TUMORS OF THE MALE SEX ORGANS

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ATLAS OF TUMOR PATHOLOGY

Section VIII—Fascicles 31b and 32

TUMORS OF THE MALE SEX ORGANS

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Published by the
ARMED FORCES INSTITUTE OF PATHOLOGY

Under the Auspices of the
SUBCOMMITTEE ON ONCOLOGY

of the
COMMITTEE ON PATHOLOGY

of the
NATIONAL RESEARCH COUNCIL

Washington, D. C.

1952

For sale by the American Registry of Pathology
Armed Forces Institute of Pathology
Washington, 25, D. C. - Price - $1.50

ATLAS OF TUMOR PATHOLOGY

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ANNA FULLER FUND

ARMED FORCES INSTITUTE OF PATHOLOGY

JANE COFFIN CHILDS MEMORIAL FUND FOR MEDICAL RESEARCH

NATIONAL CANCER INSTITUTE, U.S. PUBLIC HEALTH SERVICE

UNITED STATES VETERANS ADMINISTRATION

ACKNOWLEDGMENTS

The authors wish to express their appreciation to the various agencies and individuals whose assistance and cooperation have been invaluable in the preparation of this fascicle. The Armed Forces Institute of Pathology made available for our review the records and pathologic material on more than two thousand tumors of the male genital system.

The section on testicular tumors contains much of the material obtained by an extensive review of the testicular tumors occurring in army personnel during World War II. This study was supported by the Veterans Administration. The statistics were prepared by the Committee on Veterans Medical Problems of the National Research Council. A special debt is owed to Miss Nona-Murry Lucke for her help in the record review, to Dr. Bernard Cohen for his handling of statistical material, and to Miss Betti Moses for her painstaking review of some thousand army and veterans' medical records in our series of testicular tumors.

We wish to thank Dr. Harold L. Stewart and Dr. Sheldon C. Sommers for their careful criticism of the original manuscript.

Col. J. E. Ash, Dr. Nathan B. Friedman, Dr. S. A. Henry, and Dr. Carl A. Wattenberg have kindly given permission for the use of illustrations which were used in previous publications.

We also wish to express our appreciation to Dr. Lauren V. Ackerman, Washington University School of Medicine; Dr. W. Seaman, Washington University School of Medicine; and Dr. Carl A. Wattenberg, St. Louis, Mo., for other illustrative material contributed to this fascicle.

Dr. N. P. Rathbun and Dr. J. Arnold de Veer, Brooklyn, N. Y.; and Dr. J. D. Feek and Dr. W. C. Hunter, Portland, Oregon, have given permission to use material which they contributed to the Armed Forces Institute of Pathology.

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American Association of Pathologists and Bacteriologists:

Am. J. Path., 12: 599–624, 1936. For our figures 1, 2.

American Registry of Pathology:

Atlas of Genitourinary Pathology, 1946. For our figures 21, 27, 102, 105, 126, 133.

Dr. S. A. Henry:

Cancer of the Scrotum in Relation to Occupation. London, Oxford University Press, 1946. For our figures 127, 128.

W. B. Saunders Co.:

Moore, R. A. A Textbook of Pathology. 1951. For our figure 4.

Williams and Wilkins Co.:

J. Urol., 37: 372–384, 1937. For our figure 5.

J. Urol., 58: 378–383, 1947. For our figure 18.

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TUMORS OF THE MALE SEX ORGANS

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TUMORS OF THE PROSTATE

Introduction

The prostate gland is formed in embryonic life by a number of evaginations from the posterior and lateral walls of the posterior urethra. The male prostate is divided into five lobes: the posterior lobe, which is posterior to the urethra and the deferential canal; the middle lobe, which lies between the urethra and the deferential canal; the two lateral lobes, the glands of which empty into the sides of the verumontanum; and the anterior lobe, a vestigial structure represented by from eight to ten acini anterior to the urethra (fig. 1). The ejaculatory ducts pass downward and forward between the middle and posterior lobes. In the female the prostate remains vestigial. It corresponds only to the lateral and middle lobes of the male prostate and lacks a posterior lobe. This fact is of interest in relation to nodular hyperplasia and prostatic carcinoma. The former involves only the ambisexual part of the male prostate, while the latter is predominantly a disease of the posterior lobe, or purely male part of the prostate.

