Surgical Embryology of the Exstrophy-Epispadias Complex

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Among the developmental anomalies seen in children, few has as broad a spectrum as the exstrophy-epispadias complex which encompasses numerous abnormalities arising in the hind-end of the embryo. Table 1, the scheme proposed by Marshal and Muecke, depicts the developmental relationships of the variations within the complex. One can readily appreciate the multifaceted nature of a syndrome which can produce deformities as mild as spade penis or patulous rectum on the one hand, while involving severe, complex derangements of the urinary, genital, alimentary, and musculoskeletal systems on the other hand.

Table 1. Developmental Relationships of the Variations Within the Exstrophy-Epispadias Complex

Classical Exstrophy

Ectopia viscera abdominalis
  with mesonephric duct
Cloacal exstrophy
  with imperforate anus and fistula
  with rectal prolapse
  with inadequate anus
Male
  Epispadias
    with incontinence,
    penopubic
    with continence,
    penile
    with continence,
    balanic
  Spade penis only
Female
  Epispadias with
    incontinence
Subsymphyseal epispadias
Patulous urethra
Male and female
  Superior fissure
  Duplicate exstrophy
  Musculoskeletal deformity only.

Abnormalities found within the exstrophy-epispadias complex are exotic. The most common condition is classical exstrophy, or ectopia vesicae, in which there is separation of the lower abdominal wall and absence of the anterior vesical wall with protrusion of the posterior bladder wall. According to Campbell, exstrophy occurs once in every 40 to 50,000
live births, but in an autopsy series of over 19,000 children, he found the incidence to be 1 in 1002, suggesting the relationship of the anomaly to early death. As one progresses outward from classical extrophy in Table 1, the anomalies occur with decreasing frequency. The rare condition of cloacal extrophy, for instance, occurs in approximately 1 in 200,000 live births. Table 2 (also from Marshall and Meucke) shows the relative frequency of variations within the extrophy-epispadias scheme in a series of 72 cases. The purpose of this review is to discuss the embryogenesis of the aforementioned anomalies, a subject which has been a source of conjecture and controversy, and to present the clinical manifestations of several of the anomalies within the complex.

**Table 2. Variations of Exstrophy-Epispadias in a Series of 72 Patients**

<table>
<thead>
<tr>
<th>Variety</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spade penis only</td>
<td>1</td>
</tr>
<tr>
<td>Epispadias with continence</td>
<td></td>
</tr>
<tr>
<td>Balanic only</td>
<td>2</td>
</tr>
<tr>
<td>Penile</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>8</td>
</tr>
<tr>
<td>Epispadias with incontinence</td>
<td></td>
</tr>
<tr>
<td>Subsymphyseal</td>
<td>1</td>
</tr>
<tr>
<td>Penopubic</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>17</td>
</tr>
<tr>
<td>Classical exstrophy</td>
<td>40</td>
</tr>
<tr>
<td>Cloacal exstrophy</td>
<td>2</td>
</tr>
<tr>
<td>Superior vesical fissure</td>
<td>1</td>
</tr>
<tr>
<td>Duplicate exstrophy</td>
<td>1</td>
</tr>
<tr>
<td>Characteristic musculoskeletal deformity</td>
<td>2</td>
</tr>
</tbody>
</table>

**Total 72.**

**Embryology**

Exstrophy of the bladder has not been found in its embryologic state, due perhaps, as suggested by Patten, to the low incidence of the anomaly. It is also known that the human embryo does not pass through a stage of development which corresponds to extrophy or epispadias, suggesting that the theory of developmental arrest is not the mechanism responsible for these anomalies. Numerous other theories have been proposed. The "Berstungs Theorie" states that anterior rupture of the embryonic bladder is caused by abnormal retention of fluid. This does not, however, take into account the commonly associated anomalies of the genitalia, musculoskeletal, and intestinal tracts.

To understand the remaining theories which are based on embryologic etiologies for the anomalies, a brief review of the normal pattern of development in the cloacal region, as described by Patten, is necessary. Between the 2nd and 3rd week after fertilization, just caudal to the primitive streak, the apposition of ectoderm and endoderm takes place in the midline without the ingrowth of mesoderm. This area, the early cloacal membrane or cloacal plate, can be easily recognized. By the 4th week the caudal area has elongated and recurved so that
the cloacal membrane occupies a position ventrally, caudal to the body stalk, forming the ventral wall of the urogenital sinus. The paired primordia of the genital tubercle are also present at this time, located just lateral to the upper border of the cloacal membrane. These primordia rapidly enlarge and by the end of the 5th week are fused in the midline superior to the cloacal membrane to form the genital tubercle. This is normally accompanied by a growth of mesoderm toward the midline, thereby lengthening the area between the body stalk and the cloacal membrane. At the same time, the urorectal folds have grown medially and caudally toward the primitive perineum, dividing the urogenital sinus from the rectum.

