THE EFFECTS OF PROLONGED OESTROGENIC STIMULATION ON THE PROSTATE OF THE Rhesus Monkey

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Observations reported elsewhere (Parkes & Zuckerman, 1935; Courrier & Gros, 1935; van Wagenen, 1935) suggest that the prostatic glands of macaque monkeys do not react to oestrogenic stimulation like those of mice (Lacassagne, 1933; Burrows, 1935a, b) and dogs (de Jongh & Kok, 1935; Zuckerman & Groome, 1937). In non-primate mammals the glandular epithelium undergoes both hyperplasia and metaplasia, and the glandular acini are transformed into cysts of various size filled with desquamated epithelium. On the other hand the glandular epithelium remains unchanged in rhesus monkeys which have been injected with oestrone for as many as 89 days (Zuckerman & Parkes, 1936). This difference was made part of the basis of an embryological interpretation of the changes induced by oestrogens in the male reproductive tract (Zuckerman, 1936a). The possibility that the experimental data on different mammals were not strictly comparable because male monkeys had not been treated with oestrin for sufficiently prolonged periods made it necessary to obtain further experimental data on the question.

Experimental

Two castrated immature rhesus monkeys (Macaca mulatta) were injected intramuscularly with an oil solution of oestrone for 368 (O.M. 115) and 365 (O.M. 120) days respectively. O.M. 115 received 100γ a day. O.M. 120 was given 10γ daily for the first 34 days, 5γ daily from day 35 to day 45, and 2.5γ daily from then onwards. The maximum and minimum weights of the two animals during the experimental period were:

<table>
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<tr>
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<th>O.M. 115</th>
<th>O.M. 120</th>
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<tr>
<td>Weight</td>
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<td>2160 g.</td>
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Both animals showed the usual external responses to the injections, those of O.M. 115 being the more pronounced. At no time did either animal appear to be suffering from urinary retention. The reproductive organs were removed on the day following the last injection, and fixed in Bouin’s fluid. The prostates were cut serially, the sections being stained with Mayer’s haemalum and eosin.
The Prostate of the Rhesus Monkey

O.M. 115. The changes in the reproductive tract of this animal are in general no different from those that occur after shorter periods of oestrogenic stimulation. The true prostatic glands are unchanged, and considerable growth has taken place in the vagina masculina, in the terminal parts of the ejaculatory ducts and in the fibro-muscular stroma within which they lie.

The whole prostate is much enlarged. Pl. I, figs. 1 and 2 represent transverse sections taken through the level of the middle of the vagina masculina of the prostate of O.M. 115, the experimental animal, and of O.M. 39, a control animal, of the same age, that had not been injected. Although the total transverse area of the prostate of O.M. 115 is almost three times as great as that of O.M. 39, the area within which the true prostatic glandular tissue lies is approximately the same in both (cf. Tables I and II). The great increase in the size of the prostate of O.M. 115 is due mainly to growth in the fibro-muscular stroma that intervenes between the urethra and the part of the organ in which lie the true prostatic glands. Through this stroma, to which the name "utricular bed" may be applied, pass the ejaculatory ducts and the vagina masculina.

Although the total glandular area does not appear to be smaller than in normal controls, the glands themselves are reduced in number and more dispersed than usual, the relative amount of fibro-muscular tissue within the glandular region being greater than in normal specimens of comparable age. The epithelium of the prostatic glands proper is unchanged (Pl. II, fig. 7). The glandular epithelium in the part of the organ referred to by van Wagenen (1936) as the coagulating gland is in general also unchanged (Pl. II, fig. 6) and is tall columnar and in a few places two- or three-layered. On the other hand the epithelium of the main collecting ducts of most of the prostatic glands has undergone metaplasia. Except in the uppermost lobules of the so-called "coagulating gland", the change in their character is confined to those parts of the ducts lying within the utricular bed. In general the change is more pronounced in the distal (urethral) parts of the ducts. The metaplastic process has followed the usual course, the normal one or two layers of cylindrical cells being transformed into a heavily stratified and desquamating epithelium. In places, the ducts, many of which open into the terminal parts of the ejaculatory ducts (Pl. II, fig. 5), appear to be transformed into solid rods of cells, and in more cranial levels of the prostate some are more conspicuous structures than the vagina masculina itself.

