused with each other in this abnormal position would affect more than the structure of the penis. When the genital tubercle arises in its normal location just cephalic to the urogenital orifice, it brings a dense mass of mesenchymal tissue into the mid-line between the cloacal plate and the developing belly-stalk. In the case of tubercle primordia located too far caudally, the ventral belly-wall in this region would be unreinforced by mesoderm. It is a familiar phenomenon in embryology that in the locations where ectoderm and entoderm are in contact with each other without any intervening mesoderm a rupture is imminent. This situation exists characteristically in the oral plate as well as in the cloacal region. A similar condition is secondarily set up when the mesoderm moves out from between the base of the nasal pits and the roof of the oral cavity, presaging the rupture of the nasal pits to form the posterior nasal choanae. Thus the failure of mesoderm to reinforce the infra-umbilical part of the belly-wall would mean essentially that the urogenital portion of the cloacal membrane extended cephalically to the root of the belly-stalk. Under these circumstances it would not be surprising to find that the normal process of rupture of the urogenital membrane extended farther forward than usual. With no genital tubercle to act as a barrier not only would the caudal end of the urogenital sinus be opened to the exterior, as is normal, but the entire ventral wall of the allantois would be split open as well (fig. 7D). In the phases of development which occur shortly after

the rupture of the cloacal plate there is, as previously men-
tioned, rapid elongation of the supra-pubic region of the ab-
dominal wall. This is clearly evident in looking at the increas-
ing distance between the urogenital outlet and the umbilical
cord in a series of progressively older embryos, and is sug-
gested schematically in the drawings of figure 7. The rapid
expansion of this region would tend to further accentuate the
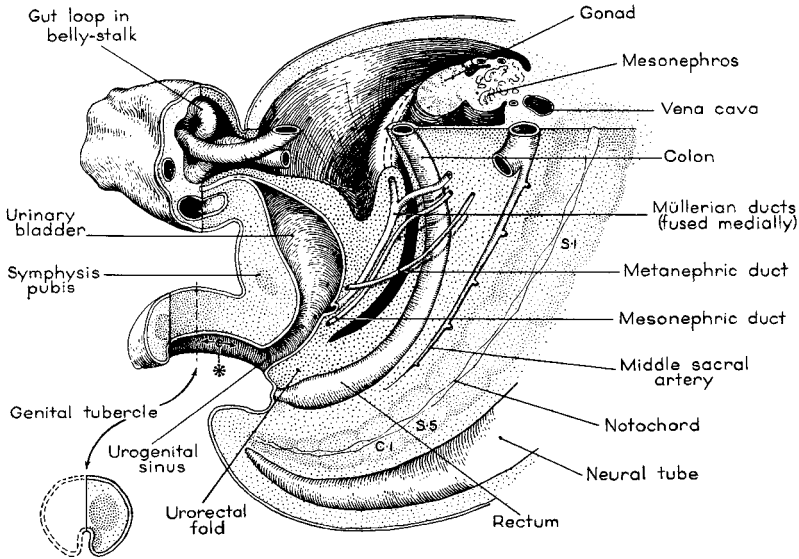extensiveness of the exstrophic condition already established.

Fig. 8   Normal relations of developing penis in an embryo of the 8th week.
Note that the urethral groove (marked by asterisk) is directly in line with the
urogenital orifice. In the schematic cross section of the genital tubercle, at the
lower left, the developing corpus cavernosum and the corpus spongiosum flanking
the urethral groove are indicated by heavier stippling.

If one now turns attention to the relations of the urethral
groove to the outlet of the urogenital sinus, the genesis of
epispadias along the lines of the hypothesis outlined becomes
more clearly evident. Figure 8 is a semi-schematic drawing
indicating the normal relations of the urethral groove to the
urogenital orifice in a human embryo of the 8th week. Notice
that the massive genital tubercle has been formed just cephalic

