Cytology of the prostate

M. K. MASON

From the Department of Morbid Anatomy, King's College Hospital Medical School, London

SYNOPSIS A series of prostates has been studied cytologically by making smears directly from surgically excised glands. The cytological findings in these smears are described. Benign conditions of the prostate can be readily diagnosed by this means but it is not a satisfactory method for finding latent carcinomas. In addition, the cells in the smears obtained from the excised glands were compared with the cells found in smears obtained by prostatic massage from a series of patients attending with prostatic disorders. It was found that direct smears from prostatectomy specimens give a useful indication of the types of benign cells which may be found in smears obtained by massage. They provide help in the differentiation of malignant from benign epithelium in the massage specimens although they give little indication of the appearances of the malignant cells themselves.

Smears made by scraping a tissue with a scalpel and spreading the material obtained on slides provide a method of diagnosis which has been little used by pathologists. This technique was much used in the middle of the last century as the cell concept became established but was later forgotten when satisfactory histological sections could be produced. It was revived by Dudgeon and Patrick (1927) and by Dudgeon and Barrett (1934) who were able to diagnose various conditions in a wide range of tissues by this method. A few authors (Herbut and Lubin, 1947; Boyer, 1950; Reese, 1954; Bamforth, 1958a) have reported using such smears during their studies of prostatic cytology but have not given an account of their findings. Direct tissue smears of the prostate could be useful in two ways. Firstly, they could be used as an alternative to sections for pathological diagnosis and possibly provide a rapid means for finding latent carcinomas. Secondly, they might help in the identification of cells in smears of the secretion obtained by prostatic massage. This paper presents the findings in a series of prostates removed at operation which were examined by means of direct smears. The appearances seen in these direct smears were also compared with those in prostatic smears obtained by massage.

MATERIAL AND METHODS

A total of 161 surgically excised prostates was examined. One hundred and fifty-nine of these were removed by routine retropubic prostatectomy and the remaining two were excised from patients in whom a pre-operative diagnosis of carcinoma had been made. The prostates were all obtained in the fresh, unfixed condition shortly after removal and serially sliced at 0.5 cm. intervals in a plane at right angles to the urethra (step section technique of Moore, 1935). The cut surface of each slice was scraped firmly with a sharp scalpel, care always being taken to cover the posterior and lateral aspects. The material on the scalpel was smeared on a glass slide numbered to correspond with the step section and immediately fixed while still wet in Schaudinn's solution. The smears were then stained with haemalum and eosin.

The step sections were fixed separately in formal saline and stained with haematoxylin and eosin in the usual way. It was thus possible to correlate the cytological findings with the histological appearance in the corresponding section.

Two hundred and eighty patients who attended the urological department with prostatic symptoms had smears prepared from the secretion obtained by prostatic massage, using the technique described by Fergusson and Gibson (1956). In addition, urine was obtained from all these patients immediately after massage, and further smears made from the centrifuged deposit.

RESULTS

BENIGN PROSTATIC CONDITIONS A considerable range of cellular components, as described below, is found in the smears made from prostates which have undergone benign enlargement. The cells are mainly found in the form of clumps and attention must be directed at these for diagnosis. Their nature can be determined by examination of the corresponding step section. Benign enlargement was present in all the prostates in this series.
Benign prostatic epithelium Sheets of epithelium, often very large, derived from the prostatic acini, are easily the most conspicuous feature in all smears. These sheets show considerable variation in appearance but in their most typical form are composed of fairly large cells (10-15μ) with ample pale pink cytoplasm, presenting a well-marked honeycomb pattern. The nuclei are uniform, about 5μ in diameter, and have rather faint chromatin markings (Fig. 1). However, there are also many other clumps which are crowded and composed of cells much smaller in size (6-8μ) and rather hyperchromic in appearance. The honeycomb pattern is inconspicuous or absent and nuclear detail is mostly obscured (Fig. 2). Clumps with an appearance intermediate between these two categories are frequently seen, while in other smears groups of cells with small pyknotic nuclei are found. Scattered single cells and nuclei are found in all smears.

