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The Foetal and Neonatal Prostate in Congenital Malformation of the Urinary Tract

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Summary. The prostates of 1 stillbirth, 14 neonates and infants as well as of one child with renal tract malformations have been examined.

The processes of proliferation of the tubule epithelium, squamous metaplasia and secretion were normal in 7 cases. Impairment of one or more of these features was noted in 7 instances. Another case showed an extreme degree of squamous metaplasia with cyst formation. Marked abnormalities in structure were found in 1 case. The derivatives of one or both Wolffian ducts were found to be absent in 5 cases.

No definite correlation appears to exist between the severity of the urinary tract malformation and the findings in the prostate.

It is of considerable interest to note that in a large number of cases with urinary tract malformations, the foetal and neonatal prostatic tissue still responded to the various hormonal stimuli to which this organ is subjected during intra-uterine life and that in particular its response to oestrogenic stimulation was hardly ever affected.

Associated congenital malformations involving other systems than the urinary tract were present in 10 of the 16 cases.

Zusammenfassung. Die Prostata von einer Totgeburt, 14 Säuglingen und 1 Kleinkind wurde histologisch untersucht. Es bestanden in allen 16 Fällen gleichzeitig Nierenmißbildungen.

In 7 Fällen waren Proliferation, Schuppenmetaplasie und Sekretion des prostatischen Epithels normal. Dagegen waren in 7 weiteren Fällen einer oder mehrere dieser Vorgänge beeinträchtigt. In einem anderen Falle wurde ein extremes Ausmaß von Schuppenmetaplasie mit Cystenbildung vorgefunden. Ein Fall zeigte auffallende Abweichungen von der normalen Drüsenstruktur. Die Derivate von einem oder von beiden Wolffschen Gängen waren in 5 Fällen nicht vorhanden.

Es war kein wesentlicher Zusammenhang zwischen der Schwere der Nierenmißbildung und den Befunden an der Prostata nachzuweisen.

Es muß besonders hervorgehoben werden, daß das prostatische Gewebe in der Mehrzahl der Fälle in normaler Weise auf die verschiedenen hormonalen, insbesondere östrogenen Reize ansprach, denen dieses Organ während des intra-uterinen Lebens ausgesetzt ist.

10 der 16 Fälle zeigten gleichzeitig kongenitale Mißbildungen in anderen Systemen.

The urinary and genital systems are intimately associated in their embryological development and anomalies of the genital tract are known to occur not uncommonly with malformations of the upper urinary tract. This was first described by Boyd (1841) and was later confirmed by other authors (Gruber, 1860; Strube, 1894; Morris, 1901; M. Zondek, 1903 and 1924; T. Zondek, 1944

and Graham, 1961), some of whom also stressed the diagnostic significance of such findings.

Following our previous investigation into the secretory activity of the maturing epididymis in cases of urinary tract malformations (Zondek and Zondek, 1964), it was thought to be of interest to investigate whether the prostate gland of the foetus and infant would be affected in such cases.

There are some reports in the literature, mainly about the macroscopical appearance of the prostate in cases with malformations of the urinary tract but the histological appearance of this organ, particularly in the foetus and infant, has to our knowledge never been investigated. This appears to be of particular interest, especially as the foetal prostate is under continuous influence of maternal and placental hormones as well as of hormones, produced by the foetus itself, which affect its histological picture during the various stages of development.

Material and Method

There were 16 cases with congenital malformations of the urinary tract, comprising one stillbirth, 14 neonates and infants and one child aged 1 year 5 months. The period of gestation ranged from 27 to 41 weeks (Table 1). One hundred and six cases of similar ages and periods of gestation served as normal controls.

The prostates were fixed in formal saline and embedded in paraffin. Sections of 5 μ were then taken in the horizontal axis at 1 mm or $^1/_2$ mm intervals. All sections were stained with haematoxylin and eosin, as well as with periodic acid Schiff (Hotchkiss method) including diastase-treated controls.

We have previously measured the volume of a large number of foetal and neonatal testes and were thus able to determine the mean testicular volume for different periods of gestation (Zondek and Zondek, 1965).

Results

The foetal prostate, in the earlier stages of gestation, shows few tubules, widely separated by supporting fibromuscular stroma. With increasing maturity, gradual proliferation of the tubule epithelium takes place and, at full-term, there is marked increase in the number of prostatic tubules which lie much closer together. There is little change in the histological appearance during the first month of life but gradual regressive changes in the epithelium are noted during the following months.

