INTRODUCTION

The art of plastic surgery is first of all the art of 'robbing Peter to pay Paul'. This is nowhere more evident than in the treatment of hypospadias, when the penis must be extended or the urethra reconstructed.

In these cases the surgeon is confronted with a skin deficiency on the urethral side of the penis, and excess of skin on the dorsum. To correct the defect on the urethral side, he often makes use of the redundancy on the dorsum. The literature describes numerous procedures based on this principle, but it ignores the following questions.

How did the redundancy occur? How can it be utilized with optimal efficiency?

To answer these questions was the object of the study which this and a following paper report.

MORPHOLOGY

Hypospadias exists when the distal part of the urethra is absent. It is a congenital defect of the genital apparatus which is seen in about 1 out of each 1000 male neonates and which can manifest itself in widely different forms.

A very small defect (fig. 1) as a rule merely leads to dystopia of the meatus. A very large defect (fig. 2) can be associated with dystopia of the meatus, curvature of the penis, penoscrotal transposition, hypoplasia of the penis, enlargement of the prostatic utricle and cryptorchism.

In the former case, feminization is so slight that there is no doubt as to the patient's sex. In the latter case, feminization is so extreme that differentiation from the female genital apparatus is possibly only by special diagnostic techniques.

Always, however, there is some feminization while its degree depends on the nature, severity and number of the feminizing factors. This may be elucidated by a brief discussion of each of these factors separately.

Dystopia of the meatus

There is considerable variation in the site and diameter of the dystopic meatus.

* Received for publication by the Editorial Board: dec. 9th, 1965
Pronounced dystopia and a retrodeviated jet soon lead to micturition in the feminine manner. Objective symptoms (dysuria, pollakiuria) indicate meatal stenosis, in which case early treatment is imperative.

Only in cases without curvature of the penis can the size of the urethral defect be estimated with accuracy. In all other cases the penis must be straightened first.

It is generally found that the disturbance in the morphogenesis of the urethra has led to some conspicuous changes in the tegument of the penis, e.g. a) a skin deficiency on the urethral side of the penis, b) an excess of skin on the dorsal side of the penis, c) oblique raphes on either side of the penis.

_re a). This deficiency is most evident in a V-shaped area (fig. 3) distal to the meatus,
which we call 'urethral delta'. The tegument of this delta is thin and adherent. A mucosa-lined groove is usually found in its central part. The slightly prominent edges gradually merge with the fold of the bifid prepuce.

re b). This redundancy is concentrated in two dog-ears found on either side of the midline, about 1 cm. apart (fig. 4) These are usually very conspicuous and in marked contrast to the deficiency on the urethral side (fig. 5).

re c). These raphes extend from a point at the edge of the urethral delta and continue dorsally to end in the centre of a dog-ear (fig. 4). Their exact direction, more proximal or more distal, is dependent on the site of the meatus and on such curvature of the penis as exists.
Curvature of the penis

Curvature of the penis can occur in various ways, viz.:
a) from skin deficiency,
b) from deficiency of periurethral tissue,
c) from urethral deficiency,
d) from deficiency of the corpora cavernosa.

Severe deficiencies are likely to result in impotentia coeundi et generandi.

A skin deficiency on the urethral side of the penis always exists, but is certainly not always important. Three categories can be distinguished.

In the first category, the penis is completely extended and the skin deficiency is of little or no importance.

In the second category, the shaft of the penis is straight but the glans shows an abrupt curvature in relation to the extended shaft. Curvatures of this type can be corrected simply by correcting the skin deficiency.

In the third category, the shaft of the penis curves. In these cases the skin deficiency is always associated with a deficiency of periurethral tissue. Correction of the skin
HYPOSPADIAS

deficiency must be preceded therefore by straightening of the corpora cavernosa
(orthoplasty).

re b). A deficiency of periurethral tissue is always found in the case of hypospadias
with curvature of the penile shaft. Extension of the corpora cavernosa in these cases is
impaired by hypoplasia of periurethral tissue on the concave side of the corpora.

