malformation in 1673 by the Danish anatomist Nicolas Steno. The important contribution to contemporary knowledge by British physicians of the nineteenth century is stressed.

Two cases which came to necropsy when the patients were 65 and 48 years of age respectively are reported in full. They bring to 12 the total number of recorded cases of the tetralogy of Fallot in which the patient survived to 40 years of age. The patient in the first case is the oldest female with the tetralogy recorded.

I wish to express my thanks to Professor Sir Stanley Davidson for permission to report Case 1, and to Dr. A. Rae Gilchrist for permission to report Case 2; also to Mr. J. N. J. Hartley and the staff of the Royal College of Surgeons Museum, Edinburgh, for the photographs of the specimens.

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"A lot of nonsense has been talked about the declining appeal of nursing," said Miss PAT HORNSBY-SMITH, Parliamentary Secretary to the Ministry of Health, when opening a Mental Health Exhibition at Chichester a few weeks ago. In fact, there were more nurses to-day than ever before, she said, despite the many new professions opening to women and industry's overwhelming demand for every pair of hands. In nursing, generally, there were 35,000 more nursing staff in 1954 than in 1948. Even on the mental nursing side, where there were still grave shortages, the number of trained nurses rose from 14,647 in 1948, to 16,369 in 1954, and the nursing assistants from 8,700 to 12,907. Mental nursing, she continued, had certain financial advantages as a career. The student nurse started her training at a salary of £285 per year, £45 higher than a general nurse. As a staff nurse, she was on a salary range of £430 to £530. Too often glib comparisons were made between the rate of pay of student nurses and office workers. The shorthand-typist had to be trained before she started her job: during that period her parents kept, clothed, and sheltered her, and probably paid fees, fares, and lunches as well. Nursing was almost the only profession where payment was made during training.

PROSTATIC SMEAR DIAGNOSIS*

BY

J. D. FERGUSSON, M.D., F.R.C.S.
Surgeon, St. Peter's, St. Paul's, and St. Philip's Hospitals and Central Middlesex Hospital; Director of Research, Institute of Urology (University of London)

AND

E. C. GIBSON, F.R.C.S.
Research Assistant, Institute of Urology (University of London)

[WITH SPECIAL PLATE]

Cytological investigation of the secretions for diagnostic purposes is well recognized as a branch of histology requiring special experience. It is necessary to be able not only to differentiate between normal, degenerating, and pathological cells exfoliated from a specific source, but also to distinguish these from contaminants derived from adjacent excretory passages. In these respects examination of the prostatic smear demands particular experience, since the material obtained by the usual method of massage (or from the centrifuged urinary deposit) is often deficient in characteristic cells and may be heavily contaminated from the seminal vesicles. Nevertheless, if prostatic massage is conducted in a systematic manner and the ensuing secretion selectively examined, a reliable estimate of the condition of the gland can often be obtained.

One of the earliest references to cytological diagnosis in genito-urinary disease was made by Thompson (1873), who claimed that in cases of cancer of the bladder and prostate microscopical recognition of cancer cells in the urine was often practicable. Mulholland (1931) detected in the urine and accurately described malignant cells which had derived from the prostate, but Papanicolaou (1946) regarded the cytology of prostatic cells in smears from centrifuged urine as difficult to interpret. Herbut and Lubin (1947), reviewing the histological diagnosis of prostatic cancer, compared the appearance of the sectioned gland with smears obtained by prostatic massage and by the "dab" technique from the freshly cut surface of the excised gland. Further observations on the cytology of the prostatic smear have since been made by Peters *et al.* (1950, 1951, 1952), in which the method of massage, the staining properties of contaminant cells, and the changes occurring after oestrogen therapy are fully discussed.

Anatomical Considerations

For many years it has been stated by clinicians that prostatic cancer generally arises in the so-called "posterior lobe" of the gland. Anatomically there is little justification for differentiating this area in normal subjects, and any lobular development must therefore be regarded as due to the hyperplastic changes so often observed in late middle life. It has been clearly demonstrated (Franks, 1954) that the normal prostate is composed of two well-defined zones of glandular tissue, an inner and an outer, surrounding the prostatic urethra (Diagram 1). Each zone is characterized by a relative paucity of glands in the sagittal plane anteriorly, thus allowing a cleavage plane to develop under certain conditions. The two glandular zones are functionally quite distinct, particularly in regard to their response to excess or lack of sex hormones, and it would appear that, whatever aetiological factors are involved, the inner zone

*Read before the Section of Urology of the Royal Society of Medicine.

of stroma and glands is particularly prone to benign hyperplasia, while carcinoma almost exclusively affects the outer.