From 15 to 30 branching tubular glands imbedded in connective tissue stroma make up the male prostate (fig. 2). The glandular epithelium consists of two layers: tall columnar, luminal cells and flattened or cuboidal basal cells. The epithelium rests on a narrow (7 to 10 microns), homogeneous, collagen-like basement membrane. The stroma consists of approximately equal amounts of smooth muscle and fibrous tissue.

The normal development and maintenance of the prostate, as well as of other male secondary sexual organs, is dependent upon endocrine stimulation by the testes. In-castrates, both human and animal, the prostate atrophies quickly. The endocrine function of the testes is in turn dependent upon gonadotropic hormone from the pituitary, and absence of the pituitary hormone also results in prostatic atrophy.

Senile atrophy of the prostate usually begins near the end of the fourth decade simultaneously with a decreased androgen excretion in the urine. Morphologic manifestations of atrophy include irregularities in character of the epithelium, loss of secretory activity by glandular epithelium, complete atrophy of acini, and atrophy of smooth muscle of the stroma with replacement by fibrous tissues (Moore, 1942).

If nodular hyperplasia of the prostate is considered non-neoplastic, then almost all prostatic tumors may be classified as malignant. Adenocarcinoma is by far the most common tumor. The remainder are epidermoid carcinomas,

Figure 1.* Anatomic sketch of prostate. Upper is transverse section at level of colliculus seminalis and lower is sagittal section. A: Posterior lobe; B: Middle lobe; C: Anterior lobe; and D: Lateral lobes. Note position of posterior lobe, inferior and posterior to ejaculatory ducts. A. F. I. P. Acc. No. 218716–21.

Figure 2.* Transverse section of normal prostate at level of colliculus seminalis showing general glandular pattern and ejaculatory ducts. A. F. I. P. Acc. No. 218716–22.

*From Moore, R. A. The evolution and involution of the prostate gland. Am. J. Path., 12: 599–624, 1936.