Similar metaplasia has occurred in the terminal parts (approximately the distal 2-2 mm.) of the ejaculatory ducts. The left duct, into which the vagina masculina opens, is more affected than the right and is considerably distended above the level where stratification ceases, its maximum diameters being 6 by 3 mm. It is not unlikely that the great distension of this duct resulted from the narrowing of the distal part of its lumen. The thickened walls of the two ejaculatory ducts are joined together just cranial to the level at which they open by a common mouth into the urethra (Pl. II, fig. 5).
The vagina masculina opens into the left ejaculatory duct immediately above the point where the latter enters the urethra. It is approximately 5.5 mm. long and extends to within 2 mm. of the uppermost level to which prostatic glands (coagulating glands) reach. The cranio-caudal diameter of the whole prostate is approximately 11 mm. The wall of the vagina masculina is very thick and is composed of a many-layered stratified epithelium from whose basal layers numerous tongue-like projections of cells project into the utricular bed. The superficial layers of the utricular cells were apparently being rapidly shed, a process which also occurs during less prolonged periods of oestrogenic stimulation.

From the region of the opening of the ejaculatory ducts to the external meatus the urethral epithelium is considerably thickened, the superficial layers of the stratified epithelium being “cornified”. Numerous mitotic figures are to be seen in the chromophilic basal zone of the urethral epithelium. The greatest amount of growth had taken place in the epithelium of the dorsal part of the prostatic urethra, the epithelium forming the ventral wall in this region being practically unchanged. A small conical process projects cranially into the urethra from the thickened epithelium of the crista urethralis.

Many leucoocytes are to be seen in the thickened urethral epithelium. Collections of lymphocytes are also very common. They mainly occur just deep to the urethral epithelium, the “nodes” increasing in frequency and size from the proximal part of the penile urethra to the opening of the urethra into the bladder. Thus lymphocytic “nodes” entirely surround the upper prostatic urethra (Pl. I, fig. 2). Similar collections of lymphocytes occur within the utricular bed (Pl. I, fig. 2) and in some of them areas of breakdown are to be seen. Many of the “nodes” are large enough to be obvious to the naked eye. Some appear to have begun by surrounding thickened collecting ducts. Except in a few of the most cranial lobules of the prostate (“coagulating gland”) lymphocytic collections do not occur in that part of the organ within which the true prostatic glands are situated.

The walls of the lobules of the seminal vesicles are considerably thickened. The epithelium of the vesicles on the other hand is much simpler than usual and in general comprises a single unfolded layer of cuboidal cells. In no region of the seminal vesicles is there any evidence of epithelial hyperplasia or metaplasia.

O.M. 120. The amount of oestrone injected into this animal was insufficient to cause any obvious epithelial changes in the prostate. The prostatic glands and collecting ducts are normal, and no growth has taken place in the terminal parts of the ejaculatory ducts. The vagina masculina is abnormal in structure and comprises a system of somewhat diffusely scattered cords of cells which end cranially in a cyst. Numerous solid tongue-like projections from the wall of this cyst extend into the utricular bed. Similar projections pass from the solid cords which connect the cyst with the crista urethralis. The urethral epithelium is normal throughout its entire extent. The few suburethral col-
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lections of lymphocytes that are present are situated in the upper part of the prostate.

The only clear evidence that the prostate of this animal has been influenced by the injections of oestrone is given by the fact that the gland is larger than normal and by the fact that the proportion of glandular tissue to fibro-muscular stroma is much less than in normal animals of comparable age (Tables I and II). The growth has mainly affected the utricular bed (see below).

The seminal vesicles of this animal exhibit changes similar to but slightly less extensive than those shown by O.M. 115.