If these facts are accepted it is easy to understand how the growth of "adenomata" from the inner zone may bring about a displacement of the outer-zone glands in a backward and downward direction, thus forming the so-called "posterior lobe" (Diagram 2). In transverse sections made through the apex, middle, and base of such a prostate (Diagram 3) it is possible to show, both macroscopically and microscopically, that most of the outer-zone glands are now situated inferiorly (near the apex), while little or no evidence of glands from the inner group remains at this level. In higher sections through the gland the bulk of the tissue is "adenomatous" and derived from the inner-zone glands, while the outer zone is represented by a thin layer posteriorly extending for a short distance on to the lateral surface of the "adenomatous" mass. This conception of the prostate in later life is of considerable importance, since, if it is conceded that cancer almost invariably arises in the outer-zone glands, the region prone to malignancy will often lie within reach of the finger for the purpose of expressing cells by pressure. Moreover, it emphasizes that, from a cytological standpoint, the apical region is most important, since cells expressed from this level will tend to be derived almost exclusively from the outer-zone glands.

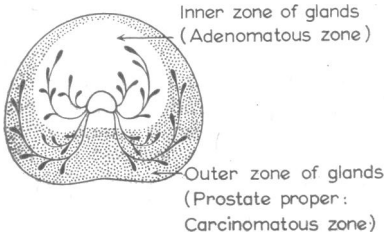

DIAGRAM 1.—Normal prostate, showing inner and outer glandular zones. (After J. C. B. Grant, *A Method of Anatomy*.)

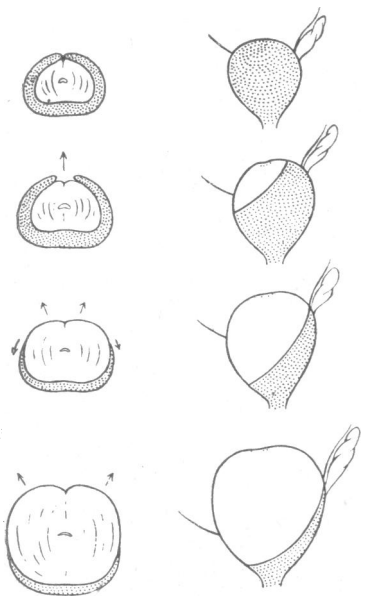

DIAGRAM 2.—Transverse sections through middle of prostate, showing changes associated with adenomatous development: hyperplasia of inner zone of glands with displacement of outer zone backwards and downwards.

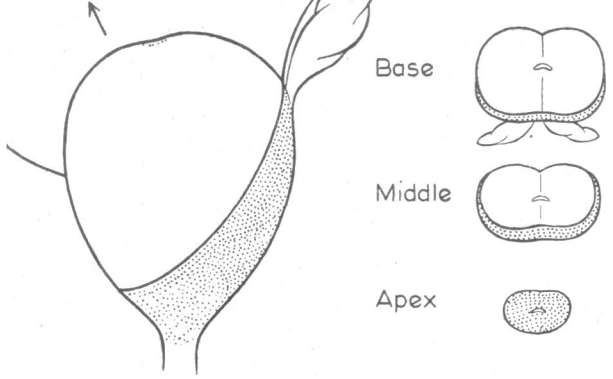

DIAGRAM 3.—Transverse sections through base, middle, and apex of hyperplastic prostate, showing proportion of inner and outer zone glands.

Technique of Obtaining Smear

The most convenient way of performing prostatic massage to obtain a diagnostic smear is to have the patient standing with his legs apart, facing the examination couch, and bent forward from the hips so that he can steady himself with one hand. If necessary he can keep his foreskin retracted with his other hand so that the operator can perform the massage and take the smear without additional assistance. The fixative, in special containers, is placed on the couch to the left of the patient, and four clean numbered microscope slides are placed on a clean piece of paper near by. The operator massages with his right index finger while watching the external meatus for signs of prostatic fluid. When this appears the drops are collected on successive slides held with the left hand and massage is discontinued. The finger should not be removed from the rectum until either sufficient fluid for making the smears has appeared at the external meatus, or the operator considers further effort would be fruitless.