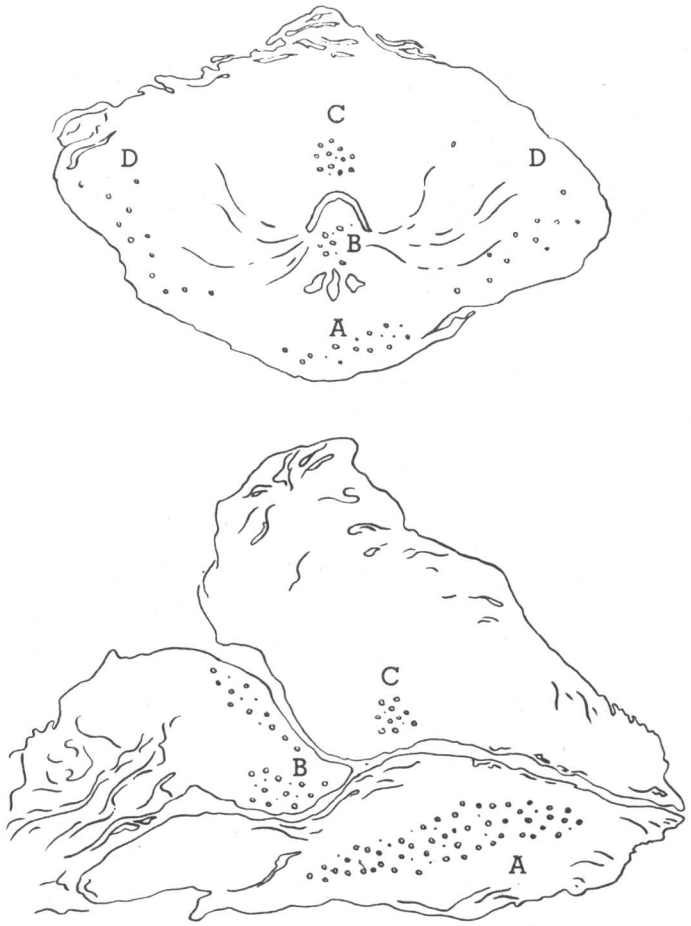

Fig. 1

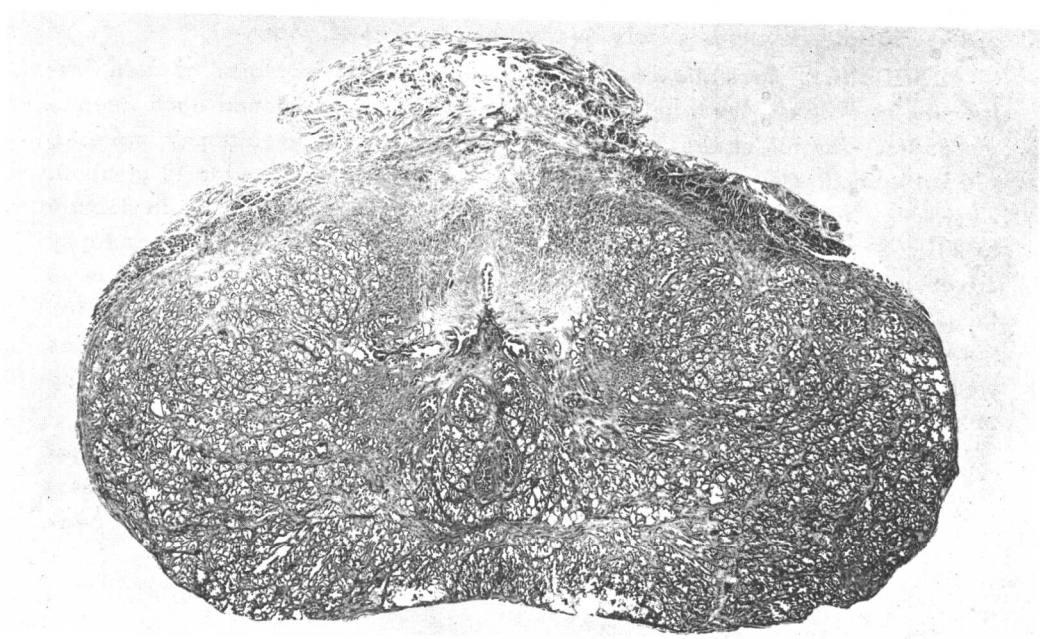

Fig. 2

probably arising from urethral mucosa, and sarcomas of the prostate and tissues of the neck of the vesicle.

Adenocarcinoma

SYNONYMS AND RELATED TERMS: Acinar carcinoma; alveolar adenocarcinoma; alveolar carcinoma; alveolar cell carcinoma; carcinoma; carcinoma simplex; cylindrical (duct) cell carcinoma; glandular carcinoma; small cell carcinoma.

DEFINITION. A malignant tumor which arises from the acinic and/or ductal epithelium of the prostate and which may vary considerably in its glandular differentiation and anaplasia.

TYPES. From a clinico-pathologic point of view, carcinoma of the prostate can be divided roughly into three types. The first type is **clinically manifest** and usually has presenting symptoms characterized by local pain and urinary abnormalities, both of which may be intensified late in the disease. The prostate is enlarged. The normal contours of the prostate are destroyed. Local tumor invasion is common, but metastases are late. These tumors are usually well differentiated adenocarcinomas. The second type, **occult carcinoma,** is characterized by metastases widespread from a small, unsuspected primary growth. There is a paucity of local symptoms with little, if any, prostatic enlargement and no change in prostatic contour. Frequently the presenting symptoms are related to metastases. The histologic structure is usually anaplastic adenocarcinoma or carcinoma simplex. The third group, the **latent carcinomas,** are small, asymptomatic tumors which do not metastasize. These tumors are found usually at autopsy, occasionally in surgical specimens. Although their significance is not apparent, they probably represent small carcinomas which would have developed into clinically manifest tumors if the patients had lived. These latent tumors support the opinion that carcinoma of the prostate develops slowly over a long period of years.

INCIDENCE. Prostatic carcinoma is a common neoplasm of men, extremely rare before the age of 40, but increasing in incidence each decade thereafter. Careful studies of large series of unselected autopsy material place the incidence of carcinoma of the prostate in all men over 40 at about 20 percent. The frequency increases from 10 to 17 percent in the fifth decade to 29 to 39 percent in the ninth decade. Incidence established from autopsy material is much higher than that based on clinical diagnoses because of the large number of latent tumors. Calculations based on the unselected autopsy series of Moore (1935) and of Rich, in which 104 prostatic carcinomas were found in 667 autopsies, would indicate that latent carcinomas of the prostate outnumber those clinically manifest about four to one.

