TUMORS
of the
MALE GENITAL SYSTEM

by
F. K. MOSTOFI, M.D.
and
EDWARD B. PRICE, JR., M.D.

AFIP
TUMORS
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MALE GENITAL SYSTEM

ATLAS
of
TUMOR PATHOLOGY
ATLAS OF TUMOR PATHOLOGY

Second Series

Fascicle 8

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by

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EDITOR’S NOTE

The Atlas of Tumor Pathology was originated by the Committee on Pathology of the National Academy of Sciences—National Research Council in 1947. The form of the Atlas became the brainchild of the Subcommittee on Oncology and was shepherded by a succession of editors. It was supported by a long list of agencies; many of the illustrations were made by the Medical Illustration Service of the Armed Forces Institute of Pathology; the type was set by the Government Printing Office; and the final printing was made by the press at the Armed Forces Institute of Pathology. The American Registry of Pathology purchased the fascicles from the Government Printing Office and sold them at cost, plus a small handling and shipping charge. Over a period of 20 years, 15,000 copies each of 40 fascicles were produced. They provided a system of nomenclature and set standards for histologic diagnosis which received worldwide acclaim. Private contributions by almost 600 pathologists helped to finance the compilation of an index by The Williams & Wilkins Company to complete the original Atlas.

Following the preparation of the final fascicle of the first Atlas, the National Academy of Sciences—National Research Council handed over the task of further pursuit of the project to Universities Associated for Research and Education in Pathology, Inc. Grant support for a second series was generously made available by both the National Cancer Institute and the American Cancer Society. The Armed Forces Institute of Pathology has expanded and improved its press facilities to provide for a more rapid and efficient production of the new series. A new Editor and Editorial Advisory Committee were appointed, and the solicitation and preparation of manuscripts continues.

This second series of the Atlas of Tumor Pathology is not intended as a second edition of the first Atlas and, in general, there will be variation in authorship. The basic purpose remains unchanged in providing an Atlas setting standards of diagnosis and terminology. Throughout this new series, the term chosen by the Committee on Tumor Nomenclature of the International Union Against Cancer is shown by a star if it corresponds to the authors’ choice, or as a synonym in bold print if it differs from the authors’ heading. Hematoxylin and eosin stained sections still represent the keystone of histologic diagnosis; therefore, most of the photomicrographs will be of sections stained by this technic, and only sections prepared by other technics will be specifically designated in the legends. It is hoped that in many of the new series a broader perspective of tumors may be offered by the inclusion of special stains, histochemical illustrations, electron micrographs, data on biologic behavior, and other pertinent information for better understanding of the disease.

The format of the new series is changed in order to allow better correlation of the illustrations with the text, and a more substantial cover is provided. An index will be included in each fascicle.

It is the hope of the Editor, the Editorial Advisory Committee, and the Sponsors that these changes will be welcomed by the readers. Constructive criticisms and suggestions will be appreciated.

Harlan I. Firminger, M. D.
PREFACE

In preparing this Fascicle for the Atlas of Tumor Pathology, we have been concerned primarily with the pathologic aspects. We have discussed histogenesis, natural history, and prognosis to some extent, but only briefly touched upon treatment, the details of which are beyond the scope of the Atlas.

The junior author has been responsible for sections on the External Genitalia (Penis and Scrotum) and the Adnexae, and the senior author for sections on the Testis and the Prostate.

Throughout this Fascicle, we have attempted to use terminology and definitions which correspond to a considerable extent to the histopathologic classification of tumors of the urogenital organs proposed by the World Health Organization.

F. K. Mostofi, M. D.
E. B. Price, Jr., M. D.
ACKNOWLEDGMENTS

The authors have been privileged to be on the staff of the Armed Forces Institute of Pathology, with access to the large collection of tumors and tumor-like conditions of the male genital system. With few exceptions, as noted in the legends, the photographs in this Fascicle were prepared from material sent in by pathologists of the Army, Navy, Air Force, Veterans Administration, and United States Public Health Service Hospitals. Many nongovernmental pathologists have also contributed their cases as part of the Urologic Registry Program of consultation and registration. To all these pathologists we owe a deep debt of gratitude. Almost all the photomicrographs were taken by Mr. Charles Edwards of the Medical Illustration Service, Armed Forces Institute of Pathology, and the quality of his work speaks for itself. The support given us by the staff of that Service is deeply appreciated.