Method of Massage

The method of expressing the prostatic secretion is, we believe, extremely important, and is based on the anatomical and physiological facts already considered. For diagnostic purposes the secretion from the apex of the gland is most informative, that from the base being relatively unimportant and often misleading owing to contamination from the vesicles. Fluid expressed from the intermediate regions has a variable cellular content depending on the distance from the apex or base. The organ may therefore be considered as built up of a series of steps, as illustrated in Diagram 4. Massage is begun as far forward as possible on one side at the level of the first step (near the apex of the gland). Pressure is applied as firmly as the patient will allow, and the finger slowly slid along the step towards the median groove. This movement is repeated several times at the same level on both sides of the gland. Similar massage is then performed at the level of each successive step, finishing at the base of the prostate superiorly. This should ensure that the first part of the prostatic secretion to enter the urethra and thence to appear at the external meatus is derived from the apical region. The succeeding fluid will likewise consist of secretion from the middle and base of the gland with increasing vesicular contamination. Having completed the massage, the finger gently presses the urethra from above downwards, following through as far as possible on to the bulbous urethra through the rectal wall. At the same time further stripping may be continued by sliding pressure exerted by the thumb on the perineum until the required amount of fluid is produced at the external meatus.

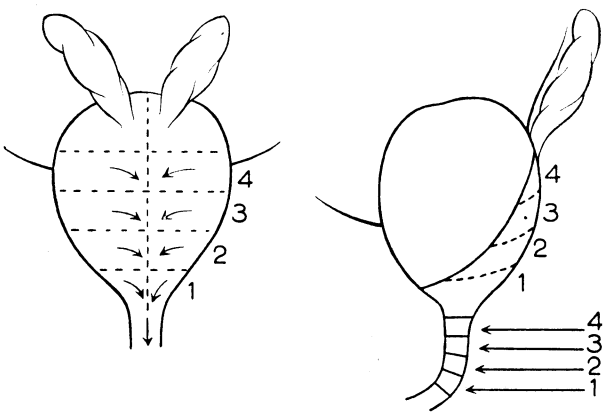

DIAGRAM 4.—Diagram illustrating "steps" in prostatic massage for smear diagnosis.

Successive drops of secretion having been obtained on several of the prepared slides, a fresh clean slide is placed

on top of each and each pair pressed lightly together. The coherent slides are then gently slid apart, producing a thin film of secretion on each which is ideal for subsequent examination. The smeared slides are then placed in the fixative solution, which is conveniently contained in cylindrical plastic receptacles specially grooved to separate the preparations and thus avoid abrasion of the smeared surfaces. Schaudinn's fluid is recommended as the fixative, and smears may be left in this for up to 48 hours before being stained with haematoxylin and eosin. It is preferable, however, to stain them within 24 hours, and, in the meanwhile, movement of the container with slides should be avoided as much as possible because of the risk of washing off the smeared material or transferring positive material from one slide to another.

Contraindications to Massage

Smear diagnosis should generally not be attempted at the first attendance of a patient, since any clinical suspicion of malignancy will almost inevitably lead to a thorough preliminary rectal examination of the gland, during which the urethra may become flooded with vesicular fluid; therefore to avoid confusing the cytological picture it is better to defer examination for a day or two.

Patients with acute urinary retention are not, as a general rule, suitable for prostatic massage, as this may increase their discomfort; moreover, the bladder spasms induced by the procedure may often cause small quantities of urine to escape into the urethra, thus diluting the secretion and reducing the concentration of representative cells. In most cases of this nature, however, some form of operative intervention is generally contemplated, and the histological diagnosis of the obstructing prostatic tissue can seldom be long in doubt. It is also useless attempting to obtain a worthwhile smear after decompression with an indwelling catheter, because of the inevitable profusion of inflammatory cells to obscure the cytological picture.

Intolerance on the part of the patient may sometimes preclude satisfactory examination. In some cases the prostate appears to be very tender, while in others rectal spasm prevents the finger from exerting pressure on the gland. In these circumstances it is advisable to repeat the attempt later with the help of a small dose of morphine, which in most instances gives adequate analgesia for the procedure to be carried out.