Gordon's survey of hospitalized cancer patients in the United States showed that cancer of the prostate made up 10 percent of the cases of cancers in males and accounted for 11.5 percent of all male cancer deaths. The peak

incidence of prostatic carcinoma is in the seventh decade, with approximately three fourths of the deaths in the seventh and eighth decades.

Carcinoma of the prostate has the same incidence in Europe as in the United States, but in China it is a rare disease. Hu and Ch'in found only one prostatic carcinoma in 379 carcinomas in men autopsied in the hospital of the Peiping Union Medical College.

ETIOLOGY. Because carcinoma of the prostate is so distinctly a disease of elderly men, its etiology and histogenesis probably depend upon some previous alteration incident to the aging process. After the age of 40 there is a gradual decrease in the biochemically active urinary androgens simultaneous with atrophy of the prostatic glands, most evident in the posterior lobe. It is in these atrophic glands that almost all of the carcinomas arise, with apparent derivation of malignant cells from atrophic. Fifty out of 52 tumors small enough to allow determination of their points of origin arose from atrophic glands (Moore, 1935). Because atrophy is most marked in the posterior lobe, it is not surprising that the great majority of tumors arise there.

The difference in behavior of the posterior lobe of the prostate and the remaining prostatic tissue is explained by the fact that the former, a distinctly male structure, undergoes atrophy with decrease in the androgen level, while the ambisexual lateral and middle lobes often fail to atrophy and instead participate in nodular hyperplasia, so frequently seen in males past middle age.

There is no causal relationship between nodular hyperplasia of the prostate and carcinoma. Because both lesions are common in older men, they frequently coexist, but the incidence of nodular hyperplasia in tumor-bearing and tumor-free prostates is the same. In addition, the two lesions are rarely morphologically related, because carcinoma usually arises in the posterior lobe of the prostate, which never participates in nodular hyperplasia. When carcinoma does arise in hyperplastic lateral lobes, the two lesions—i.e., carcinoma and hyperplasia—are usually discrete (fig. 6).

COURSE AND TREATMENT. The course of untreated, clinically manifest carcinoma of the prostate is relatively rapid. In a series of 1,000 cases reviewed some 20 years ago by Bumpus, more than one half of the tumors metastasized within a year after onset of symptoms. The average duration of life from onset of symptoms was 31 months. Two thirds of the patients who presented metastases died within nine months and those without metastases lived an average of 12 months. Death most frequently resulted from urinary complications secondary to urethral obstruction.

Present day therapy has improved the hopeless outlook reflected by the above figures. For the small group of patients (approximately five percent) whose tumors are sufficiently localized to allow complete excision, radical

perineal prostatectomy offers a better than 50 percent chance of a 5-year survival. In the hands of the leading proponent of this procedure, H. H. Young, radical resection carried a mortality of only about seven percent. Because carcinomas of the prostate almost always arise in the subcapsular region and are usually found in the posterior lobe, any operation short of radical perineal prostatectomy can only be a palliative procedure.

For the remaining 95 percent of the patients in whom the tumor has either metastasized or extended far enough to make complete resection impossible, androgen control offers definite temporary relief and a significant prolongation of life. The growth of both normal and, in most cases, malignant prostatic epithelium is dependent on androgen stimulation. Either the removal of the source of androgens by orchiectomy or the inhibition or neutralization of androgenic stimulus by administration of estrogens produces an adverse effect on the tumor (figs. 18, 19). With either of the above methods or with a combination of the two, 80 percent of patients show symptomatic relief and clinical improvement. In an appreciable number, the tumor becomes smaller. Intestinal obstruction, urinary obstruction, and even transverse myelitis secondary to tumor growth have in some instances disappeared completely as a result of androgen control (Ackerman and Regato). Usually, however, after a period of months (or, less frequently, years) tumors in patients improved by androgen control begin to grow again, and neither intensification nor change in type of androgen control is effective. The previously sensitive tumor cells eventually become independent of the effect of androgens and perhaps are then similar to the 20 percent of tumors originally insensitive to androgen control. The administration of estrogen may cause certain undesirable side effects such as gynecomastia, dependent edema, and testicular atrophy. The development of these changes has no correlation with the response of the tumor to treatment (Wattenberg and Rose).