to the urogenital sinus outlet and that at its root the symphysis pubis is beginning to be foreshadowed by a precartilaginous concentration of mesenchyme. Notice also, as compared with earlier stages (figs. 5, 6), the increased distance between the root of the genital tubercle and the umbilical cord. If we suppose that the genital tubercle started to develop in the location indicated by the drawings B and D in figure 7, it would have formed opposite the level at which
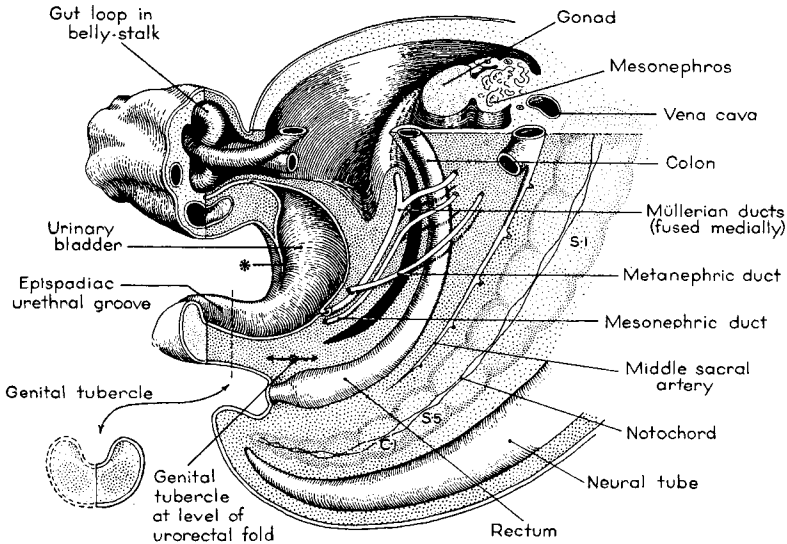

Fig. 9 Hypothetical stage in the genesis of exstrophy of the bladder and epispadias. Compare with figures 7D and 8. Note that the belly-wall in the midline (see asterisk) is composed of a thinning plate of ectoderm and entoderm unreinforced by mesoderm.

the urorectal fold grows to the surface and divides the cloacal outlet into a urogenital orifice and an anal orifice. If this occurred, the urethral grove would then be formed on the dorsal surface of the developing genital tubercle in the relations characteristic of epispadias (fig. 7F). At the same time the failure of convergence of mesodermal tissue in the midline between ectoderm and entoderm would leave a thin area in the ventral body-wall. (See the asterisk in figure 9.) As

the ventral body-wall in this region is rapidly elongated there would be the inevitable tendency for this thin area to break through, establishing the characteristic exstrophic condition of the bladder extending from the urethral groove to the umbilical cord. The same series of events would of course make entirely impossible any fusion of the pubic arch in its normal location (fig. 2). In the hypothetical series of events just outlined the orifices of the ureters would remain in about
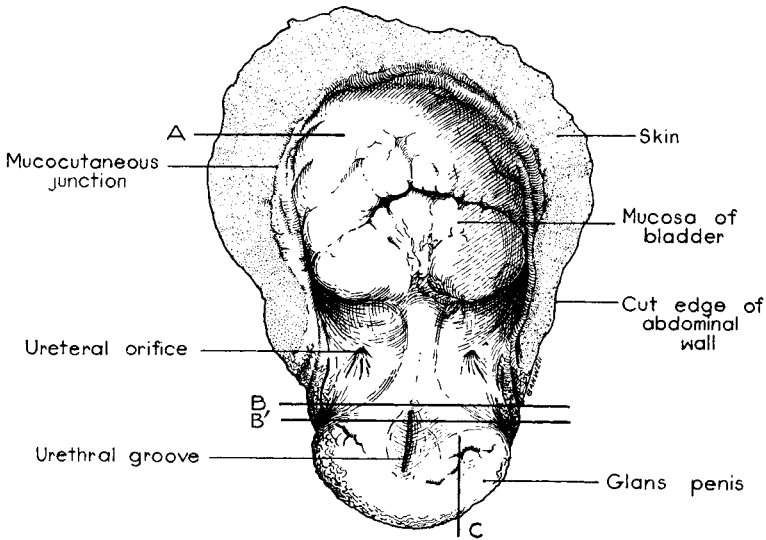

Fig. 10   Sketch of a specimen of exstrophy of the bladder and epispadias from an adult male. This material was generously loaned by the Mayo Clinic (their number 371–20) through the courtesy of Dr. Jesse E. Edwards, with permission to make sections from it. Blocks for sectioning were taken at the places indicated by the heavy lines with key letters A, B, B′, and C.

their usual relative positions. (Compare their points of outlet in figure 9 and in figure 10.)