Cytological Examination of Smear

Smear Expectations

At the outset it must be stressed that it is not possible in every case to obtain prostatic fluid containing enough cells to permit diagnosis, but failure can often be foreseen at the time of the first rectal examination. The cellular content of the smear is probably related to the activity of the epithelium and the patency of the prostatic ducts. Thus in normal and slightly adenomatous glands, where there is average epithelial activity and the ducts remain patent, moderate numbers of prostatic cells, sufficient for accurate diagnosis, may be confidently expected. In large "adenomatous" glands, however, the ducts are often blocked by stromal hyperplasia and the residual glandular tissue is rendered atrophic by pressure, so that only scanty cells can be expressed. In carcinoma of the prostate, provided the ducts are not blocked by excessive scirrhous reaction, abundant cells can be expected, but if attempts are made to express secretion from an advanced scirrhous growth a sparse smear will often result.

It may well be that the prostatic cells present in a good smear are mainly, if not entirely, derived from the outer zone of glands, since the prostate, being a solid organ, does not transmit pressure changes at the periphery equally throughout its mass. If, therefore, epithelial activity is present in the outer zone, as in the normal or the carcinomatous gland, cells may be expected in the smear in corresponding proportion. If, however, the outer zone of glands is atrophic because of pressure from adenomata arising in the inner zone, or if the ducts of the outer-zone glands are obstructed by extreme scirrhous reaction in advanced carcinoma, the cell content of the smear may be scanty.

Cell Types

(*a*) *Normal Prostatic Cells.*—These usually occur singly, or occasionally in small groups of two or three (Special Plate, Fig. 1). They are oval or round in shape when isolated, but often polygonal when in small groups, being slightly larger than the accompanying leucocytes. The cytoplasm stains lightly, but the cell borders are sharply defined; the nucleus is round or oval and is centrally placed, occupying one-half to two-thirds of the cell. The nuclei show only slight variation in size, and the chromatin detail is fine with no coarse patches or hyperchromasia. Nucleoli are occasionally seen, but are not common. This type of cell occurs in the normal prostate and in the prostate after middle age with or without adenomatous changes, but in the latter the cells tend to be slightly larger than in young adults.

(*b*) *Cancer of Prostate.*—The characteristic smear contains numerous cells which are aggregated in groups or clumps rather than occurring singly (Plate, Figs. 2 and 3). The diagnosis is made mainly on the appearance of the groups rather than on the features exhibited by isolated and individual cells. In these groups the nuclei tend to be overcrowded, overlapping each other markedly, and the chromatin is patchy and hyperchromatic. The nuclei may vary greatly in size, being on the average larger than those of benign cells. Nucleoli are occasionally seen throughout the group, as in Fig. 3. There is little cytoplasm, and that which is present provides an irregular and very indistinct edge to the syncytial clump.

(*c*) Other cells which may confuse the cytological picture are: (i) Transitional cells derived from the bladder, urethra, and prostatic ducts. These are fairly large polygonal cells with a central nucleus which is much smaller in proportion to the size of the cell than in the case of the prostatic cells. (ii) Histiocytes, which may be found in a variety of sizes and shapes. There is ample cytoplasm, which is either foamy with lipoid or granular with debris. The nucleus is eccentric and usually indented. The cytoplasm may contain large numbers of degenerated leucocytes, sperms, or prostatic cells, and the appearance may resemble that of a collection of malignant nuclei. The liberal amount of cytoplasm, however, usually makes for easy identification. Sometimes many histiocytes fuse together to form a foreign-body giant cell. (iii) Miscellaneous cells or bodies: sperms, spermatids, corpora amylacea, vesicular fluid, and blood cells can also be seen at times.

Changes After Oestrogen Therapy

Following oestrogen treatment two characteristic types of cell make their appearance (Plate, Fig. 4): (*a*) The glycogen cell—a round or oval cell with a sharp cell margin and filled with glycogen. The nucleus is oval, relatively small, and eccentric, giving the appearance of being pressed against the cell membrane by the contained glycogen. These cells occur in smears from both benign and carcinomatous glands within a few days of starting oestrogen therapy and disappear four to five days after its cessation. (*b*) Squamous cells—large, flat, polygonal cells with small pyknotic nuclei closely resembling the superficial vaginal epithelium. These appear a few days after the glycogen cells, but may persist for many months after oestrogen withdrawal. It is believed that the glycogen cells are epithelial cells derived from the prostate which have become filled with glycogen as a result of excessive oestrogen stimulation. They can be seen in sections of the prostate of newborn infants, where the effect is no doubt due to the maternal hormone. It is stated that they appear in the smear more quickly in cases of benign hyperplasia than in cases of carcinoma, but we have had no experience of this. The squamous cells are modified, transitional