Recent reports indicate that survival rates of patients treated by androgen control are significantly higher than rates for both those untreated and those treated merely to relieve urinary obstruction. A more exact statement of the prognosis with androgen control awaits the reports of larger follow-up series.

CYTOLOGIC DIAGNOSIS. The identification of cancer cells in expressed secretion of the prostate may be helpful in confirming the diagnosis of carcinoma.

CARCINOMA OF THE PROSTATE IN ANIMALS. In sharp contrast to its frequent occurrence in man, carcinoma of the prostate is apparently rare in animals. In dogs carcinoma of the prostate comprises only from one to two percent of all tumors, and in other species the incidence is even lower. Adequate study of canine material has failed to find any latent carcinomas of the prostate in old dogs, a significant observation in view of the 20 percent incidence of such tumors in human males over 40 years.

Experimental attempts to produce adenocarcinoma of the prostate in animals have been uniformly unsuccessful. In contrast to the known stimulating effects of androgens on human prostatic carcinoma, androgen administration to animals has not produced prostatic tumors. However, in animals as in men, prolonged administration of estrogens results in a squamous metaplasia of prostatic epithelium (fig. 17) but not in neoplasia. By injection of benzypyrene directly into animal prostates, Moore and Melchionna produced after 110 days epidermoid carcinomas and leiomyosarcomas but not adenocarcinoma.

BIOCHEMISTRY. Of special interest in carcinoma of the prostate are the acid and alkaline phosphatases. These enzymes hydrolyze phosphoric esters, the acid form operating optimally at pH 5 and the alkaline at approximately pH 9. The enzymes are analyzed in vitro by measurement of the rate at which they liberate phosphoric acid from phosphoric esters. Acid phosphatase is produced only by adult prostatic epithelium and its malignant variant (Gutman, Sproul, and Gutman). Alkaline phophatases are found in many places in the body. The alkaline phosphatase of bone is frequently altered by osseous metastases of prostatic carcinoma.

Acid phosphatase is normally formed by prostatic epithelium and eliminated with prostatic secretions. In prostatic carcinoma, however, the acid phosphatase presumably formed by metastasizing tumor cells finds its way into the blood stream, elevating the serum acid phosphatase. When carcinoma of the prostate is absent or contained within the vicinity of the prostate, the serum acid phosphatase level does not exceed three King Armstrong (KA) units. In 85 percent of prostatic carcinomas with metastases, the serum acid phosphatase is elevated. In 50 percent the elevation is 10 KA units or more. An elevation of serum acid phosphatase to 10 KA units or more is an absolute indication of metastatic prostatic carcinoma (Gutman, Gutman, and Robinson).

The osseous metastases of prostatic carcinoma frequently stimulate bone formation, and in approximately 85 percent of patients with osseous metastases, the serum alkaline phosphatase is also elevated. This elevation, however, is not specific for prostatic carcinoma, in contrast with the serum acid phosphatase elevation.

The metabolic activity and acid phosphatase production of both malignant and normal prostatic epithelium are dependent upon androgenic stimulation. The elevated serum acid phosphatase level in prostatic carcinoma is further raised by the administration of androgens, while it is reduced in from 80 to 90 percent of patients by orchiectomy or estrogen administration. The variability in the drop of serum acid phosphatase following androgen control therapy apparently depends upon the variability in the degree to which different tumors depend upon androgen (Huggins and Hodges).

Figure 3. Carcinoma of prostate. Tumor can be seen as poorly defined subcapsular white area in right lateral portion of posterior lobe. A. F. I. P. Acc. No. 218710–23.

Figure 4. Advanced carcinoma of prostate. White tumor tissue occupies most of the posterior lobe and left lateral lobe. There is capsular invasion in left lateral posterior sector, and irregular extension into middle lobe and right lateral lobe. Note intact posterior capsule, which is rarely invaded by tumor. Urethra is uninvolved, as is usual until late in the course of the disease. (From Moore, R. A. A Textbook of Pathology. Philadelphia: W. B. Saunders Co., 1951.) A. F. I P. Acc. No. 218716–24.