Underneath the thin integument of the urethral delta we find a fibrotic layer
which may extend far laterally and proximally and is very adherent. Complete
excision of this layer is indicated.

re c). A urethra of insufficient length can contribute considerably to curvature of the

Fig. 4. Oblique raphes
culminating in ‘dog-ears’.
shaft. Mobilization of the hypoplastic distal part and retroposition of the dystopic meatus are required if the corpora cavernosa are to be extended completely. In rare cases, a fibrotic strand may extend like a cord between the dystopic meatus and the glans, giving rise to bow-stringing. This strand is probably a vestige of the urethral plate. Its complete excision is likewise indicated.

Correction of the curvature is greatly impeded in the presence of aplasia on the concave side of the corpora cavernosa. This, however, is rare.

**Penoscrotal transposition**

Transposition of the scrotum and penis exists when the insertion of the two scrotal halves is no longer lateral and distal to the base of the penis, but is proximal to this
HYPOSPADIAS

base (fig. 6). This anomaly is observed chiefly in severe forms of hypospadias. In extreme cases a suprapenile scrotum may form.

**Hypoplasia**
Like penoscrotal transposition, this anomaly is seen chiefly in severe cases of hypospadias, and it contributes considerably to the typical features of hypospadias. Impotentia coeundi et generandi can result.
Enlargement of the prostatic utricle

The chance of there being an enlargement of the prostatic utricle increases distinctly with increasing severity of hypospadias. This has been shown by such authors as Howard (1948), Boissonnat (1945) and Kjellberg (1957). Cyst formation due to obstruction of the mouth of the utricle in the urethral wall can be a cause of retention of urine McKenna & Kiefer (1943), Landes & Ransom (1949) and Smith & Forsythe (1959). Madison (1958) found that infection of the utricle can give rise to pyuria.

Cryptorchism

This anomaly is found in 10–20% of cases of hypospadias (an incidence significantly above the normal). Cryptorchism in hypospadias, therefore, must not be regarded as an anomaly ‘sui generis’ but as further evidence of the defect which gives rise to hypospadias.

Evidently, the severity of the anomaly is determined by the degree of feminization involved. On this basis, and in view of the unreliability of the conventional classifications based on the site of the meatus (Van der Meulen 1964), the following classification of hypospadias is suggested.

Grade I. Dystopia of the meatus.
Grade II. Dystopia of the meatus and curvature of the penis:
   a) of the glans relative to the extended shaft,
   b) of the shaft.
Grade III. Dystopia of the meatus, curvature of the penis and penoscrotal transposition.

Embryology

Early during the second month of pregnancy – in the 5 mm stage – mesenchymal proliferation leads to the formation of an eminence roughly the shape of a horseshoe on the anterior side of the cloacal region; this eminence is the genital tubercle. It is flanked by the genital swellings, which later are to from the scrotum.

The two caudal extensions of the tubercle (the urethral folds) are separated by the urethral groove, the floor of which is formed by the cloacal membrane.

The relatively more marked mesenchymal proliferation in the cranial part of the cloacal region causes the urethral groove gradually to assume a position on the caudal side of the genital tubercle. The external urethral orifice is formed by perforation of the cloacal membrane on the anterior side of the primitive perineum. This orifice is the communication between the pars phallica of the urogenital sinus, which extends over the proximal one-third of the genital tubercle, and the urethral groove in the distal two-thirds of this prominence.

The urethral plate is perpendicular to the floor of the urethral groove (figs. 7 and 8). This plate is a lamellar structure formed by proliferation of the walls of the pars phallica, in the 10 mm stage.
The surface epithelium of the floor of the urethral groove responds to contact with the in-growing urethral plate, first by proliferation and then by retrogression. The groove, thus deprived of its integument, has been called the primary urethral groove, by Glenister (fig. 8).