FURTHER OBSERVATIONS AND DISCUSSION

The findings reported above confirm the view that the prostatic glands of rhesus monkeys are unresponsive to oestrogenic stimulation. The glands presumably either develop from epithelium of the urogenital sinus which is unresponsive to oestrogens, or they become unresponsive after they have budded from the sinus.

The enlargement of the prostate in non-primate mammals as the result of oestrogenic stimulation is in large part due to hyperplasia and metaplasia of the epithelium of the true prostatic glands. The view that benign enlargement of the prostate in man is also a result of oestrogenic stimulation, as formulated by those who have investigated non-primate mammals only (e.g. Burrows, 1935b), is based on the belief that the prostatic glands in man would react in the same way as do those of non-primate mammals. This belief is hardly tenable in view of the facts reported above, for it is unlikely that the human prostate will react more like that of a mouse than like that of a monkey. The fact remains, however, that the primate prostate does increase in size as the result of oestrogenic stimulation, and it is necessary to analyse the nature of this growth.

Tables I and II give the total area (a) and the separate areas of (b) the glandular part, (c) the utricular bed (as defined above) and (d) the urethral part of transverse sections of the prostates of normal rhesus monkeys (Table I), and of rhesus monkeys that had been injected with oestrone (Table II). In each case the section measured was taken at a level through the middle of the vagina masculina. The sections were projected on to squared paper and the glandular area (see Pl. I, figs. 1 and 2), the utricular bed and urethra (Pl. I, fig. 2), drawn and measured. In only one case (O.M. 36) was it not possible to demarcate the urethral from the utricular area by the limits of its circular muscle. In eight of the twenty-four specimens listed in Tables I and II the glandular area forms a compact mass as in Pl. I, fig. 1. In the remaining sixteen it is broken up into separate lobules (Pl. I, fig. 2). All the specimens had been fixed and prepared in the same way. The animals have been aged according to the tables for body weight and dentition published by Schultz (1933, 1935).
The extent of the prostatic growth which occurs as a result of the injection of oestrone can be realized by comparing the total areas of the specimens listed in Table II with those of comparable age in Table I. The increase becomes apparent after as few as 14 days of injection (O.M. 36) and is considerable after a year's treatment (O.M. 115). Presumably an even greater increase would be indicated if it were possible to obtain a three-dimensional instead of a two-dimensional view of the growth-process.

Table I. Dimensions of mid-utricular transverse sections of the prostates of normal rhesus monkeys. For explanation see text

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<th>No.</th>
<th>Age</th>
<th>Oestrone daily I.U.</th>
<th>Days</th>
<th>Whole organ actual sq. mm.</th>
<th>(a) Glandular area actual sq. mm.</th>
<th>%</th>
<th>(b) Utricular bed actual sq. mm.</th>
<th>%</th>
<th>(c) Urethra actual sq. mm.</th>
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Table II. Dimensions of mid-utricular transverse sections of the prostates of rhesus monkeys that had been injected with oestrone. For explanation see text

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<tr>
<th>No.</th>
<th>Age</th>
<th>Oestrone daily I.U.</th>
<th>Days</th>
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Table I suggests that the absolute area of glandular tissue remains relatively constant until the fourth year of life, and that a considerable increase occurs by the time maturity is reached. Even in the earlier stages, however, the glandular region as a rule comprises more than 50 per cent of the total transverse area of the prostate. The proportion becomes greater as maturity is
reached. The absolute area of the utricular bed on the other hand increases very little, and decreases relatively as the prostate grows. In no instance does the utricular bed comprise more than 15 per cent of the transverse area of the prostate, and it is usually less than 10 per cent. The urethral area, on the other hand, appears to increase gradually, so that its relative area does not decrease until full maturity is reached.