Squamous metaplasia was already noted in the prostate at a gestational age of 26 weeks. It increases with advancing maturity of the foetus and the squamous cells are eventually shed into the tubular lumen. Metaplastic changes with or without desquamation in all stages may be present in the same specimen. Some tubules may become distended and even present a cystic appearance. The site of the metaplasia was in the utricle (utriculus masculinus), the urethra and the glands and ducts, mainly those in proximity to the urogenital sinus. In the younger foetus or infant, the squamous metaplasia was usually more advanced in the utricle than in the glands and ducts.

There is usually a gradual regression of metaplastic changes after birth. We already noted earlier regression in a number of our controls who were either stillborn or had survived for only a short period. Many tubules showed lumina of

Table 1

Case No.	Age	Urinary system	Genital system		Associated congenital malformations
			Prostate[a]	Other genital organs	
1	Premature (36 weeks) lived 2 hours	Agenesis of both kidneys and both ureters	Only a trace of secretion. Both ejaculatory ducts absent. Otherwise normal	Testes normal. Large number of Leydig cells. Both epididymides, vasa deferentia and seminal vesicles absent	Bilateral talipes
2	Premature (35 weeks) lived 2 days	Agenesis of left kidney and left ureter. Right kidney normal	Only a trace of secretion. Left ejaculatory duct absent. Otherwise normal	Testes normal Left epididymis, vas deferens and seminal vesicle absent. Other genital organs normal	None
3	Premature (38 weeks) lived 6 hours 45 min	Agenesis of left kidney and left ureter. Right kidney slightly enlarged. Several small bladder diverticula	Utriculus masculinus very large and distended. Left ejaculatory duct absent. Otherwise normal	Testes normal. Left epididymis, vas deferens and seminal vesicle absent. Other genital organs normal	Bilateral hare-lip. Atresia of oesophagus and tracheo-oesophageal fistula. Cardio-vascular malformations. Meckel's diverticulum. Exomphalos. Skeletal malformations. Webbing of toes.
4	Premature (30 weeks) lived 45 min	Agenesis of right kidney and right ureter. Left kidney very small, consisting of fibro-cystic tissue only. Left ureter threadlike	Extremely underdeveloped. No proliferation of tubule epithelium, no secretion but evidence of early squamous metaplasia. Both ejaculatory ducts absent	Both testes lying in the abdominal cavity. Both epididymides, vasa deferentia and right seminal vesicle absent. Left seminal vesicle immmature	Left hare-lip and cleft palate. Tracheo-oesophageal fistula. Hypoplasia of both lungs. Right congenital dislocated hip. Bilateral talipes calcaneo-varus
5	Full-term lived 1 hour 30 min	Agenesis of left kidney and left ureter. Right kidney consisting of a mass of cysts from which the ureter emerges	Both ejaculatory ducts absent. Otherwise normal	Left testis normal. Right testis absent. Both epididymides, vasa deferentia and seminal vesicles absent	None

Table 1 (Continued)

Case No.	Age	Urinary system	Genital system		Associated congenital malformations
			Prostate[a]	Other genital organs	
6	Premature (36 weeks) lived 3 hours 30 min	Hypoplasia of both kidneys, each kidney consisting of a small cyst cc. 1 cm. in diameter. Ureters very small. Bladder small	Marked disorganisation of structure but approximately normal degree of proliferation of tubule epithelium, squamous metaplasia and secretion	Both testes hypoplastic and lying in the abdominalcavity. Other genital organs normal	Hypoplasia of both lungs. Spina bifida. Recto-vesical fistula. Imperforate anus
7	Premature (39 weeks) lived 4 hours	Hypoplasia of both kidneys; each kidney about half normal size	Extreme degree of squamous metaplasia with cyst formation. Strong secretory activity	Both testes hypoplastic. Other genital organs normal	Hydranencephaly. Bony abnormalities of skull. Pituitary gland and pituitary fossa absent. Facial abnormalities
8	Full-term (41 weeks) still-born	Marked hypoplasia of right kidney. Right ureter very narrow. Left hydronephrosis due to partial stenosis of left ureter	Normal	Normal	Achondroplasia. Bilateral talipes equino-varus
9	Premature (33 weeks) lived 2 weeks	Horseshoe kidney	Normal	Volume of testes not known. Other genital organs normal	None
10	Premature (37 weeks) lived 30 min	Horseshoe kidney	Normal	Both testes hypoplastic. Other genital organs normal	Arnold-Chiari syndrome. Bilateral talipes equino-varus.
11	Lived 1 year 5 months	Horseshoe kidney	No tubules in anterior lobe and in antero-lateral lobes. Large number of tubules in the other lobes	Normal	Mongrel. Cardio-vascular malformations
12	Premature (36 weeks) lived 1 hour	Polycystic kidneys	Normal	Both testes hypoplastic. Other genital organs normal	Bilateral congenital dislocation of hip. Bilateral talipes