In the 35 mm stage, this primary urethral groove becomes deeper as a result of disintegration of the part of the urethral plate which adjoins the floor of the primary groove. The resulting groove is described as the secondary urethral groove (Glenister).

The primary and secondary grooves jointly form the definitive urethral groove.

Development, as described, is the same in both sexes until the 45 mm stage. The subsequent sexual differentiation determines the definitive form of the male and female genitals.
Fig. 8. a. primary urethral groove (P.U.G.)
b. secondary urethral groove (S.U.G.). Formed as a result of the disintegration of the adjacent part of the urethral plate (U.P.)
c. definitive urethral groove (D.U.G.). Formed by fusion of P.U.G. and S.U.G. The line of junction between the surface epithelium and the epithelium derived from the urethral plate is marked E.J.

ORGANOGENESIS

The urogenital sinus and the external genitals are bipotential. Unlike the wolffian and müllerian ducts, which are unipotential, they can develop either in the masculine or in the feminine direction.

Modern theories based on Wiesner's monohormonal hypothesis, and elaborated by investigators such as Jost, envisage the course of this differentiation as follows.

FEMINIZATION

Feminine organogenesis is not dependent on the presence of ovaries. Female hormones play no role in it and it is not influenced by castration. There is in fact hardly any sexual differentiation but:

- the definitive urethral groove fails to close and continues to be flanked by the urethral swellings;
- the genital tubercle shows retardation of growth and curves in the caudad direction;
- the genital swellings develop to become the labia majora.
HYPOSPADIAS

MASULINIZATION

Masculine organogenesis occurs under the influence of the morphogenetic hormone produced by the foetal testis. This hormone suppresses further growth of the müllerian ducts and stimulates the growth of the bipotential primordia in the masculine direction. Castration of mammals before the onset of sexual differentiation leads to a completely feminine development. This castration effect can be abolished by administration of testosterone.

Normal differentiation takes the following course:
- the definitive urethral groove closes from its base to its apex, thus forming the urethra. Only epithelium originating from the urogenital sinus or the urethral plate contributes to this formation. Surface epithelium plays no role in it (Glenister);
- the genital tubercle continues to grow and does not curve;
- the base of the genital tubercle shows cranial displacement, probably as a result of the growth which leads to the formation of the corpora cavernosa; due to this displacement, the genital swellings come to be localized caudad to the tubercle;
- the genital swellings fuse to form the scrotum.

PATHOGENESIS

In animal experiments, hypospadias has been reproduced in various ways, viz.:
1) By castration of embryos. By castrating rabbit embryos, Jost demonstrated that the time at which the morphogenetic secretion of the testis is disturbed determines the severity of the resulting malformation. He obtained a series of anomalies ranging from a completely feminine genital tract to a grade I hypospadias.
2) By hormonal medication of embryos. Hypospadias can be reproduced in both sexes by administration of hormones: androgens in female test animals and oestrogens in males. The effect of these hormones on sexual differentiation can be summarized as follows.

Androgens were found to have a distinct masculinizing effect on the morphology of the urogenital sinus and the growth of the corpora cavernosa in opossums. They stimulate the differentiation of the urethral plate (Burns 1942).

Oestrogens had a fibrosing effect on the corpora cavernosa in rats (Greene, Burrill and Ivy 1938) and a stimulating effect on the growth and differentiation of periurethral tissue in opossums (Burns).
3) By vitamin A deprivation. Vitamin A deficiency led to hypospadias in rat embryos (Wilson & Warkany 1959).
4) By irradiation. Russell (1950) reproduced a variety of congenital malformations by irradiating mouse embryos, one of which showed hypospadias.

The results of these experiments tend to indicate that human hypospadias is probably caused by functional disturbances, i.e. permanent or transient disturbances in the testicular morphogenic secretion.