Generous use has been made of pertinent material from the First Series of this Atlas for which we extend our appreciation to Dr. Frank J. Dixon. Our thanks also to Dr. G. Barry Pierce, Jr. and Dr. Juan Rosai for the electron photomicrographs of testicular tumors and to Dr. Edwin R. Fisher for those of the prostate. Special thanks are due to Dr. L. C. Stevens, Jr. of Jackson Memorial Laboratory, Bar Harbor, Maine, who gave us several sections of teratomas in mice from which the photographs were selected for inclusion in this Fascicle. Dr. Pierce also provided illustrations of his transplant material of murine teratomas from Stevens.

Our sincere appreciation to Dr. Harlan I. Firminger who has given us invaluable aid in his capacity as Editor of the Second Series. Last but not least, we are grateful to our families both in the office and at home without whose patience, support, and understanding this work would not have been possible.

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   F. K. Mostofi, M. D.
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# TUMORS OF THE MALE GENITAL SYSTEM

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TUMORS OF THE TESTIS

INTRODUCTION

Tumors of the testis are relatively rare, yet they constitute the fourth most common cause of death from neoplasia in younger men. No other organ, except the ovary, manifests the broad spectrum of clinical behavior or the wide structural range of neoplasia as that encountered in the testis. Clinically, diagnosis is delayed in almost one of every four patients. Therapeutically, it is agreed that orchiectomy should be the initial therapy, but there is considerable disagreement concerning the desirability and nature of further treatment. No satisfactory clinical classification is available; therefore, the urologist, the radiotherapist, and the chemotherapist are essentially dependent upon the histopathologic diagnosis of testis tumors. Yet, limited experience of individual pathologists with these tumors, coupled with their structural variability and diagnostic diversity, has resulted in confusion and uncertainty about their pathologic characteristics and classification.

Attempts by some investigators to classify testicular tumors on the basis of the cell of origin have led to confusion. Initially, such a classification appears quite simple with division of primary testis tumors into those of germ cell origin, and those originating from other elements. Despite evidence to the contrary, some pathologists still insist that the majority of testis tumors classifiable as of germ cell origin have two different origins: (1) seminoma arising from germ cells, and (2) embryonal carcinoma, teratoma, and choriocarcinoma arising from misplaced embryonic totipotential cells that have escaped the influence of organizers. Theoretical discussion of this concept would be of little practical concern were it not for the insistence by the same pathologists that the pathologic classification and nomenclature be based on such a theoretical histogenesis.

The first comprehensive effort to classify testicular tumors on a histopathologic basis was made by Friedman and Moore; their classification included seminoma, embryonal carcinoma, teratoma, teratocarcinoma, choriocarcinoma, and nongerminal tumors. On the basis of this classification, a subsequent report on survival and mortality of the patients was prepared by Dixon and Moore. They clearly stated they had grouped their cases into five categories solely for convenience in reporting, but such grouping has since erroneously been construed as a histologic classification. The classification proposed in this fascicle is based on Friedman and Moore’s classification; however, a more precise definition of embryonal carcinoma is included, and the varied components that may be present in a tumor are also discussed.

Friedman and Moore believed that embryonal carcinoma, teratoma, and choriocarcinoma originated from germ cells. This was a theoretical concept at the time; however, subsequent investigations by Stevens and coworkers, and Pierce and associates have confirmed their observations.
Based on this concept, 93 percent* of primary testicular tumors originate from germ cells and present one or more of the following five histologic patterns: seminoma, embryonal carcinoma, infantile embryonal carcinoma, teratoma, and choriocarcinoma. Proper classification of germ cell tumors must recognize the potentiality of germ cells and the capability of neoplastic germ cells to manifest a wide range of cell, tissue, or organ types recapitulating embryonic, extra embryonic, and somatic development. The key to proper classification is recognition of the five basic cell types and the realization that development of neoplasia may be along one line in both the primary tumor and the metastases, and along one or more lines in the primary tumor and the same, or different line(s) in the metastases.

