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THE HUMAN PROSTATE IN ANENCEPHALY

By
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ABSTRACT

The prostate glands of 8 anencephalic monsters and 36 controls have been examined particularly with regard to metaplastic changes which occur in response to oestrogenic stimulation during pregnancy. Although oestriol levels in mothers of such monsters have been reported to be low, it was noted that with one exception, these organs showed marked and, in some instances, extreme metaplastic changes, sometimes even surpassing the appearances in normal controls. In contrast to the above findings there was a diminished proliferation of glands noted in the majority of cases. There was also diminished glandular secretion or no secretion whatsoever. The significance of these findings has been discussed.

The testis and epididymis of the human anencephalic have been discussed by us in previous publications (Zondek & Zondek 1965a,b). The prostate in anencephaly has, however, so far received scarcely any attention in the literature. Various reports by previous authors have described the appearance of squamous metaplasia in the epithelium of the prostate of the normal foetus, beginning at about 20 weeks of gestational age, gradually increasing in degree with advancing maturity and then regressing after birth (Aschoff 1894; Schlachta 1904; Halban 1904; Moore 1936; Sharpey-Schafer & Zuckerman 1941; Brodie & Goldman 1940; Andrews 1951). These changes are found in the utricle (uterus masculinus), the prostatic urethra and the prostatic tubules. Most frequently involved are usually the glands and ducts in closest proximity to the urethra and utricle, mainly those situated dorsal and slightly lateral to the urethra, but others can also be involved. The squamous cells are eventually desquamated. All these appearances increase in degree with advancing maturity, and metaplastic changes with or without desquamation may be present.
in the same specimen. Sometimes very large and even cystic lumina can be noted. A secretion of the prostatic glands has been reported by Schlachta (1904) and the other above mentioned authors. There is a gradual regression of these changes after birth.

The development of squamous metaplasia of the prostatic epithelium of the human foetus is now generally ascribed to the stimulation by oestrogens (Burrows 1935; Sharpey-Schafer & Zuckerman 1941, and others). This is of special interest as the utricle and prostatic urethra are considered homologues of the vagina (Meyer 1909; Vilas 1933; Brodie & Goldman 1940). There have, however, recently been reports of low oestriol levels in mothers bearing anencephalic foetuses (Frandsen & Stakemann 1961, 1964, and others), and in the amniotic fluid in such cases (Aleem et al. 1969). We considered it, therefore, to be of special interest to examine the prostate in cases of anencephaly, especially with regard to the appearances of squamous metaplasia in this gland. In view of the rare occurrence of male anencephalics, it has taken us several years to collect the specimens for this investigation.

MATERIAL AND METHOD

Our investigation was carried out on the prostates of 8 male anencephalics (gestational age: 32–44 weeks) and the histological findings were compared with those of 36 controls. Of the anencephalics, one case was of 32 weeks gestation, one case of 38 weeks gestation, whilst of the remaining 6 cases one was full-term and 5 were post-mature (40+ to 44 weeks). Six cases were still-born, one had survived for 30 min and another for 6½ h.

There were 36 controls of similar periods of gestation of which 6 were 32 weeks, 6 were 38 weeks, 15 were full-term and 9 were post-mature (40+ to 42 weeks). Twelve of the controls were still-born, whereas the time of survival of the remaining 24 controls ranged from a few minutes to 52 h.

In order to study appearances shown at other periods of gestation and survival, we also examined the prostates of 20 normal cases whose period of gestation and time of survival differed from those of the above cases. These 20 cases included a foetus of 26 weeks of gestation and some infants who had survived for periods ranging from a few days to 6 months.

The findings in the testes and epididymides of 5 of the above anencephalic cases have been already described elsewhere (Zondek & Zondek 1965a,b).

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 ½ mm intervals. All sections were stained with haematoxylin and eosin, as well as with periodic acid Schiff (Hotchkiss method) including diastase-treated controls.

RESULTS

The foetal prostate, in the earlier stages of gestation, shows few tubules, widely separated by supporting fibro-muscular stroma. With increasing maturity,
gradual proliferation of the glandular epithelium takes place and, at full-term, there is a marked increase in the number of prostatic tubules which lie much closer together. In contrast to the controls, most of our anencephalic cases showed a marked lack of proliferation of glandular epithelium (Table 1).

Squamous metaplasia and hyperplasia of the prostatic tubules increase with advancing maturity of the foetus. 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, 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. All but one of our anencephalic cases showed a very marked degree of hyperplasia and squamous metaplasia and in 3 cases, this was associated with the formation of extremely large cysts which were even visible with the naked eye. In 2 instances, the colliculus seminalis was so prominent, probably due to the marked degree of hyperplasia and metaplasia in its ducts and the adjoining ones, that it was bulging into the prostatic urethra, being attached to its posterior wall only by a narrow pedicle. On several microscopical levels, the appearance was that of an islet floating freely in the lumen of the urethra (Figs. 1 and 2). We have never seen a similar picture in any of our controls.