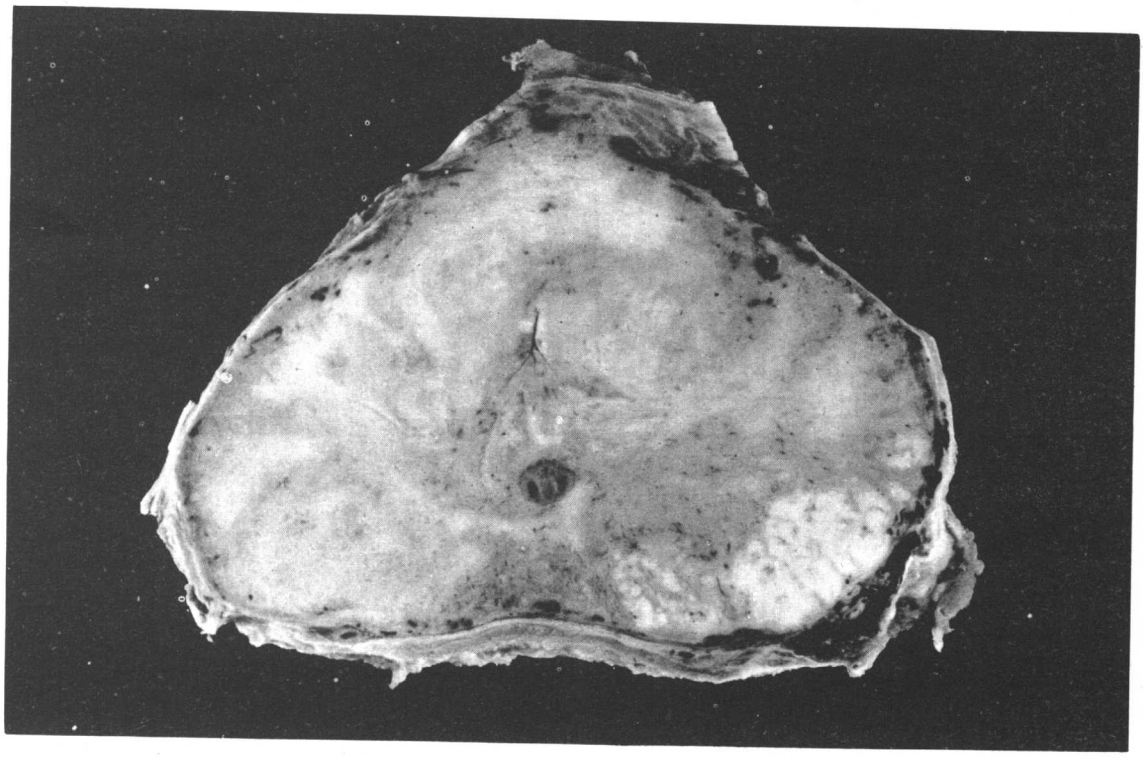

Fig. 3

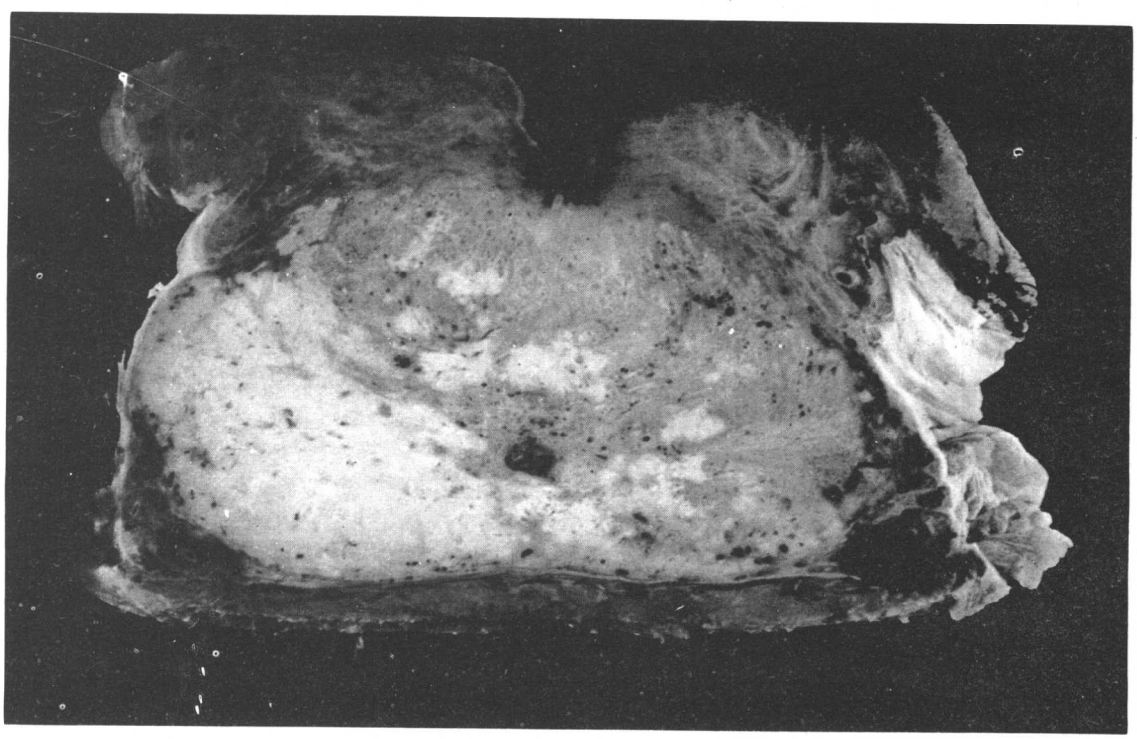

Fig. 4

In those patients showing a favorable response to orchiectomy, there is a return of elevated serum acid phosphatase to normal or near normal limits within 24 to 48 hours. It remains at normal for the duration of the remission, usually a matter of months, and rises again as tumor growth is resumed. There is also an immediate increase in the serum alkaline phosphatase following orchiectomy, which indicates osteoblastic activity presumably in the region of osseous metastases. This activity gradually declines, reaching normal in from three to four months. Administration of estrogens produces changes in acid and alkaline phosphatase levels similar to, but more gradual in their development than, those caused by orchiectomy.

GROSS. Between one half and three fourths of all prostatic carcinomas arise in the posterior lobe. The middle lobe is rarely involved. Of 66 carcinomas with known origins, 76 percent arose in the posterior lobe, 9 percent in the lateral lobes, 15 percent in the anterior lobe, and none in the middle lobe (Moore, 1935). According to Gaynor, over 95 percent of all prostatic carcinomas are located in the subcapsular region. Multicentric origin is reported in from 10 to 20 percent.

The size of prostatic carcinomas varies from microscopic proportions to entire replacement and moderate enlargement of the prostate by neoplasm (figs. 3, 4). There is no correlation between the size of the prostate and the presence of