Clumps of benign prostatic epithelium are sometimes found in prostatic smears obtained by massage. They are easily recognizable when present as sheets of well-spaced cells with a honeycomb pattern. More difficult to recognize are the slightly crowded groups of rather darkly staining cells which must be differentiated from casts of malignant prostatic epithelium. These clumps are probably derived from a knot of epithelium in a hyperplastic acinus similar to that shown in Fig. 3 and may be numerous if a vigorous massage is performed under anaesthesia. They are smaller in size than the majority of malignant clumps and typically are comma shaped with one irregular border (Fig. 4). It is difficult to see the nuclear detail in the individual cells but some of them show a stippled pattern.

Duct epithelium Clumps of cells which are probably derived from atypical epithelium in the ducts may be seen in some cases of prostatitis (Figs. 5 and 6). They were recognized in two of the prostates in this series in which a chronic inflammation was present. The individual cells have no definite outline and tend to be oval in shape. The cells overlap and show some variation in size (4-7μ). The chromatin is in small discrete clumps and a small nucleolus is present.

It is likely that this epithelium appearing in massage specimens provides the source of the atypical cells seen in some cases of prostatitis. Such clumps present a rather crowded appearance with some variation in cell size. The groups are quite small and a variety of inflammatory cells are also present in these smears.

Transitional epithelium Scrapings were usually made away from the urethral area but transitional cells were occasionally found in the smears. The clumps are crowded and there is overlapping of the cells which are slightly spindle shaped. The cells are large (10-17μ) and show moderate variation in size. The nucleus (6-10μ) is slightly vesicular and contains one to three small nucleoli or sometimes has a single prominent one. Isolated transitional cells may also be found.

Fibromuscular stroma The majority of smears contain a few groups of stromal cells, the number being in inverse ratio to the degree of glandular proliferation. Stromal cells are easily recognized as a straggly group of very narrow spindly nuclei lying in all directions and situated in an uneven pink-staining background. Stromal cells, for obvious reasons, are not a feature of smears obtained by prostatic massage.

Squamous metaplasia This is frequently noted in sections of the prostate. The corresponding cells in the direct smears may be confused with malignant cells but are readily identified when their nature is realized. They appeared in the smears from 14 of the prostates removed for nodular hyperplasia.

They present as an irregular sheet of large cells, up to 20μ in diameter, which have an irregular outline with a number of pointed projections tending to lie in one direction. The nuclei (7-10μ) vary in size, and show some anisocytosis (Figs. 1 and 7). Groups of cells derived from areas of squamous metaplasia are occasionally noted in massage specimens obtained from patients on oestrogen therapy.

Other cells A few lymphocytes and polymorphs are common but they are increased in number in some or all of the smears when there is a prostatitis. Prostatitis was present in 15 of the excised glands in this series. Atypical duct epithelium may also be found in these prostates (Figs. 5 and 6). Foamy macrophages are not uncommon and there were two cases in which large groups of histiocytes were found. These give an impression of a disorderly collection of hyperchromatic cells, rather than an organized clump (Figs. 8 and 9). A diagnosis of non-specific granulomatous prostatitis (Symmers, 1950) may be made if they are accompanied by Langhans type giant cells.

Histiocytes are also a feature of a small proportion of the smears obtained by prostatic massage and were noted in two of the patients who had a massage performed. They are of considerable importance as they may readily be mistaken for malignant casts. In massage specimens, they again are found in groups with an ill-defined outline and may be present in fairly large numbers (Figs. 10 and 11). They have a rather eosinophilic and poorly defined cytoplasm. In one of these cases numerous giant cells were also present and it is likely that this patient had a granulomatous prostatitis although this diagnosis has not been proven.
FIG. 1. A group of cells showing a normal honeycomb pattern at the bottom and squamous metaplasia at the top (× 320).

FIG. 2. A typical clump of small, dark, closely packed benign prostatic epithelial cells. It is difficult to see the details of individual nuclei (× 320).

FIG. 3. Section corresponding to Fig. 2 showing crowded epithelium in a hyperplastic prostatic acinus (× 500).

FIG. 4. A clump of benign cells obtained by massage and derived from a 'knot' of epithelium in a prostatic acinus. Note the characteristic comma-shaped clump with one irregular edge. Such clumps must be differentiated from malignant casts (× 500).
FIG. 5. Slightly irregular epithelial cells, probably derived from a prostatic duct (× 320).