The utricle varied in shape and size from case to case. Its appearance in the anencephalic cases did not differ from the controls. The proliferation of the

<table>
<thead>
<tr>
<th>Type of case</th>
<th>Period of gestation</th>
<th>No. of cases</th>
<th>Incidence and degree of proliferation of the tubule epithelium</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>nil</td>
</tr>
<tr>
<td>Anencephalic</td>
<td>32 weeks</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Control</td>
<td>32 weeks</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Anencephalic</td>
<td>38 weeks</td>
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<td>0</td>
</tr>
<tr>
<td>Control</td>
<td>38 weeks</td>
<td>6</td>
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<tr>
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<td>6</td>
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<tr>
<td>Control</td>
<td>40-42 weeks</td>
<td>24</td>
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Table 1.
Incidence of proliferation of the tubule epithelium in the prostates of 8 anencephalics and 36 controls. The degrees of epithelial proliferation are recorded in increasing values of +.
Full-term anencephalus, aged 44 weeks. Still-born. Prostate. The colliculus seminalis is bulging into the prostatic urethra and is attached to its posterior wall by a pedicle, which is not shown on the photograph. There is a very marked degree of squamous metaplasia. Haematoxylin and eosin. \( \times 36 \). A = urethra. B = colliculus seminalis.

Fig. 1.

Full-term anencephalus, aged 44 weeks. Still-born. Prostate. The colliculus seminalis is bulging into the prostatic urethra and is attached to its posterior wall by a pedicle, which is not shown on the photograph. There is a very marked degree of squamous metaplasia. Haematoxylin and eosin. \( \times 36 \). A = urethra. B = colliculus seminalis.

tubular epithelium and the squamous metaplasia in the prostates of the anencephalic cases and the controls were recorded using the classification of Andrews (1951) but the excessive metaplastic changes in 2 of the anencephalics necessitated an additional degree of classification \(+ + + + +\) (Table 2). There is usually a gradual regression of metaplastic changes after birth. However, we already noted earlier regression in 5 of our full-term controls, who were either still-born or had survived for up to 2 days, and in one full-term anencephalic. In such cases, there was only a slight degree of active metaplasia or, in one full-term stillbirth, no sign of metaplasia whatsoever. Many tubules showed lumina of various sizes, but these were rarely unduly dilated or cystic. The lumina were preponderantly empty but occasionally a lumen would still contain the débris of desquamated cells, indicating that the organ had previously gone through the process of squamous metaplasia. This stage may be termed »Post metaplasia«.

Secretion was first noted in the prostate of a foetus aged 26 weeks which showed some PAS positive secretion in only a few glandular lumina. Incidence and degree of secretion increased with advancing maturity and, at full-term, a fair number of tubular lumina were often found to be filled with secretion.
Fig. 2.
Higher power view of Fig. 1. Haematoxylin and eosin. × 90.

Table 2.
Incidence of squamous metaplasia in the prostates of 8 anencephalics and 36 controls.
The degrees of squamous metaplasia are recorded in increasing values of +.

<table>
<thead>
<tr>
<th>Type of case</th>
<th>Period of gestation</th>
<th>No. of cases</th>
<th>Incidence and degree of squamous metaplasia</th>
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<td>Anencephalic</td>
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<td>1</td>
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<tr>
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<td>6</td>
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<tr>
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<td>1</td>
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</table>

The secretion was mainly confined to the more peripheraly situated tubules and was preponderantly noted in the lateral and anterior lobes. In three of our anencephalic cases, the prostatic secretion was found to be less than in the controls and, in 2 post-mature cases, no secretion was noted at all (Table 3).
There did not appear to be any correlation between the degree of squamous metaplasia and the secretion of the prostatic glands.

The prostate gradually increases in size with advancing maturity. The volume of the prostates of the anencephalic cases corresponded approximately to that of the controls.

In some instances, the seminal vesicles had an appearance with narrow slit-like lumina, normally only seen in earlier stages but the muscular wall was always well developed. Both seminal vesicles were absent in 2 cases and, in a further case, the seminal vesicle, testis, epididymis and ductus deferens were absent on the left side.

The testes of the anencephalic foetus were markedly smaller in volume than those of the controls. In 3 cases, the number of Leydig cells was very small, and in another 3 cases, the Leydig cells were absent. However, the appearance of the Leydig cells was normal and the seminiferous tubules also showed the picture seen in the controls of similar age groups.

With the exception of one case, one or both epididymides showed a lesser degree of secretion than the controls and this was associated with some under-development of the organ in 3 cases. These findings in the testes and epididymides of anencephalic monsters are similar to those described by us previously. Cryptorchism was encountered in one case and in another, the penis was found to be underdeveloped. Congenital malformations affecting other systems were present in 2 cases.