tumor. Gross identification of carcinoma of the prostate, especially the small latent forms, is difficult and often impossible, as is indicated by the frequency of histologically demonstrable carcinomas in unsuspected routine autopsy sections. The tumors grossly discernible are usually at least five mm. in diameter. They are irregular in outline, usually in contact with the capsule, and not sharply demarcated from the surrounding tissue. About half the carcinomas have a distinct yellow flecking, are firm, and may be granular on cut surface. The remainder are gray to white, homogeneous or slightly fibrillar, and hard. There are two lesions which may be confused upon gross examination with carcinoma: focal atrophy and hyperplastic tuberculosis. In the former, the atrophic area is also firm, irregular, and not sharply delimited but identifiable by its bluish white, translucent appearance. The tuberculous lesion (fig. 5) has a yellow-white color closely resembling that of carcinoma, but usually has a moderately sharp, scalloped border and is relatively soft (Moore, 1935).

Gross invasion of the prostatic capsule is not unusual. However, in spite of frequent early invasion both of lymphatics within the prostate (fig. 13) and of the prostatic capsule, invasion of adjacent structures is late and relatively uncommon. Posteriorly, in the region of Denonvilliers' fascia, the capsule is especially resistant to tumor extension (fig. 4). This accounts for the extremely rare invasion of the rectum by prostatic carcinoma (1.5 percent—Young).