FIG. 6. Section from corresponding area of prostate shown in Fig. 5, showing a duct lined by epithelium with similar features. Adjacent parts showed a prostatitis (× 500).
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FIG. 7. Low-power view of corresponding section to Fig. 1 showing a prostatic infarct, with adjacent squamous metaplasia (× 150).

FIG. 8. A group of histiocytes obtained by scraping a prostate (× 400).

FIG. 9. The same cells as those in Fig. 8 (× 1,150).
FIG. 10. Histiocytes in a massage specimen (x 500).

FIG. 11. The same as Fig 10 (x 1,150).

Finally, corpora amylacea are a feature of many smears.

It is most important to recognize the epithelium derived from the seminal vesicle, which is found in about 5% of massage specimens. It appears in clumps, often large, with an irregular outline. The individual cells are hyperchromatic, crowded and overlapping and it is difficult to see any nuclear detail. The nucleus of many of the cells has a characteristic triangular shape which is an important feature in the differentiation from cancer cells (Figs. 14 and 15). Brown pigment may be seen in some cells and spermatozoa are always present in the smears.

Smears made directly from an excised seminal vesicle (Figs. 12 and 13) show cells with similar characteristics to those noted in massage specimens. Pigment is rather more conspicuous, however, and a little more nuclear detail can be seen.

CARCINOMA OF THE PROSTATE Cells derived from the more extensive prostatic carcinomas, whether clinically apparent or latent, can usually be readily identified in smears of the excised gland as large, typically malignant cells with heavy nuclear markings (Figs. 16 and 17). With the better differentiated latent tumours, well-spaced clumps of cells with rather large nuclei and nucleoli may be seen, but the appearances can be regarded as no more than suspicious of malignancy. The majority of latent carcinomas, however, are small and well-differentiated and they are impossible to diagnose from smears alone (see Table). A study of the sections in such cases shows that the individual cells are virtually identical with those found in benign parts of the gland.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Histological</th>
<th>Cytological</th>
</tr>
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<tbody>
<tr>
<td>Nodular hyperplasia only</td>
<td>133</td>
<td>146</td>
</tr>
<tr>
<td>Nodular hyperplasia and prostatitis</td>
<td>15</td>
<td>11</td>
</tr>
<tr>
<td>Nodular hyperplasia and granulomatous prostatitis</td>
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<td>1</td>
</tr>
<tr>
<td>Carcinoma (clinically apparent)</td>
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<td>2</td>
</tr>
<tr>
<td>Carcinoma (latent)</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>161</td>
<td>161</td>
</tr>
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Prostatic smears obtained by massage, on the other hand, proved a most successful method for establishing the diagnosis in patients suspected clinically of having a carcinoma. A final diagnosis
Seminal vesicle epithelium in a scraping (× 500).

The same as Fig. 12 (× 1,150).

Seminal vesicle epithelium in a massage specimen (× 500).

The same as Fig. 14 (× 1,110).
FIG. 16. A direct scraping of a prostate, showing malignant epithelium on the left and normal epithelium on the right (× 500).

FIG. 17. Corresponding section to Fig. 16 showing an adenocarcinoma (× 150).
of carcinoma was made in 70 of the 280 patients on whom massage was performed. A positive smear was obtained in 48 (68·6%) of these. In 38 of these patients the nature of the prostatic enlargement was doubtful when they were first seen, and cytology enabled a definite diagnosis to be made. None of the smears was falsely reported as positive but there were 12 cases in which the smear was incorrectly reported as suspicious of malignancy. In 11 of these cases there were only small numbers of prostatic clumps and these showed a minor variation in cell size and some crowding. Prostatitis was present in nine of these cases. In the other case, groups of histiocytes were mistaken for prostatic epithelium.

A comparison between the malignant cells obtained by pre-operative massage and by scraping the excised gland (Figs. 16 and 18) shows little similarity. In massage specimens the majority of malignant cells are found in the form of well-outlined 'casts' (Figs. 18 and 19) which is not a feature of the malignant cells obtained by scraping the prostate. The individual cells are crowded and overlap each other and in most of them there is little nuclear detail to be seen. Scattered individual malignant cells are rare in massage specimens and difficult to identify.