In the absence of any embryological stages giving direct evidence as to how exstrophy and epispadias arise, one must look for suggestive circumstantial evidence in the relations found in the fully established condition. An epispadiac penis is an exceedingly difficult specimen to procure for sectioning. If the individual lives, some kind of plastic operation is

ordinarily attempted. In the case of autopsies, it is difficult to get permission to remove the area involved. After trying many sources that we thought might yield such material we were finally successful through the cooperation of Dr. Jesse Edwards of the Mayo Clinic. He sent us a specimen which had been obtained in 1920 from an autopsy on an adult with epispadias and exstrophy. The farsightedness of the Clinic in preserving and adequately cataloging such material as part of their permanent scientific collections, and their generosity in making it available to workers in another institution, cannot be passed by without comment. This specimen is sketched as figure 10 and the locations from which we took blocks for sectioning are indicated by the heavy lines bearing the key letters A, B, B' and C. If our interpretation of the manner in which these conditions arise is correct then one would expect to find the urethral groove in the dorsal angle between the corpora cavernosa of the penis. Furthermore, the groove might be expected to be flanked by a V-shaped mass of erectile tissue representing the corpus spongiosum urethrae. Figure 11 is a photomicrograph of the section taken at the level of the line B in figure 10. In spite of the difficulty of sectioning and staining the material because of the 31 years it had been kept in preserving fluid,[1] the two corpora cavernosa with their tunicae albugineae are clearly recognizable, and in the angle between them, dorsally, is the urethral groove flanked by well developed erectile tissue representing the abnormally located corpus spongiosum. A somewhat more highly magnified section of this region a little nearer the deeper part of the groove, at the level of B' in figure 10, is shown in the photomicrograph reproduced in figure 12. The topographical relations in this region are exactly similar to

those shown at the level B with the exception of the greater depth of the groove.

There are some interesting considerations in connection with this abnormal urethral groove. One of these has to do with the character of the lining epithelium. In the normal formation of the urethra the original epithelial lining of the groove is an incompletely differentiated type of stratified squamous epithelium, in keeping with its primary cutaneous origin. After the urethral groove is closed the character of
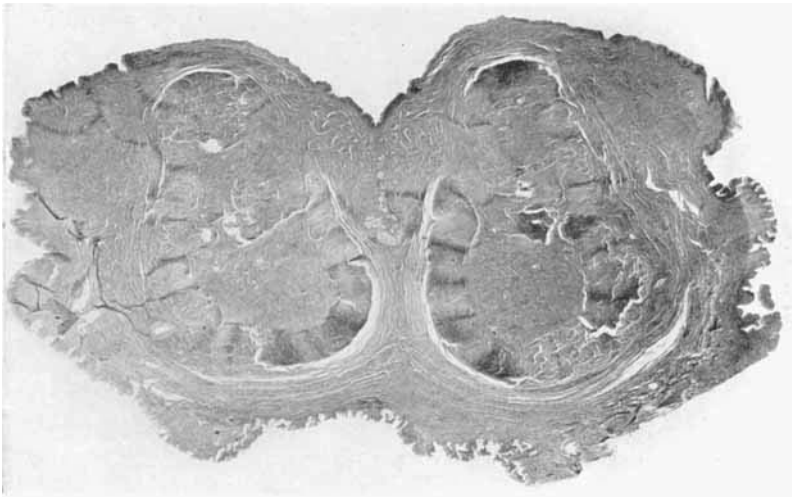

Fig. 11   Photomicrograph of section at line B in the diagram of figure 10. Note especially the open V-shaped corpus spongiosum situated in the dorsal angle between the paired corpora cavernosa.

the lining epithelium gradually changes. The superficial squamous cell layers are cast off and the persisting germinative cell layer produces new surface cells which are columnar in type. The metaplasia is a gradual one occurring during the latter part of gestation. In male infants at birth it is usual to find islands of stratified squamous epithelium still persisting here and there in the definitive type of stratified columnar epithelium lining the urethra (figs 15–18). *A priori* one might expect that an unclosed urethral groove would

retain its original type of stratified squamous epithelium. That proved to be true for the shallower parts of the groove (fig. 13), but in the bottom of the short, deeper part of the open groove the epithelium was stratified columnar like that of a normal closed urethra (fig. 14). From this it would appear that more than mere closure of the groove is involved in the change in epithelial type.