About 6 percent* of testicular tumors are categorized as gonadal stromal tumors including Leydig-Sertoli-granulosa-theca cell neoplasms. The cells producing these tumors represent the hormone producing elements of the gonads. The frequency with which such cell types are associated with each other leads us to postulate a common cell of origin.

We designate this common cell as the specialized gonadal stroma, which term means the supporting element of the primitive germ cell. In their primitive stage, these cells consist of spindle-shaped fibroblast-like cells; in their differentiated stage, they are recognizable as Leydig and Sertoli cells in the male and theca-granulosa-lutein cells in the female. The tumor may develop along one or more lines with diverse clinical and endocrine manifestations, depending upon the differentiation and predominance of the constituent cell.

A small group of tumors, usually encountered in patients with gonadal dysgenesis, consists of both germ cell tumors (mostly seminomas) and varying amounts of gonadal stromal elements in various stages of differentiation.

Tumors of the ductal system, the fibrovascular stroma, and the capsule comprise about one percent of testicular tumors.

**EMBRYOLOGY OF THE TESTIS**

Based on studies of early embryos, beginning at the 13 somite stage, it has been demonstrated that germ cells migrate from the endoderm of the yolk sac near the allantoic evagination, through the mesentery of the hind gut, toward the mesonephric folds, to the gonadal or genital ridge. This migration is by active movement of individual cells.

Grossly, the maximum extent of the genital ridge, the primordium of the testis, is from the sixth thoracic to the second sacral segments. By the end of the second month, the gonad is an elongated body which extends from the diaphragm to the site of the future abdominal inguinal ring. Its cranial portion partly covers the adrenal gland, and its caudal pole is attached indirectly by means of gubernaculum to the abdominal wall. From the fourth to the seventh month, the testis lies in the iliac fossa at or near the internal ring. The testis lingers near the abdominal inguinal ring until actual descent into the inguinal bursa which begins at approximately the seventh month. The testis reaches its final destination in the scrotum during the eighth prenatal month.

Microscopic study of the evolving genital ridge begins when a slight thickening of coelomic epithelium on the dorsomesial angle of the body wall overlying the mesonephros is seen in embryos of ovulation age (OA) 28 and 29 days. The genital ridge is clearly defined in embryos at OA 33 to 35 days. The mesothelium is thickened and the

*Figure is based on highly selective material in the American Testicular Tumor Registry.
underlying mesenchyme is more densely cellular than that of the adjacent mesonephros. Van Wagenen and Simpson were unable to determine whether the strands of cell nuclei, lying perpendicular to the surface, were rows of mesenchymal cells or were continuous with the surface mesothelium.

By OA 37 to 38 days, a gonad has evolved from the thickened genital ridge and projects into the coelomic cavity as an elongated body. The gonad is comprised of small cells of uniform size, and gives no clue to indicate its future sexual differentiation. A broad homogeneous peripheral zone has enclosed a core in which the cells are separated by capillaries and sparse primitive connective tissue into an arrangement suggesting cords. In the male, the cordlike arrangement becomes more distinct. By OA 42 days, the homogeneous distribution of cells disappears as cordlike structures begin to appear in the central region. Whether the primary sex cords are formed by invagination of mesothelium or by differentiation from gonadal blastema has not been resolved. Also by OA 42 days, the peripheral zone, the anlage of tunica albuginea, is narrow but irregular in width and comprised of closely packed small cells with spherical deep-staining nuclei. Central to the tunics, cords of cells (the future seminiferous tubules) are distinct, because of their larger size, lighter staining reaction, and the radial arrangement of the nuclei. The cords are uniform in width and converge at the hilus. The precursors of the straight and rete tubules lie near the mesorchium. By OA 48 days, the seminiferous tubules are distinct and the regions between the cords are packed with cells. Some of the cells have enlarged nuclei, but the cell borders are indistinct.