Table 1 (Continued)

Case No.	Age	Urinary system	Genital system		Associated congenital malformations
			Prostate[a]	Other genital organs	
13	Full-term lived 44 hours	Polycystic kidneys with hydronephrosis and hydroureter. Hypertrophy of bladder	No proliferation of tubule epithelium in lateral lobes. Strong proliferation in middle and posterior lobes. Evidence of marked degree of previous squamous metaplasia. Strong secretory activity	Normal	None
14	Full-term lived 3 weeks	Left polycystic kidney. Left ureter normal. Pyelonephrosis of right kidney	Some degree of immaturity. Appearance corresponding to an earlier period of gestation	Both testes extremely hypoplastic and lying in the abdominal cavity. Other genital organs normal	None
15	Full-term (cc. 41 weeks) lived 3 months	Right hydronephrosis. Right ureter normal. Left kidney and left ureter normal	Very few tubules, but some tubules are cystically dilated. Evidence of a marked degree of previous squamous metaplasia. Moderate secretory activity	Both testes extremely hypoplastic and lying in the abdominal cavity. Seminal vesicles immature but their fibromuscular wall is well developed	Cardio-vascular malformations
16	Premature (27 weeks) lived 4 hours 30 min	Left polycystic kidney. Atresia of left ureter. Right kidney and right ureter normal	Normal	Normal	None

[a] Unless stated otherwise, the various processes in the prostate, i.e. proliferation of the tubule epithelium, squamous metaplasia and secretory activity corresponded in degree to those seen in normal controls.

various sizes which were preponderantly empty but occasionally still contained the débris of desquamated cells, indicating that the organ had previously gone through the process of squamous metaplasia. We have termed this stage "Post metaplasia".