Another point of interest is the way the erectile tissue of the corpus spongiosum urethrae follows along the epithelial lining of the urethral groove whether the groove is in its normal position in the ventral angle between the corpora cavernosa or in the abnormal dorsal location characteristic of epispadias. One is tempted to speculate that the formation of the urethral groove and its associated corpus spongiosum urethrae is linked, perhaps by induction, to some tissues at the orifice of the urogenital sinus. More information is needed on this matter and on the related problem of the controlling factors in the abortive development of the corpus spongiosum in female embryos.

Sections taken at the line A of figure 10 show the characteristic mucocutaneous junction. In certain parts of the bladder mucosa in this particular case there were patches of tubular glands very suggestive of those appearing in the mucosa of the colon and rectum. This is a condition known to occur frequently in exstrophic bladders and is readily understandable in the light of the origin of the lower part of the bladder by the partioning off of a part of the cloaca by the urorectal fold. This of course means that the primordial lining of the bladder was originally directly continuous with the primordial lining of the rectum.

The section taken at the line of C of figure 10 clearly shows the glans penis flattened out over the tip of one of the corpora cavernosa and continuous with the V-shaped corpus spongiosum urethrae. The histological pictures within these sections are so familiar and so characteristic that the inclusion of photomicrographs does not seem justified.

Earlier in the paper it was indicated that cases in which the penis or the clitoris is divided into two halves are very closely related to the more typical cases of epispadias. In interpreting this condition we would start with the same basic assumption made in interpreting epispadias — the development of the paired primordia of the genital tubercle in a relatively more caudal location than the normal one. If one supposes this basic disturbance to be further complicated by some delay in their differentiation and convergence toward the mid-line the conditions illustrated in figure 3 seem to fall readily enough into line.

Incidentally, the relations of the hemiclitorides to the vaginal orifice in the case illustrated in figure 3B are of interest. If they arose in the manner we have postulated, the caudally displaced halves of the clitoris would lie directly opposite the point of external presentation of the urorectal fold. It will be recalled that the fused portions of the Müllerian ducts that form the vagina develop in the urorectal fold. Thus the position of the hemiclitorides flanking the outlet of the vagina, as they do in this case, is entirely in keeping with the hypothesis outlined.

SUMMARY

The clue to the embryological mechanisms involved in the genesis of exstrophy of the bladder lies in the correct interpretation of the commonly coexisting epispadias. Hypothetical stages in disturbed development are postulated which seem to explain the manner in which these associated anomalies may arise. The starting point is with embryos young enough to show the genital tubercle primordia still in their primary paired condition. The initial departure from normal is believed to be the formation of these primordia too far caudally with reference to the proctodaeum, so they are located at the level at which the urorectal fold will present externally. The corpora cavernosa would then develop just caudal to the urogenital outlet, and the urethral groove would form in their dorsal angle instead of its usual location in their

ventral angle. This would establish the relations characteristic of epispadias. The same abnormal position of the genital tubercle would entail, also, an absence of the ingrowth of mesenchyme which normally converges toward the midventral line just cephalic to the urogenital orifice. Thus when the cloacal membrane breaks through there is no mesodermal bar to the cephalic extension of this rupture. The likelihood of its extending all the way to the umbilicus, as is characteristic of exstrophy, is enhanced by the exceedingly rapid elongation occurring at this time in the region between the urogenital orifice and the umbilicus.

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12   Photomicrograph, more highly magnified, of the region of the urethral groove at the level of the line B' in figure 10. A conspicuous mucous gland is present surprisingly high in the groove (M.G.). The small rectangles show the locations of figures 13 and 14.

13   Photomicrograph ($\times$ 270) of the stratified squamous epithelium characteristically present in all but the deepest parts of the groove. The location of the area shown is indicated by the upper small rectangle in figure 12.