By OA 55 days, the cells between the cords have increased greatly in number; some are enlarged, have distinct boundaries, and are identifiable as Leydig cells. Peripherally, between the cords and the tunics, these cells are present in clumps. Apparently, Leydig cells develop from original gonadal blastema, either by way of gonadal cords or from mesenchymal stroma.

Theca and granulosa cells of the ovary and Sertoli and Leydig cells of the testis have a common function: they constitute the specialized supporting stroma for germ cells, and the hormone producing cells of the gonad. Although a common cell of origin for these four cell types has not been completely resolved, such a common cell of origin is demonstrated in recent studies and provides a holistic explanation for the diversity of endocrine and pathologic manifestations of tumors of these cells (Van Wagenen and Simpson). By OA 55 days, the cells of the tunica albuginea become more differentiated and assume characteristics of loose connective tissue. After OA 60 days, the

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Diagram I

This is a schematic representation of the interrelationship of gonadal stromal cells.
Leydig cells begin to decrease in number and size. Gillman’s failure to observe germ cells in male human embryos during the second and third month is believed to have been due to the thickness of the sections, which masked their presence (Witschi; Narbaitz).

In fetuses of menstrual age 3.5 months, the sex cords radiate from the straight and rete tubules, which persist as solid strands of cells near the hilus. The sex cords remain straight, except for some peripheral arching, until OA 4 to 4.5 months when they begin to coil near the tunica albuginea. During the next 4 to 6 weeks, these convolutions generally increase; connective tissue between the tubules also increases as the Leydig cells decrease in number and size. Concurrently with this increase in connective tissue throughout the testis, the tunica albuginea begins to show a separation into two zones: an outer fibrous zone and an inner vascular zone. The straight and rete tubules start to acquire a lumen in fetuses of OA 5 to 6.5 months. From this time until birth, changes in the testis are slight.

ANATOMY

The adult testis is surrounded by a dense fibrous capsule, the tunica albuginea, which in turn is covered by the visceral layer of the tunica vaginalis. At the hilus, there is a condensation of fibrous tissue forming the mediastinum testis from which fibrous tissue septa extend into the testicular parenchyma, dividing the latter into about 250 conical compartments. Each compartment contains from one to three convoluted seminiferous tubules. Interstitial connective tissue is generally sparse and contains scattered compact clumps of interstitial cells in the postpubertal testis. During the prepubertal period, there is a gradual maturation of the seminiferous tubules, and spermatogenesis is established by the twelfth to the sixteenth year. The number of interstitial cells of Leydig vary greatly during different periods of life and among individuals. They are numerous in late fetal life, presumably as a result of placental gonadotropins, but after birth they regress and remain inconspicuous until puberty when they again increase in number to reach adult proportions.

The convoluted seminiferous tubules join at the apex of each lobule and pass abruptly into the first section of the system of excretory ducts—the tubuli recti. At the transition of seminiferous tubules into collecting ducts, the spermatogenic cells disappear and only Sertoli cells remain—tall columnar cells with vacuolated lipid containing cytoplasm. These short straight ducts enter the mediastinum and form a system of irregular anastomosing dilated spaces lined by flat or low cuboidal epithelium—the rete testis. At the upper part of the posterior edge of the testis, the vasa efferentia (ductuli or canaliculi efferentes) form a number of spiral winding and convoluting structures (coni vasculosi) which gradually fuse into a single ductus epididymis and gradually straightens out and merges into the ductus deferens.

Involutional changes in the testis related to age are extremely variable in time of onset. A decrease in the number of spermatogenic elements is usually associated with thickening of the tubular basement membranes. As the spermatogenic cells decrease, there is generally a concomitant increase in the number of Sertoli cells. If atrophy continues, these too finally disappear. As physiologic atrophy progresses, there is generally an increase in the amount of interstitial connective tissue; changes in the Leydig cells are quite variable, but generally these cells become more prominent resulting in the appearance of a relative hyperplasia.
Blood is supplied to the testis from the internal spermatic arteries that originate from the abdominal aorta at, or just below the level of the renal arteries. The right spermatic vein drains into the inferior vena cava below the renal veins, while the left spermatic vein drains into the left renal vein.