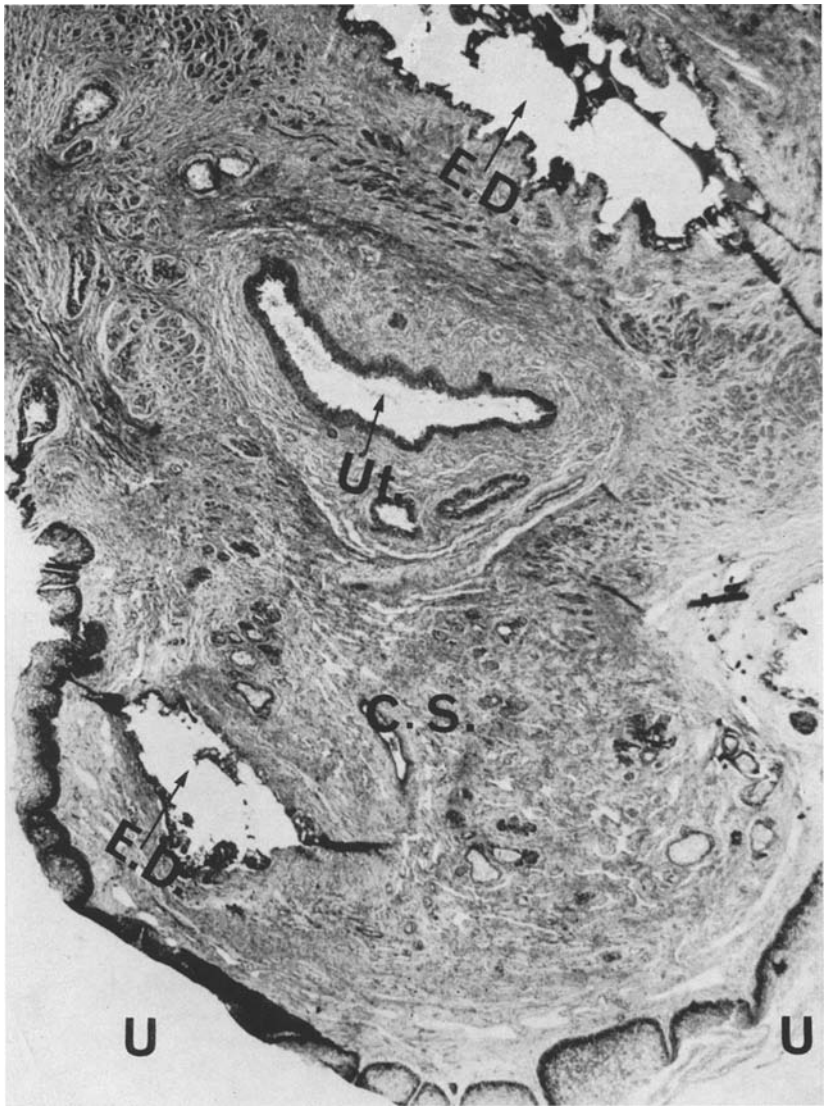

Fig. 1. Case 6. Neonate, aged 36 weeks. Lived for 3 hours and 30 minutes. Bilateral renal hypoplasia. Prostate. The ejaculatory ducts lie anterior and posterior to the utriculus masculinus. The colliculus seminalis is bulging into the prostatic urethra. The utriculus masculinus and some of the small lumina show evidence of previous metaplasia. There is marked squamous metaplasia of the prostatic urethra. ×50. *E.D.* Ejaculatory duct, *C.S.* Colliculus seminalis, *Ut.* Utriculus masculinus, *U* Urethra

A weak degree of PAS (periodic acid Schiff) positive secretion was first noted in the prostate of a foetus, aged 26 weeks. The secretory activity increased with advancing maturity and in the later weeks of gestation, a fair number of tubular