14   Photomicrograh ($\times$ 270) of the stratified columnar epithelium lining the deepest portions of the urethral groove. The location of the area shown is indicated by the lower rectangle in figure 12.
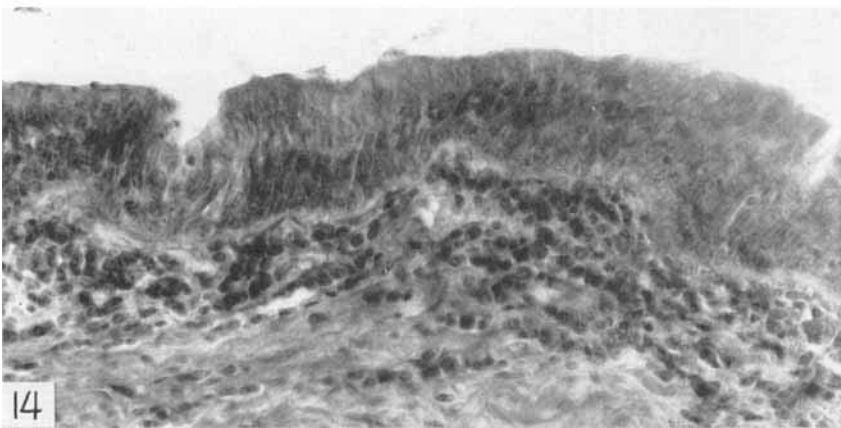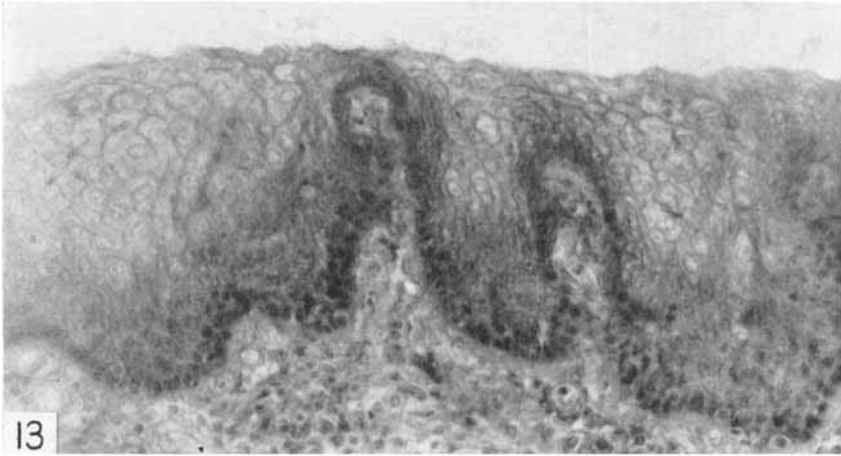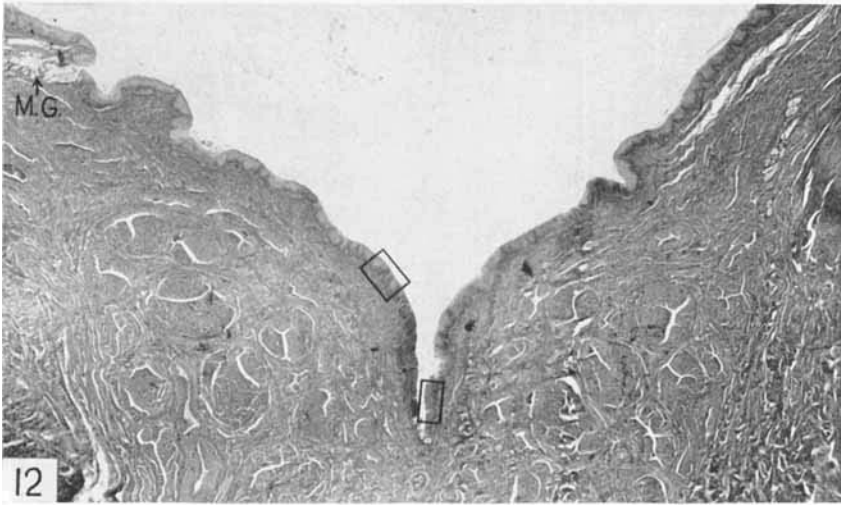
PLATE 2

15   Photomicrograph ($\times$ 83) of penile urethra of newborn infant showing incomplete conversion of the epithelium to the stratified columnar type character-istic of the adult. The rectangles show the locations more highly magnified in figures 16, 17 and 18.

16, 17 and 18   Photomicrographs ($\times$ 245) showing various phases in the con-version of the epithelium from fetal to adult type.