Table II shows that the relative extent of the glandular area decreases considerably as a result of prolonged oestrogenic stimulation, although the actual glandular area increases somewhat. Since the glands themselves are more widely dispersed in the prostates of animals that have been injected with oestrone, it follows that growth in the glandular area is due mainly to an increase in its fibro-muscular elements. The urethral part also increases in actual area as a result of oestrogenic stimulation, but its relative area does not increase. The main growth in the prostate is plainly in the utricular bed, in which there is both a considerable absolute and a considerable relative increase in size. Thus the greatest actual area of a utricular bed in the control series is 4.7 sq. mm. (O.M. 149) and the greatest relative area 14.6 per cent (O.M. 164), whereas the greatest absolute area in the injected series is 43.5 sq. mm. (O.M. 115) and the greatest relative area 52.6 per cent (O.M. 115). The tables also give the dimensions of the utricular bed together with the urethral part of the prostate, and this measure also indicates clearly the nature of the changes which occur as a result of oestrogenic stimulation ($c + d$).

The various relations between the parts of the prostate in the normal and in the injected series of animals are shown diagrammatically in Text-figs. 1-4. Text-fig. 1b shows the mean actual proportions of the parts of the prostate in the ten experimental animals listed in Table II. Text-fig. 1a shows the mean actual proportions, drawn to the same scale, of the parts of the prostate in the nine normal animals of comparable age listed in Table I. Text-fig. 2 shows the mean relative proportions of the parts of the prostate in the same two groups of animals. Text-fig. 3b shows the actual proportions of the parts of the prostate of O.M. 115, the animal that had been injected within oestrone for a year. Text-fig. 3a shows the corresponding proportions, drawn to the same scale, in O.M. 39, a normal control of comparable age. Text-fig. 4 shows the relative proportions of the parts of the prostate in these two animals. These diagrams very clearly demonstrate the great increase that takes place in the size of the utricular bed under the influence of oestrone, and the relative decrease that occurs in the glandular area.

It is plain that as the prostate increases in size under the influence of oestrogenic stimulation, the true prostatic glandular tissue is pushed outwards by growth in the utricular bed so that it comes to form an investment to the organ (cf. Pl. I, figs. 1 and 2). One of the widely held clinical views concerning the aetiology of benign enlargement of the prostate in man is that adenomata develop in the so-called middle prostatic lobe and by their growth displace the ejaculatory ducts towards a “false capsule” of the organ that is
formed by the compressed true prostatic glands. In favour of this view is the well-known fact that when an enlarged prostate is carefully enucleated the ejaculatory ducts are usually left uninjured. The origin of the adenomata has given rise to several theories. Recently the view has been put forward in a series of papers (Zuckerman & Parkes, 1935, 1936; Zuckerman, 1936 a, 1936 b) that the *epithelial* changes in benign enlargement constitute hyperplasia in

**Fig. 1.**  
*a*, the mean actual proportions of the parts of the prostate in the first nine normal control animals listed in Table I;  
*b*, the mean actual proportions of the parts of the prostate in the ten experimental animals listed in Table II, drawn to the same scale. Horizontally lined area = utricular bed. Clear area = urethral part. Vertically lined area = glandular part.

**Fig. 2.**  
*a*, the mean relative proportions of the parts of the prostate in nine normal control animals;  
*b*, the mean relative proportions of the parts of the prostate in the ten experimental animals. Different areas as in Text-fig. 1.

response to oestrogenic stimulation of a true uterine rudiment of the Müllerian ducts. The view that the uterus masculinus is primarily concerned in the pathological process has since been restated by Cunéo (1936). The hyperplasia of a glandular system lying within a stroma which reacts to oestrogenic stimulation as intensely as does the utricular bed of monkeys would undoubtedly produce a structural alteration in the prostate indistinguishable from that of benign enlargement.
It is of great interest, as the results of the experiment with O.M. 120 clearly show, that the fibro-muscular tissue of the utricular bed and of the urethral part of the prostate is much more sensitive to oestrogenic stimulation than any epithelial tissues within the prostate. It is also more sensitive than the stroma of the glandular region.

The metaplasia that occurs in the ejaculatory ducts raises a difficult problem. The change is restricted to the epithelium of the distal parts of the ducts. That of the seminal vesicles does not undergo growth in response to oestrogenic stimulation. The ejaculatory ducts, however, like the seminal vesicles, are derivatives of the Wolffian system, the epithelium of which would not a priori be expected to react to oestrogenic stimulation. The collecting ducts are derivatives of sinus epithelium, and, unlike the ducts themselves,
their distal extensions, which comprise the prostatic glands proper, are unresponsive to oestrogenic stimulation.