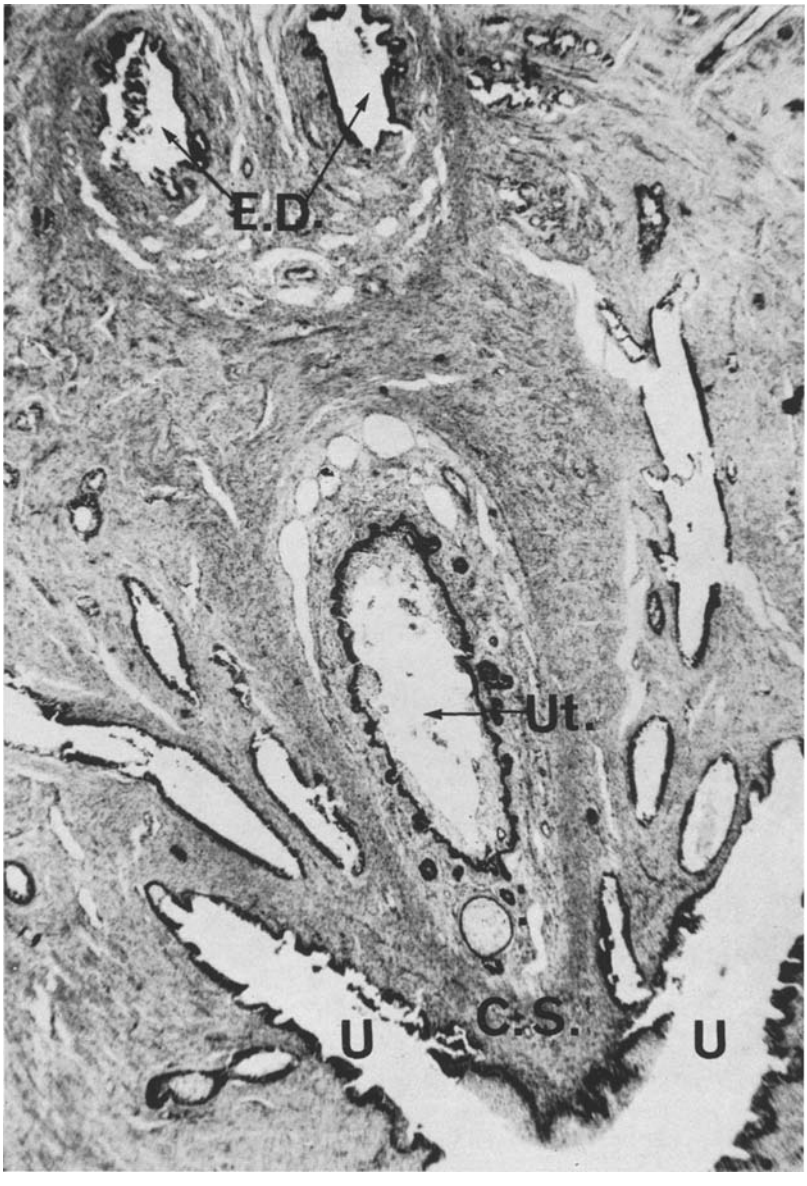

Fig. 2. Control. Neonate, aged 37 weeks. Lived for 15 minutes. Prostate. The ejaculatory ducts are lying posterolateral to the utriculus masculinus. There is some desquamating squamous metaplasia in the utriculus masculinus and in some of the tubular lumina. The posterior wall of the prostatic urethra shows squamous metaplasia. ×50. *E.D.* Ejaculatory duct, *C.S.* Colliculus seminalis, *Ut.* Utriculus masculinus, *U* Urethra

lumina were often found to be filled with secretion. The secretory activity was mainly confined to the more peripherally situated tubules and was usually found in the lateral and anterior lobes. Secretion of varying degree was still noted in the

prostates of those of our controls who had survived for a few months but there was only a trace of prostatic secretion in a child aged 13 months.

Although the lobes of the foetal and infant's prostate are not sharply demarcated, it is yet possible to determine the site of the various lesions by studying their relationship to the urethra, the seminal vesicles and the ejaculatory ducts.

There was one case with bilateral and there were 4 cases with unilateral renal agenesis (Cases 1 to 5). In 2 of these, the solitary kidney consisted of cystic tissue only (Cases 4 and 5). In contrast to normal controls, only a trace of secretion was seen in the prostates of Cases 1 and 2, but both proliferation of tubule epithelium and squamous metaplasia were within normal limits. This also refers to Cases 3 and 5, but here the secretory activity of the prostate was normal as well. The utricle of Case 3 was extremely large and distended. A similar observation was made in 3 controls. The prostate of Case 4 showed extreme underdevelopment, with only a few tubular buds, but no proliferation of tubule epithelium and no secretion, although an early degree of squamous metaplasia was already noticeable. In all these 5 cases there was uni- or bilateral agenesis of the epididymis, the vas deferens and the seminal vesicle and whenever these organs were absent, the ejaculatory duct on the corresponding side was also missing. The gonads were always well developed, with the exception of Case 5 where the testis, lying on the same side as the solitary hypoplastic kidney, was absent.

The prostate of the neonate with severe bilateral renal hypoplasia (Case 6) showed very marked disorganisation of its structure. The major part of the prostate was occupied by the colliculus seminalis which protruded into the urethra and was attached to its posterior wall by a narrow pedicle and, on some sections, gave the appearance of floating freely in the urethral lumen. The ejaculatory ducts, which are normally situated posterolateral or lateral to the utriculus masculinus, were here lying one anteriorly and one posteriorly to it (Figs. 1 and 2).

The prostate of the second case with bilateral renal hypoplasia (Case 7) was normally developed but showed an extreme degree of squamous metaplasia with cyst formation as well as strong secretory activity. It should be noted that the associated congenital malformations in this case comprised hydranencephaly with absence of the pituitary gland and the pituitary fossa. The adrenal glands were normal.

An unusual distribution of prostatic tubules was noted in 2 cases (Cases 11 and 13). In one of these, a neonate with polycystic kidneys (Case 13), the prostate showed only very few tubules in its lateral lobes, in contrast to strong proliferation of the tubule epithelium in its middle and posterior lobes. There was also strong secretory activity as well as evidence of marked previous squamous metaplasia. The findings in the prostate of the child with horseshoe kidney (Case 11) were somewhat similar to those in the previous case. There was complete absence of tubules in the anterior lobe and the antero-lateral lobes of the gland as compared with a large number of tubules in the other lobes. As usual in a child of this age, there were no longer any signs of squamous metaplasia and only little secretion.