Patten and Barry theorized that caudal displacement of the paired primordia of the genital tubercle to the point where the urorectal fold divides the primitive cloaca into urogenital and anal components is responsible for the derangement of epispadias. With fusion of the paired genital primordia in the midline, the urogenital portion of the cloaca would be in a cephalic position in relation to the genital tubercle and the anal portion would be just caudal to the genital tubercle, creating the situation for epispadias when the urogenital portion of the cloacal membrane undergoes its normal rupture. This also creates the dorsal grooving of the corpora cavernosa. If the primordia of the genital tubercle were located even further caudally, the ventral abdominal wall in the area would be unreinforced by mesoderm, that is, the infraumbilical area of the anterior abdominal wall would be covered only by the urogenital portion of the cloacal membrane and with the normal rupture of this membrane the characteristic exstrophic appearance of the bladder would occur, extending from the base of the penis to the umbilicus. This would also account for the lack of fusion of the pubic arch in its normal location. The more caudally the paired primordia of the genital tubercle arise, the larger the defect created with rupture of the cloacal membranes. If the genital tubercle arose at the same level or caudal to the area of the anal portion of the cloacal membrane, rupture of this portion would leave the bowel exstrophic also. One can appreciate that in Patten and Barry's scheme, varying the caudal displacement of the paired primordia of the genital tubercle can account for many variations of the exstrophic situation.

Marshall and Muecke, while collecting numerous cases of exstrophy and epispadias, found several deformities previously not included as part of this anomalous complex but appearing to fit into the sequence as milder forms of epispadias and/or exstrophy. They theorized that if the genesis of abnormalities were one of division or nonunion starting at the end of the urinary tract and progressing upward, then lesser degrees of epispadias would be more common. They found, however, the reverse to be the case. That is, abnormalities which appear to be located at the vesical outlet, with vesical exstrophy and epispadias, account for some 90 per cent of the cases. They also noted that the defect in the exstrophy-epispadias complex was always midline and longitudinal in character and theorized that if the cloacal membrane itself was overdeveloped or persistent beyond the normal stage of regression, a urogenital opening larger than normal might be expected. An abnormally large and/or persisting cloacal membrane would act as a wedge to the developing structures of the lower abdominal wall. This would leave the involves structures normal but separated. They also affirm that the mesodermal derivatives of all structures in the area of an exstrophy are intrinsically well developed and the bones abnormal only to the degree that might be expected from a wedge effect.

Marshall and Muecke rebut the Patten and Barry theory by suggesting that if the paired primordia of the genital tubercle are displaced caudally, one might expect, with more
severe degrees of exstrophy, to find the corpora located on the perineum or dissociated from their bony attachments (which rarely occurs). Following the wedge effect of the large or persistent membrane, an excessive or perhaps premature split of the cloacal membrane extending toward the body stalk would lay open the underlying vesical primordia, the internal surface of the cloacal membrane being the ventral wall of the cloaca, with this wall becoming the anterior portion of the bladder. With varying degrees of split of the cloacal membrane, one can see that this theory not only explains exstrophy but also the division of the corpora giving rise to the epispadiac groove usually found in males or the bifid clitoris in females. For epispasdasia alone, the degree of persistence or overdevelopment of the cloacal membrane would be less, resulting in less separation and more minor deformities. For the more severe abnormalities, such as cloacal exstrophy, one would have to vary only the precise time at which the abnormal cloacal membrane divides as well as the extent of the division in relation to the closure of the urorectal septum. With earlier division and more extensive split, a more marked defect would occur. If split of the abnormally developed cloacal membrane occurred prior to the time of complete formation of the urorectal septum, some stretching of the septum would occur and an abnormally patulous rectum would result. If eversion of structures lying under the cloacal membrane occurred prior to the completion of the urorectal septum, an imperforate anus could result, or at various stages in development of the urorectal septum a rectovaginal or rectovesical fistula could occur. With split of the cloacal membrane prior to the time the urorectal septum has divided the cloaca, the vesical primordia would be left lateral to the exstrophic bowel, an arrangement frequently seen in cloacal exstrophy.

**Experimental Evidence**

Considerable support for the wedge-effect theory of Marshall and Muecke is given by the excellent embryologic experiment performed by Muecke on chick embryos. An inert plastic graft was inserted into the area of the cloacal membrane primordia in chicks at 48 to 52 hours of incubation. With this plastic graft simulating a persistent cloacal membrane and acting as a wedge, chicks with varying degrees of infraumbilical defects were produced. The size of the graft in relation to the of the defect was insignificant, that is, many of the defects produced were much larger than the size of the graft alone. Chicks who underwent the same operative procedure but who did not have insertion of the graft were normal. The exstrophic chicks, as is the case in man, had all structures present but deformed by the infraumbilical defect. This was the first experimental production of exstrophy, an anomaly which is normally not seen in the chick and rarely, according to Muecke, in mammals except for man. This may be due to abnormalities produced in structures surrounding the cloacal membrane. These structures, such as the allantois, perform vital functions in the chick and some mammals but not in man. This would, as Muecke notes, account for the increased incidence of extrophic defects in man and the paucity of cases in other animals.