I have elsewhere (1936a) suggested that epithelial metaplasia and stratification in response to oestrogenic stimulation may in general be a primary response of tissue in whose development oestrogen-sensitive sinus epithelium has played a part. This hypothesis suggests that the original epithelium of the ejaculatory ducts is replaced by oestrogen-sensitive sinus epithelium. According to some authorities, e.g. Vilas (1932), a corresponding replacement of Müllerian by sinus epithelium occurs in the human vagina, and this view, as is pointed out elsewhere (Zuckerman, 1936a), is abundantly supported by endocrinological evidence. That there is a general tendency for the epithelium of the urogenital sinus of the monkey to extend in a cranial direction is indicated by the frequency of cranially directed diverticula from the prostatic urethra. Shallow pockets are by no means uncommon, and the following examples represent only the more obvious instances of such diverticula.

**O.M. 115, Pl. II, fig. 1.** The vagina masculina opens into the left ejaculatory duct. Vintemberger (1926) states that such an arrangement occurs in 8 per cent of cases in man. According to Bloomfield & Frazer (1927) the Wolffian and Müllerian ducts in man remain separate in their entire extent and open close together into the urogenital sinus. To my knowledge there is no evidence which points to an opposite conclusion in other Old World Primates, and consequently it follows that the distal part of at least the left ejaculatory duct of O.M. 115 represents an evagination or diverticulum of the urogenital sinus into which both the terminal part of the genital cord (vagina masculina) and the left Wolffian duct (vas deferens) open.

**O.M. 101, Text-fig. 5.** The two ejaculatory ducts (E) and vagina masculina (V) join together before they open by a common mouth into the prostatic urethra (U). For the same reasons given above, it would seem that the common opening represents an upward extension of the urogenital sinus.

**M.M. 20, Text-fig. 6.** On both sides a urethral diverticulum (UD) passes dorsally and cranially into the prostate. That on the left side is shown as a solid block of cells. That on the right has a patent lumen and is shown connected to the urethra by a strand of cells. The ejaculatory ducts (E) and vagina masculina (V) open into the urethra in the normal manner.

**M.M. 24, Text-fig. 7.** Two urethral diverticula (UD) are shown lying between the urethra (U) on the one hand and the vagina masculina (V) and ejaculatory ducts (E) on the other.

**O.M. 21, Text-fig. 8.** A right accessory ureter (AU) opens into the cranial part of a blind urethral diverticulum (UD) which passes upwards in the crista urethralis. The diverticulum is about 1·25 mm. long, and just before it opens into the urethra it is joined by a very narrow tubular diverticulum which opens further caudally into the prostatic urethra at about the same level as the ejaculatory ducts (E). The vagina masculina (V), which is about 4·6 mm. long, opens into the distal part of the prostatic urethra about 0·7 mm. more caudally.
The Prostate of the Rhesus Monkey

Text-figs. 5–8. Tracings of projections of the prostates of four monkeys, demonstrating urethral diverticula. The varying thickness of the outlines indicates varying responses to oestrogenic stimulation. The urethra of O.M. 21, Text-fig. 8, is incomplete in the section and has been indicated by interrupted lines. E, ejaculatory duct; V, vagina masculina; U, urethra; UD, urethral diverticulum; AU, accessory ureter.
I have observed similar urethral diverticula in marmosets (*Hapale jacchus*). Thus large dorsally and cranially directed diverticula occur in two of three specimens, M.M. 69 and 71 (Pl. I, figs. 3 and 4). In one specimen the uterus masculinus opens into the diverticulum.

The relative frequency of urethral diverticula of the kind described above suggests that there is a tendency for sinus epithelium to track cranio-dorsally in the region of the opening of the Wolffian and Müllerian ducts. Such a view is consonant with Vilas' (1932) and Koff's (1933) findings regarding the development of the vagina. It is not being unduly speculative, therefore, to suggest that the epithelium of the distal parts of the ejaculatory ducts which undergoes metaplasia in response to oestrogenic stimulation represents oestrogen sensitive sinus epithelium that has replaced the original Wolffian epithelium.