Hardly any tubule proliferation had taken place in the prostate of the full-term infant with right hydronephrosis (Case 15). Some of the tubules were cystically dilated and filled with desquamated metaplastic cells, evidence of a marked degree of previous squamous metaplasia. There was moderate secretory

activity. The seminal vesicles were immature with slit-like lumina but their fibromuscular wall was well developed.

The prostate of the full-term infant with one polycystic kidney (Case 14) had a rather immature appearance, showing only a moderate degree of proliferation of tubule epithelium, weak secretion and not much evidence of previous squamous metaplasia. The picture corresponded to an earlier period of gestation.

The prostates of the remaining 5 cases were normal (Cases 8, 9, 10, 12 and 16). Their urinary tract malformations were as follows: marked hypoplasia of the right kidney and hydronephrosis of the left kidney (Case 8); horseshoe kidney (Cases 9 and 10); polycystic kidneys (Case 12); left polycystic kidney and atresia of the left ureter (Case 16).

Cryptorchism was present in 4 cases (Cases 4, 6, 14 and 15) and in 3 of these the testes were hypoplastic. The prostate appeared abnormal in all 4 cases with cryptorchism but was normally developed in the 3 infants whose hypoplastic testes had descended normally and were lying in the scrotum (Cases 7, 10 and 12).

A large number of Leydig cells was present in the testes of the case with bilateral renal agenesis whose mother was suffering from diabetes mellitus (Case 1).

Associated congenital malformations affecting one or more other systems were present in 10 cases (62.5%) and in 6 of these, there were primary skeletal malformations (37.5%). Congenital malformations were present in 15 of the 106 controls (14.1%).

Discussion

The foetal prostate, like the other reproductive organs of the foetus, is under the continuous influence of maternal and placental hormones as well as of hormones produced by the foetus itself. The different processes of its growth, proliferation of the tubule epithelium, squamous metaplasia and secretion are probably determined by different hormonal stimuli.

The secretory activity of the foetal and neonatal prostate which has been investigated by us in a large number of cases (Zondek and Zondek, 1970, 1971), has received only little attention in the literature so far.

Whereas it is generally recognised that squamous metaplasia of the prostatic epithelium and probably the growth of the fibromuscular tissue of the foetal prostate can be attributed to stimulation by oestrogens (Burrows, 1935; Sharpey-Schafer and Zuckerman, 1941; Andrews, 1951, and others), the exact nature of the stimulus which causes proliferation of the tubule epithelium and secretion in the foetal prostate is still unsettled, although, as in the adult, androgens may be responsible for the secretory activity of this organ in the foetus as well.

The foetal pituitary and adrenal glands may also play an essential part in influencing the various processes occurring in the foetal prostate and this has been discussed by us elsewhere (Zondek and Zondek, 1970). Another important factor to be considered is that the effect of a hormonal stimulus depends to a great deal on the condition and responsiveness of the peripheral target organ. This also applies to the period before birth. According to Willis (1962), endocrine effects in the developing embryo can occur only if the appropriate recipient organs have attained a stage of development in which they are sensitive to the particular hormone. If the maturing prostate is considered to be a target organ, it is therefore

obvious that different factors are necessary for its normal development in regard to squamous metaplasia, proliferation of the tubule epithelium and secretion.

The prostatic tubules develop from the endodermal prostatic urethra around the opening of the Wolffian ducts and new tubules continue to form during later foetal months (Willis, 1962). If such development is arrested during some stage of foetal life, this may, perhaps, account for the unusual distribution of tubules, noted in 2 of our cases (Cases 11 and 13). An extreme instance in this category was the infant, aged 3 months, with unilateral hydronephrosis (Case 15), in whose prostate practically no tubule proliferation had taken place. It is of interest to note that, in contrast to these findings, there was still evidence of marked previous squamous metaplasia and the fibromuscular walls of the immature seminal vesicles were well developed, suggesting that there had been a good response to oestrogenic stimulation. Even more striking was the extreme underdevelopment of the prostate of the case with unilateral renal agenesis (Case 4) and it is all the more remarkable that there was already some evidence of early squamous metaplasia.