epithelial cells from the prostatic ducts and urethra. Changes in the malignant cells also occur after the institution of oestrogen therapy. The nuclei tend to become indistinct and stain poorly, and cells are sometimes seen with vacuolated cytoplasm and degenerating nuclei. Following successful treatment the malignant cells tend to disappear entirely, although their reappearance at a future date cannot be excluded. Some of our cases of cancer of the prostate which have initially responded well to oestrogen therapy have later suffered a relapse with clinical evidence of increased malignant activity. In these cases repeated smear examinations have shown large numbers of glycogen cells (indicating effective oestrogen absorption) associated with the reappearance of clumps of malignant cells apparently unmodified by continued treatment (Plate, Fig. 5).

Results of Cytological Examination

The results of cytological examination of prostatic smears which follow relate to a consecutive series of 100 cases of prostatic disease in which histological preparations were later available for comparison. It has been inevitable, in compiling a series of this sort, that a number of additional cases have been examined in which either a smear has been unobtainable or the opportunity for subsequent histological examination has not presented. Such cases have been excluded from the analysis, but it is of interest to note that in the latter group a diagnosis of cancer was made in four instances from the prostatic smear alone. Two of these cases later developed osteosclerotic metastases (of the prostatic type) with elevation of the serum acid phosphatase level, while another, although showing no radiological evidence of secondary deposits, had a raised serum acid phosphatase content of 14 King–Armstrong units, which decreased after oestrogen therapy.

In the 100 cases in which both smear and prostatic tissue were available for study the smear diagnosis was invariably made independently by a cytologist who was not aware of the clinical and histological features of the case. Although handicapped in this manner, a definite cytological diagnosis was recorded for 93 patients, and in 89 instances this agreed with the final assessment—an accuracy rate of 95.7% (see Table). Of 38 cases where cytological diagnosis indicated prostatic cancer, confirmatory histological evidence was obtained in 36. In the remaining two, in which obstructing prostatic tissue was removed by "cold-punch" resection, careful examination failed to reveal malignant tissue. However, the subsequent appearance of typical secondary deposits in the skeleton together with elevation of the serum acid phosphatase level confirmed that the cytological diagnosis was correct. From seven patients were obtained smears of adequate cellular content in which the appearance, although suggestive of malignancy, did not justify a firm diagnosis. Histological examination subsequently confirmed two cases as malignant. Smears from the remaining 55 cases gave no indication of the presence of cancer, but two patients were later shown to have the disease. Detailed review of the remainder has given no grounds for disagreement with the cytological diagnosis.

Comparison of Smear and Histological Diagnosis in 100 Cases

Smear Diagnosis	Subsequent Histology	Final Diagnosis	Smear Accuracy (%)
38 carcinoma ..	34 carcinoma 4 benign*	36 carcinoma 2 benign	94·7
7 ? carcinoma ..	2 carcinoma 5 benign†	2 carcinoma 5 benign	
55 benign	2 carcinoma 53 benign	2 carcinoma 53 benign	96·4
100 cases	100 cases	100 cases	

* Two cases developed radiological signs of secondary deposits from carcinoma of prostate with raised serum acid phosphatase level.
† Two patients have died. No evidence of carcinoma found at necropsy, but massive sections of capsule not made. Three patients being followed up and are well.

The occasional lack of correspondence between the cytological diagnosis and that based on histological examination may be explicable to some extent by the frequent coexistence of "adenomatous" hyperplasia with cancer. If hyperplasia predominates, a small area of cancer may easily be overlooked on routine examination of the enucleated or resected prostate, or, indeed, may fail to have been removed at operation. Instances in which, clinically, the prostate is adjudged hyperplastic and yet the smear reveals cancer cells are of particular interest in suggesting the possibility of detecting growths at a sufficiently early stage for surgical removal. On the other hand, it must be remembered that latent or occult microscopic foci of malignancy are frequently found at necropsy in the prostates of elderly men who have never evinced signs of prostatic disease. The evidence of cytological examination alone, unsupported by clinical manifestations, should therefore not be taken as an indication for operative treatment. It must, indeed, be emphasized that, in the present state of our knowledge of prostatic cancer, smear diagnosis is of value mainly as a confirmatory test in patients presenting symptomatic evidence of prostatic disease. In this role, if carried out systematically and by an expert, it can furnish results closely comparable with those of prostatic biopsy with neither the attendant anaesthetic hazard nor the risk of undue trauma, haemorrhage, or infection. Furthermore, it can be repeated many times on the same material—an advantage presented by no equivalent method of investigation. Apart from its value as a diagnostic aid, it is thus well adapted to research work on human prostatic cancer, and also affords a useful indication of the response or otherwise to hormonal therapy.