**Clinical Manifestations**

The clinical manifestations of entities within the exstrophy-epispadias complex have been alluded to in the previous discussion of embryogenesis. A brief discussion of several of these anomalies along with the presentation of illustrative cases is germane to this review.
**Epispadias**

Epispadias is the opening of the urethra on the dorsum of the penis or absence of the upper wall of the urethra. In its mildest form, balanitic epispadias, the urethral opening is located dorsally on the glans or at the coronal sulcus with a groove extending distally onto the glans. The intact portion of the urethra proximal to the meatus is located dorsally in the penis, and there may be slight dorsal chordee. This is probably the most common type of incomplete epispadias in the male, according to Campbell.

In penile epispadias the urethra can open anywhere on the dorsal shaft of the penis proximal to the coronal sulcus. The spade-like penis is grooved dorsally and covered with urethral mucosa from the tip of the glans to the urethral meatus. The prepuce usually hangs ventrally. In this particular case, retraction of the distal meatal verge revealed a second opening which, when catheterized, led into the bladder as did the dorsal opening. A voiding cystogram revealed a complete duplication of the urethra, which occurs relatively frequently in epispadias and may be complete or incomplete.

In complete epispadias or first degree exstrophy, the urethra is open to the bladder neck and is usually associated with incontinence.

In the female, epispadias is classified by Campbell as clitoris (in which only a bifid clitoris is present), subsymphyseal, or complete. Incontinence is present in the complete form and associated deformities, such as separation of the labia and pubic bones, occur in varying degrees.

According to the Marshall and Muecke scheme, the embryogenesis of epispadias would involve a shorter persistence or less overdevelopment of the cloacal membrane, resulting in less symphyseal separation and few, if any, infraumbilical defects.

Coincident urinary anomalies are common with epispadias and, in fact, with all abnormalities of the hindgut complex. These include upper urinary anomalies such as agenesis of one kidney, as shown on the excretory urogram. Note also the wide separation of the pubic bones in this particular case. Vesicoureteral reflux has been shown to occur in up to 75 per cent of patients with all degrees of epispadias, making it imperative that all of these patients undergo thorough urinary tract evaluation and reconstruction, if necessary, prior to repair of the epispadias.

Treatment of epispadias depends on the degree of the defect and associated anomalies. Those patients without incontinence usually have satisfactory results, while the amelioration of incontinence may be difficult by present reconstructive means.

**Exstrophy**

Exstrophy of the bladder, in which the anterior wall of the abdomen and bladder are absent, was the most common defect in Marshall and Muecke's series of 72 patients, accounting for 55 per cent of the deformities. Gross and Cressan, in reviewing a 20-year experience of epispadias and exstrophy, found 18 cases of epispadias and 80 cases of exstrophy. The degree of exstrophy may vary from only a small fissure superiorly to complete
exstrophy, which is the rule. There is epispadias and wide separation of the pubic bones. The figure shows this deformity as it occurs in the male with the posterior bladder wall protruding above the spade-like penis. The pubic bones are splayed and the scrotum may be cleft or bifid and separated. Cryptorchism is common and vesicoureteral reflux occurs in most patients. Concomitant findings in the female are also shown. Note also the patulous and prolapsing rectum due to stretching and weakening of the urorectal septum by early splitting of the cloacal membrane in the embryologic period.

**Cloacal Exstrophy**

Cloacal exstrophy, or vesicointestinal fissure, is one of the most extensive lesions in the exstrophy-epispadias complex. It fortunately occurs rarely, once in approximately 200,000 live births, according to Tank and Lindenauer. The clinical manifestation is characterized by exstrophy of the bladder, which is bivalved on either side of the midline. A ureteric orifice occurs in each bladder half. Between the two hemibladders is an area of intestinal mucosa which is the exstrophic ileocecal area. The distal opening of the ileum lies at the cephalic margin and the proximal opening of a blind hind and/or tail gut at the caudal margin. There may be one or two vermiform appendices opening into the exstrophic cecum. An omphalocele is frequently present above the exstrophic bowel, and atresia of the small intestine is common. The pelvic bones are widely separated and the anus is imperforate. Genital deformities occur in all cases. In the male the penis is usually bifid with each pubic rami. The testes are normally undescended. In females the clitoris is usually divided and the majority have duplex vagina and bicornuate uteri.

Urinary tract anomalies occur in over 50 per cent of these cases while spina bifida and myelomeningocele are commonly associated anomalies.

The embryogenesis of this defect would encompass early extensive splitting of the abnormal cloacal membrane before the urorectal septum has horizontally divided the cloaca. Eventration of the dorsal wall of the intestinal primordia occurs and the vesical primordia are left as paired halves on either side of the intestinal exstrophy.

Survival with this defect was not reported until 1960 and resulted from surgical relief of small bowel obstruction, correction of omphalocele, and recognition and treatment of excessive fluid loss from the small bowel. Surgical repair encompasses major reconstructions of the intestinal, urinary, and genital tracts. Several successes have been accomplished in recent years.