One may assume that the marked disorganisation of the structure of the prostate in the case with extreme bilateral renal hypoplasia (Case 6) was also developmental in origin. It is of particular interest to note that, in spite of its very abnormal appearance, the organ was still able to respond to hormonal stimulation and was showing proliferation of tubule epithelium, marked squamous metaplasia and secretion.

We have suggested elsewhere that the various processes in the foetal prostate may be affected by the presence of gross pituitary and adrenal abnormalities, for example in anencephalic monsters (Zondek and Zondek, 1970). In this connection, our case with severe Central Nervous System malformations and absence of the pituitary gland is of special interest (Case 7). Whereas its prostate showed the same extreme degree of squamous metaplasia and cyst formation, described by us in the prostates of anencephalics, it was found to be secreting strongly, thus contrasting with the weak or even absent secretory activity noted in the anencephalic's prostate and thus suggesting a connection between normal adrenal glands and prostatic secretion.

Diminished response of the prostatic tissue to one or more hormonal stimuli may have been responsible for the features of immaturity noted in some of our cases, all of which had normal pituitary and adrenal glands. The appearances varied from a picture of generalised immaturity corresponding to an earlier period of gestation (Case 14) to marked diminution of one feature only, i.e. only minimal secretion in the presence of normal proliferation and squamous metaplasia (Cases 1 and 2).

The examination of the testes of the case with bilateral renal agenesis (Case 1) offers some further interesting information. The mother was suffering from diabetes mellitus. We have reported elsewhere that the testes of foetuses from diabetic mothers may show a larger number of Leydig cells than controls and we have attributed this to a raised level of Human Chorionic Gonadotrophin (HCG) which may occur in pregnant diabetic women (Zondek and Zondek, 1967). It is of special interest to note that the testes of this case, in spite of its extremely severe

urogenital malformations, had not only developed normally but were also able to respond to stimulation by HCG as shown by the presence of a high number of Leydig cells.

It should be stressed that whereas proliferation of the tubule epithelium and/or secretion were found to be affected in a number of our cases, squamous metaplasia was usually unimpaired. As we have pointed out elsewhere, squamous metaplasia may proceed normally, or at times to an excessive degree, even in the presence of low maternal oestriol levels (Zondek and Zondek, 1970, 1971).

According to Brody and Goldman (1940), some cases are mentioned in the literature where a very large utricle, bulging into the urethra in the region of the colliculus, caused urethral obstruction and even hydronephrosis occurred. This type of complication was not noted in our cases with a grossly distended utricle (Case 3 and 3 controls).

The derivatives of the Wolffian and Müllerian ducts, especially their lower parts (epididymis, vas deferens, uterus, and vagina), are usually absent or hypoplastic on the affected side in cases with unilateral renal agenesis (Nicholson, 1927), and on both sides in cases with bilateral agenesis (Willis, 1962), while the gonads are well formed. These were also the findings in our cases with this type of renal malformation.

It is of interest to note that all 4 cases with cryptorchism were associated with an abnormal appearance of the prostate, independently of the size of the testis. No abnormality, however, was encountered in those 3 cases where the hypoplastic testes had descended normally and were lying in the scrotum. We are now investigating the prostate in cases with cryptorchism *not* associated with urinary tract malformations (in preparation).

The frequent occurrence of associated congenital malformations affecting other systems, with frequent involvement of the skeletal system, is of interest. This is in agreement with our previous observations in which we noted associated congenital malformations in 45 of 57 stillbirths, neonates and infants with horseshoe kidney (78.9%) and primary skeletal malformations in 15 instances (26.3%) (Zondek and Zondek, 1964).

In conclusion it may be stated that congenital malformations of the urinary tract in the foetus and neonate may be associated with abnormal findings in the foetal and neonatal prostate. These may be due to delayed development or to diminished response of the foetal prostatic tissue to certain hormonal stimuli or even to marked abnormalities in the structure of the gland. No definite correlation appears to exist between the severity of the urinary tract malformation and the findings in the prostate. As regards fertility of the surviving cases in adult life, one has also to consider that any impairment of prostatic function in the foetus and neonate may be only of a temporary nature and that the organ may show normal development when the child reaches puberty.

It is also of considerable interest to note that in a large number of cases with urinary tract malformations, the foetal and neonatal prostatic tissue still responds to the various hormonal stimuli to which the organ is subjected during intra-uterine life and that in particular its response to oestrogenic stimulation is hardly ever affected.

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