Summary

Cytological examination of the prostatic smear offers a reliable method of estimating the condition of the gland with regard to malignancy, giving results comparable to those of biopsy without the attendant risks.

The technique of obtaining a smear, including the method of massage, is given, and contraindications are discussed.

The cellular content, both normal and pathological, of prostatic fluid is described and illustrated. Changes in the cell population and in malignant cells following oestrogen therapy are also described.

Results of cytological examination of smears in 100 cases of suspected malignancy are recorded and compared with the histological findings. Smear diagnosis was 95.7% accurate as compared with histological diagnosis. The occasional lack of correspondence between the two methods may be due to the frequent coexistence of "adenomatous" hyperplasia with cancer.

In the foregoing series of cases we have been fortunate in having had all our prostatic smears examined and interpreted either by Dr. G. Ayengar (late of the Chester Beatty Institute) or by Dr. J. Bamforth in the laboratories of the Imperial Cancer Research Fund. The measure of our indebtedness to them is reflected in the results, which represent the product of special ability and long experience and, indeed, emphasize the need for such qualities in reaching a reliable cytological diagnosis. Our thanks are also due to Miss F. Wadsworth (medical artist) and Mr. A. N. Finch (photographer) and to the secretarial staff of the Institute of Urology for valuable assistance in the production of this report.

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J. D. FERGUSSON AND E. C. GIBSON: PROSTATIC SMEAR DIAGNOSIS

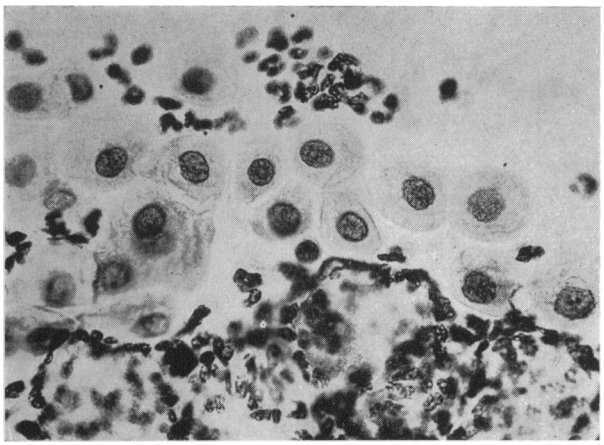

FIG. 1.—Prostatic smear (×500) showing a loose group of normal prostatic epithelial cells amidst leucocytes.

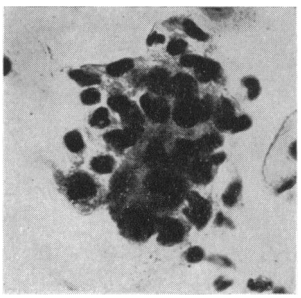

FIG. 2.—Group of malignant cells (×300). Note density, large size, and irregularity of nuclei, which tend to overlap. Cell margins are ill defined, and the whole appears as a syncytial mass.

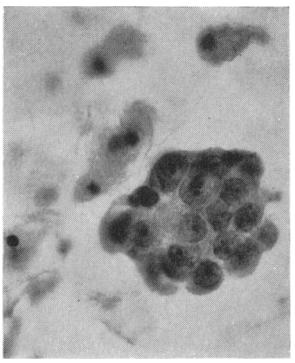

FIG. 3.—Prostatic smear (×300) from patient with adenocarcinoma. Note indistinct cell margins and well-defined nucleoli.

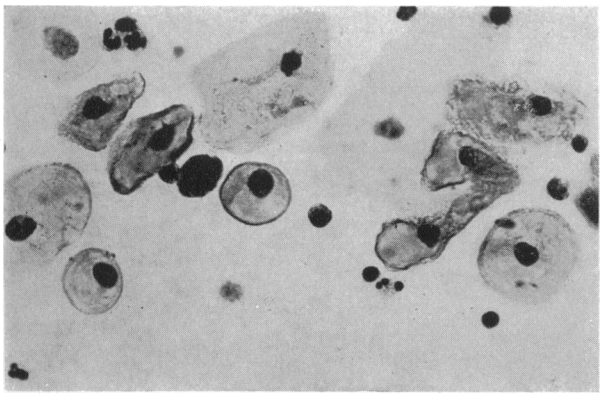

FIG. 4.—Prostatic smear (×500) from case of prostatic cancer treated with oestrogens. Round glycogen cells and squamous cells clearly shown.