**DISCUSSION**

The most remarkable findings in this investigation were the extreme degree of squamous metaplasia and cystic changes in the prostates of most anencephalic infants in comparison with the controls. Hyperplastic, metaplastic and

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**Table 3.**

Incidence of secretion in the prostates of 8 anencephalics and 36 controls. The degrees of secretion are recorded in increasing values of +.

<table>
<thead>
<tr>
<th>Type of case</th>
<th>Period of gestation</th>
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<td>0</td>
</tr>
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<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Control</td>
<td>38 weeks</td>
<td>6</td>
<td>0</td>
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<tr>
<td>Anencephalic</td>
<td>40–44 weeks</td>
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<tr>
<td>Control</td>
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<td>0</td>
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cystic changes do occur in normal foetal prostates to a varying degree, but the extreme changes, noted in the majority of our anencephalic specimens, occurred only rarely in the controls.

Benirschke (1956) mentioned that the squamous epithelial changes in the neonatal prostate may also be present in the anencephalic. We have also noted such a case of our own with similar findings (Zondek & Zondek 1965a,b). Nichols (1968, personal communication) examined the prostate of an anencephalic monster whose mother had low oestradiol levels. He noticed extreme metaplastic changes in the prostate.

As previously mentioned, the development of squamous metaplasia is due to oestrogenic stimulation (Burrows 1935; Zuckerman 1936; Sharpey-Schafer & Zuckerman 1941; Sweyer 1944; Andrews 1951). Mothers of anencephalic monsters have, however, low oestriol levels in the blood (Frandsen & Stake-mann 1961, 1964, and others) and in the amniotic fluid (Aleem et al. 1969).

Although the oestradiol levels in anencephalic monsters are very low, the levels of oestrone and oestradiol in relation to those of oestriol appear to be relatively high. Oestrone and oestradiol are formed mainly, if not exclusively, by the placenta from foetal and maternal dehydroepiandrosterone sulphate. Part of the oestrone and oestradiol secreted by the placenta goes to the foetus. The anencephalic monster may have a decreased ability to hydroxylate these two oestrogens in the 16-position, but no evidence has been reported of a decreased conjugating ability in such a monster. There may be little or no endogenous testosterone formed to counteract the oestrogen effect, since the testicles of such monsters are unlikely to get a proper stimulation by pituitary gonadotrophins (Diczfalusy 1968, personal communication; Diczfalusy et al. 1964). This is in accordance with our previous observations on the testis in anencephaly (Zondek & Zondek 1965b).

Another finding was the prominence of the colliculus seminalis in 2 anencephalics, probably due to the marked degree of hyperplasia and metaplasia in its ducts and the adjoining ones. This can, however, not be compared with the 7 normal cases, quoted by Brodie & Goldman (1940) in which the utricle became large enough to bulge into the urethra in the region of the colliculus and was grossly visible. The utricle in our anencephalic cases, showing a prominent colliculis seminalis, was not distended. According to Brodie & Goldman (1940), some cases are mentioned in the literature where urethral obstruction and even hydronephrosis occurred.

Most anencephalic monsters appeared to have a reduced proliferation of glands and they were secreting less or not at all. So far, no definite explanation can be offered for these findings.

The muscular wall of the seminal vesicles, even if they had a primitive appearance, was always well developed. This may be suggestive of oestrogenic stimulation (Zuckerman & Sandys 1939).
The testes in all anencephalics showed a marked degree of hypoplasia as already previously reported by us and the number of Leydig cells was reduced.

The epididymides, as previously reported by us, showed abnormalities in some cases as well as a reduced amount of secretion (Zondek & Zondek 1965a).

The prostatic utricle (uterus masculinus) is usually the first structure in the prostate to show oestrogenic changes, i.e. squamous metaplasia. As this structure is a derivative of the Müllerian ducts, it appeared to be interesting to do a comparative study of the female vagina, also a derivative of the Müllerian ducts, in which squamous metaplasia in the newborn has already been described in the literature (Fraenkel & Papanicolaou 1938). This study is in progress. We have observed marked squamous metaplasia in the vagina of an anencephalic infant and shall report on a series of such cases in another publication.

It is generally recognised that anencephalic foetuses are frequently post-mature. This also applies to our series. Five of our 8 cases had passed the 40th week of gestation at delivery.

In conclusion, it may be stated that although oestriol levels in mothers of anencephalic foetuses have been reported to be low, it was noted that with one exception, the prostate of these monsters showed marked and, in some instances, extreme metaplastic changes, sometimes even surpassing the appearances in normal controls. This appears even more remarkable in view of the gross pituitary and adrenal abnormalities in such cases.

There was also a diminished proliferation of glands and diminished or even absent glandular secretion in the majority of cases. No definite explanation can be offered for these latter findings so far, but different hormonal stimuli may be responsible for the various processes occurring in the foetal prostate (squamous metaplasia, proliferation and secretion) and these may be affected by the gross pituitary and adrenal abnormalities in the anencephalic monster.

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