**DISCUSSION**

It is apparent that benign prostatic epithelium presents a wide range of appearances and the classical 'honeycomb' pattern is a feature of only some of the clumps that are seen. This is to be expected in an organ which has not only a secretory cycle, as demonstrated by Moore, Price, and Gallagher (1930), but also an atrophic change with advancing age (Moore, 1936). The fact that much of the epithelium obtained by scraping the prostate appears in crowded, darkly staining clumps is important as it demonstrates the possible appearance of such groups in massage specimens, where they can be confused with malignant cells. The rather characteristic cuboidal epithelium which may be found in the ducts is probably the source of the atypical cells, which may be misdiagnosed as malignant, in the prostatic fluid obtained by massage from some patients with prostatitis (Jönsson and Fajers, 1950; Reese, 1954). Smears made directly from the prostate, therefore, provide a useful and rapid method for the diagnosis of benign conditions. It must be emphasized that clumps of cells, both in smears obtained by scraping the prostate and in those obtained by massage, are essential for diagnosis. The overall appearance of the clumps and the arrangement of the cells within them are of more importance than the details of the individual cells. Direct smears are particularly helpful in demonstrating the variety of benign cells, including histiocytes, which may be found in prostatic fluid obtained by massage. Similar studies by Peters (1950) and by Garret and Hamm (1963) on the seminal vesicle demonstrated the origin of the seminal vesicle epithelium found in a proportion of prostatic smears.

Smears taken from the excised prostate proved disappointing as a method for finding carcinomas and did not avoid the labour of cutting many sections in order to find latent tumours. Ten latent carcinomas were found histologically in this series, an incidence of 6·3%, but only one of them, a large tumour, was diagnosed with certainty from the smears, though suspicious cells were found in two other cases. The reasons for this failure are the
small size of many of the lesions, so that they were missed completely when the smears were made, together with the virtually normal appearance of the individual malignant cells. Sections are still necessary, even if the diagnosis is made from the smears, as they show the differentiation of the tumour and the extent of invasion. The lack of similarity between malignant cells obtained by massage and by scraping the excised gland is attributable to the former coming from the ducts, where they may have undergone some degeneration; consequently more detail can be seen in malignant cells obtained by scraping the organ. In addition, the well-outlined casts which are so characteristic of malignant prostatic cells in massage specimens are not seen in scrapings of the gland. Such studies therefore are of little help as a guide to the appearances of malignant cells in massage specimens. In spite of this, the presence of malignant cells in the form of casts in the prostatic secretion makes their recognition straightforward in nearly all cases. Their appearances have been studied by Peters (1950, 1951) and by Bamforth (1958 a and b). Seminal vesicle epithelium and histiocytes are the principal cells which must be differentiated. In addition, crowded benign epithelial clumps and the atypical epithelium associated with a prostatitis must also be recognized.

Examination of the prostatic secretion for the presence of malignant cells is an easy procedure. A positive result can be expected in a reasonable proportion of patients with prostatic carcinoma and it is a very helpful investigation in cases where the nature of the prostatic enlargement is doubtful. The findings have been reported in detail elsewhere (Mason and Powley, 1964). One of the difficulties in investigating patients suspected of having a prostatic carcinoma is to obtain confirmation of the diagnosis, as histological material is seldom obtainable. A raised serum acid phosphatase, a good therapeutic response to stilboestrol, or unequivocal signs of malignancy on rectal examination are also acceptable as proof of prostatic carcinoma (Mimpriss and Ferguson, 1958), but a number of patients remain in whom a positive prostatic smear cannot be confirmed. The cytological findings in positive smears obtained from confirmed cases of carcinoma in this series were similar to those from patients in whom no confirmation was available, and there seems no reason to believe that any false positive reports were issued. The accuracy of cytological diagnosis in the present series is comparable to that reported by other workers (Reese, 1954; Fergusson and Gibson, 1956; Frank and Scott, 1958). Examination of the prostatic secretion seems undoubtedly to be a procedure which is well worth attempting in patients in whom carcinoma of the prostate is a possible diagnosis.

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REFERENCES