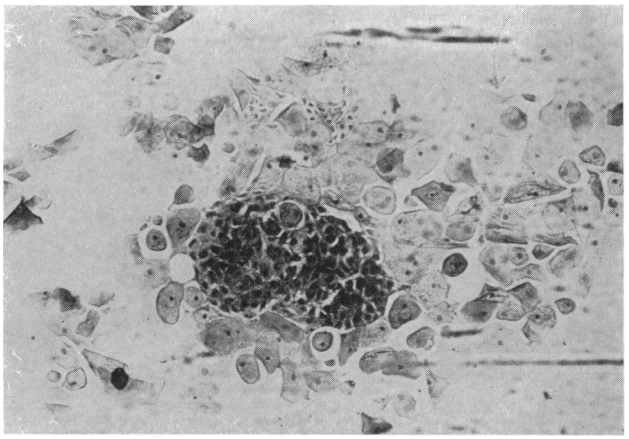

FIG. 5.—Prostatic smear (×500) from patient with clinical evidence of growth reactivation despite continued oestrogen therapy (500 mg. stilboestrol daily). Note clump of malignant cells surrounded by numerous glycogen and squamous epithelial cells.

R. M. MARQUIS: TETRALOGY OF FALLOT

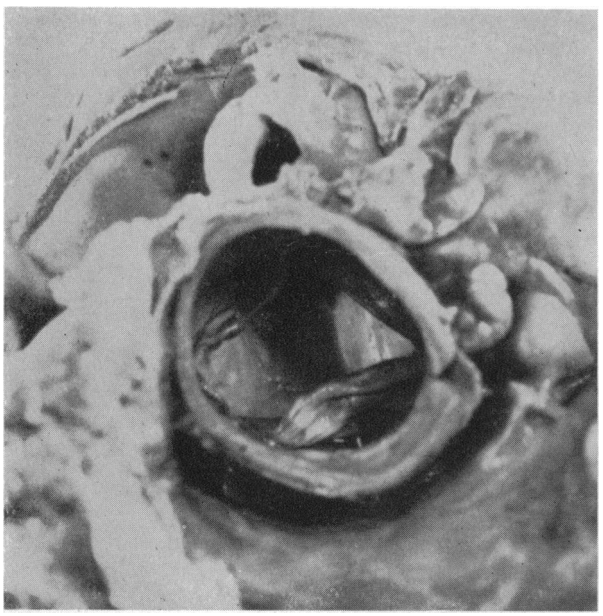

FIG. 1.—Case 1: View of heart looking down aorta, with aortic cusps pinned back to show saddle-top of muscular ventricular septum. Overriding position of aorta and narrow orifice of pulmonary valve clearly seen.

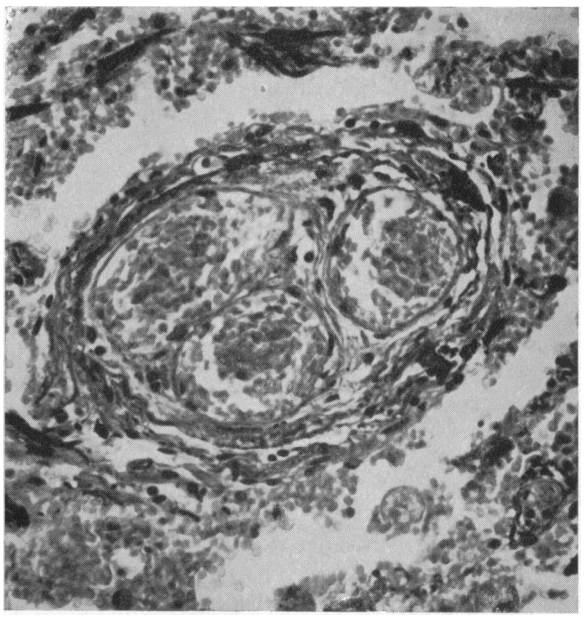

FIG. 2.—Case 1: Photomicrograph of a small pulmonary vessel with multiple channels simulating recanalization. (Verhoeff-van Gieson stain. ×280.)

[*Figs. 3 and 4 overleaf*