The different reactions to oestrone of the prostatic glands and of their collecting ducts could possibly have come about in the following way. The primordial prostatic tubules may have been derived from a region of the urogenital sinus that is originally insensitive to oestrogenic stimulation. Sensitivity in this region and in the collecting ducts may have been attained later either by a change in the character of the original epithelium or by the replacement of that epithelium by more caudally disposed sensitive cells. On the other hand the lack of response of the glands might be due to the later specialization of cells which primarily arose from oestrogen-sensitive sinus epithelium. In favour of this view is the fact that in the rhesus monkey the urethral openings of the prostatic glands, which presumably give the topographical relations of the embryonic prostatic tubules, are in fact placed almost entirely in the uppermost part of the region of the urethra which responds to oestrone (*Zuckerman, 1936a*). Additional support for the view that differential specialization during development may occur in the prostatic buds is the fact that the epithelium of the acini of Cowper's glands in the rhesus monkey also fails to respond to oestrone. Cowper's glands are undoubtedly developed from a region of the sinus which is sensitive to such stimulation. The alternative to the view that the epithelium of these bulbo-urethral glands becomes insensitive to oestrogenic substances during embryogenesis is to assume that the sensitivity of the sinus (and of some of the tubular structures which open into it) is a characteristic acquired after the glands to which the sinus gives rise have budded. Such a view seems less likely than the one which implies that glandular organs derived from the urogenital sinus become specialized after they have budded.

**SUMMARY**

1. Two immature castrated male rhesus monkeys were injected daily with oestrone for a period of a year. The prostates of both animals were greatly increased in size. The epithelium of the true prostatic glands was unchanged and hyperplasia and metaplasia had taken place only in the epithelium of the urethra, the vagina masculina, the terminal parts of the ejaculatory ducts, and the collecting ducts of the prostate.
The Prostate of the Rhesus Monkey  

2. The nature of the prostatic growth induced by oestrone is analysed, and is shown to consist mainly in growth of the utricular bed—the region intervening between the urethra and the glandular area.

3. The occurrence of urethral diverticula is described and their presence is discussed in relation to the epithelial changes that occur under the influence of oestrone in structures that open into the urogenital sinus (urethra).

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REFERENCES


EXPLANATION OF PLATES

PLATE I

Fig. 1. Transverse section of mid-utricular level of prostate of normal rhesus monkey (O.M. 39). The glandular area has been outlined. Adventitious tissue ventral to the urethra is not clearly demarcated from the muscle. ×6.

Fig. 2. Transverse section of comparable level of prostate of monkey of similar age (O.M. 115) that had been injected daily for 368 days with 100γ of oestrone. The dark areas surrounding the urethra and within the utricular bed (area between urethra and enclosed glandular area) are collections of lymphocytes. ×6.

Fig. 3. Large urethral diverticulum intervening between urethra on one hand and ejaculatory ducts and uterus masculinus on the other. Marmoset (M.M. 71). ×32.

Fig. 4. The figure shows the opening of a urethral diverticulum into the urethra of a marmoset (M.M. 69). ×32.
PLATE II

Fig. 5. The horseshoe bar represents the conjoined terminal parts of the ejaculatory ducts of O.M. 115. The structure within the bar is the vagina masculina, and the plates of cells lying outside it are the walls of collecting ducts of the prostatic glands. The dorsal wall of the urethra is thickened. The ventral wall is normal except for the presence of an unusually large collection of lymphocytes. × 17·3.

Fig. 6. Glands in the cranial part of the prostate of O.M. 115. They are normal in appearance. × 93.

Fig. 7. Normal glands in the body of the prostate of O.M. 115. × 93.
Fig. 1.

Fig. 2.

Fig. 3.

Fig. 4.

ZUCKERMAN—THE PROSTATE OF THE RHESUS MONKEY
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