The pathogenesis of these functional disturbances is not entirely clear. Sorenson maintains that both endogenous and exogenous factors play a role. A statistical ana-
ysis of his findings disclosed that endogenous factors of importance in the aetiology of hypospadias are transmitted by recessive genes; the fact that the malformations are less frequent than might be expected (reduced manifestation) can be attributed to a complex interaction between endogenous and exogenous factors, which frequently causes a modification in the expression of a single pair of genes. The risk of familial occurrence is consequently relatively small. Parents who already have a child with hypospadias face a risk of less than 12.5% that a subsequent child will show the same anomaly (SORENSON).

MORPHOGENESIS

In the discussion of the morphology of hypospadias and its varieties, mention was made of a few characteristics for which the literature offers no explanation. They are:
- the integumental deficiency on the urethral side of the penis;
- the integumental redundancy on the dorsal side of the penis;
- the two oblique raphes.

The author believes that these characteristics – found in all varieties of hypospadias (VAN DER MEULEN 1964) – are caused by duplication (fig. 9) in the ectoderm-lined edges of the urethral groove, which are known (Glenister) not to be involved in the formation of the urethra. Because of this duplication a considerable proportion of the integument in the region of the urethral groove is displaced to the dorsum of the penis. Consequently, a skin deficiency is formed on the urethral side of the penis and a redundancy of skin on its dorsum (the dog-ears). Fusion of the edges of the folds is associated with the formation of the raphes.

Fig. 9. Duplication of the ectoderm-lined edges of the urethral groove, as viewed by the author. Formation of the oblique raphes (O.R.).

SUMMARY

New discoveries with regard to the embryological evolution and sexual differentiation of the human genital apparatus have led to a more exact knowledge of hypospadias. The author reviews this progress and suggests a new classification in which due allo-
wance is made for the fact that increasing severity of the defect is accompanied by a more marked tendency to feminisation. A theory is presented which explains many features of the remarkable morphology of hypospadias and also throws a different light on the nature of such rare anomalies as a congenitally short urethra and congenital urethral fistula (Van der Meulen 1964).

RESUME
De nouvelles découvertes dans la domaine de l'évolution embryologique et de la différenciation sexuelle de l'appareil génital humain ont conduit à une connaissance plus exacte de l'hypospadias. L'A. traite de ces progrès et propose une nouvelle classification qui tient compte du fait qu'une aggravation de la malformation se traduit par une tendance plus forte à la feminisation. Une théorie est présentée qui non seulement explique beaucoup des caractères de la morphologie remarquable de l'hypospadias, mais encore projette une lumière différente sur la nature des anomalies rares qui sont le brachy-urètre congénital et la fistule urétrale congénitale (Van der Meulen 1964).

ZUSAMMENFASSUNG

Zur Erklärung der vielen Eigentümlichkeiten der merkwürdigen Morphologie der Hypospadien wird eine Theorie aufgestellt; diese Theorie wirft ein neues Licht auf die Art solcher seltenen Abweichungen, wie eine kongenital kurze Urethra und eine kongenitale Urethrafistel (Van der Meulen 1964).

SAMENVATTING
Nieuwe ontdekkingen op het gebied van de embryonale ontwikkeling en de geslachtsdifferentiatie van de geslachtsorganen bij de mens hebben geleid tot een nauwkeuriger kennis van de hypospadiën. De auteur geeft een overzicht van deze vorderingen en stelt een nieuwe indeling voor, waarbij voldoende rekening is gehouden met het feit dat de neiging tot feminisatie sterker wordt naarmate het defect ernstiger is.

Een theorie wordt geïntroduceerd ter verklaring van vele eigenaardigheden in de opmerkelijke morfologie van de hypospadiën; deze theorie werpt een nieuw licht op de aard van dergelijke zeldzame afwijkingen als een kongenitale korte urethra en een kongenitale urethrafistel (Van der Meulen 1964).

REFERENCES
Boissonnat, P.


Burns, R. K.

J. C. VAN DER MEULEN