Lymphatic drainage of the testis has been studied in detail by Rouvière, by Jamieson and Dobson, and by Ray and associates. The capillary plexus is so close together that puncture at any point gives a good injection.

Lymphatic capillaries form a network around seminiferous tubules. From interstitial tissues, vessels proceed in the septa to a network in the tunica albuginea. These vessels collect at the dorsolateral margin of the testis, from there 4 to 8 lymph channels run into the funiculus spermaticus (Rouvière). The 4 to 8 collecting lymphatic channels leave the hilum and ascend with veins in the spermatic cord, through the inguinal ring, into the retroperitoneum, over the psoas muscle to the point where the spermatic vessels cross the ureter. Here they part from the blood vessels and from each other and fan out caudally like a fountain into concave arches to be distributed in relation to the aorta and the vena cava up to the level of the renal vessels. In the upper part of the abdominal course, some vessels divide with intercommunicating anastomoses permitting any vessel to empty its contents into more than one lymph node. Lymphatic vessels from the right testis terminate most commonly in lymph nodes lateral, anterior, or medial to the vena cava. Those of the left testis drain into lymph nodes lateral to the aorta below, and both lateral and anterior to the aorta above the level of the inferior mesenteric artery, and by way of lymph channels following the left spermatic vein, they usually reach a lymph node above the left renal artery. From the retroperitoneal lymph nodes, dissemination is most frequently through the thoracic duct into the left supraclavicular lymph nodes and/or into the subclavian vein.

The epididymal lymphatics drain into the external iliac nodes. Therefore, the external iliac nodes may be the site of metastasis for primary epididymal tumors as well as testicular tumors that have invaded the epididymis. Inguinal lymph node metastasis may result from scrotal involvement when lymphatic channels have been disturbed by prior surgery in the scrotum, or when massive retroperitoneal metastases may result in retrograde lymphatic spread. However, inguinal metastases may be seen in the absence of either condition.

References


Friedman, N. B. Personal communication, 1945.


TUMORS OF GERM CELL ORIGIN

EPIDEMIOLOGY

INCIDENCE AND PREVALENCE. Dixon and Moore reported an incidence rate during the period from 1940 through 1947 of 2.88 per 100,000 in a selected United States Army population ranging from 20 to 30 years of age. They calculated the incidence to be 3.14 per 100,000 in the entire male population in the United States between the ages of 18 and 44. Clarke in the United States and MacKay and Sellers in Ontario, Canada have reported incidence rates of 2.1 to 2.2 and 2.5 per 100,000, respectively, which is also the range of incidence reported in the British Isles.

The United States Census Bureau attributed 0.64 percent of all male cancer deaths to testicular tumor; in England, the comparable figure was 0.52 percent. Statistics vary on the relative frequency of testicular tumors in comparison with other genitourinary tumors. This perhaps is attributable by the age of the specific hospital population. It is estimated in London that 0.8 to 1.3 percent of all genitourinary deaths are attributable to cancer of the male genital organs, while in Ontario, the figure is 5.2 percent. In both the United States and Canada, however, testicular tumor accounts for 11 to 13 percent of all cancer deaths in the age group 15 to 34 years. Testicular tumor represents the fourth most lethal tumor, following leukemia, Hodgkin’s disease, and brain tumor in this age group.

Clemmesen reported a doubling of the mortality rate from testicular tumor from the period 1943-1947 to 1958-1962 (3.2 vs. 6.3 per 100,000) in Copenhagen. A similar trend is suggested by reports of Grumet and MacMahon in the United States and Howden in Auckland. These figures cover all testicular tumors, but also represent rates for germ cell tumors because of their overwhelming preponderance.

GEOGRAPHIC AND RACIAL DISTRIBUTION. Tumors of the testis are especially rare among the Black population both in America and Africa, but they do occur. Leydig cell tumor, lymphoma initially manifested as primary testicular tumor, and granulomatous orchitis are the most frequent lesions seen in Blacks (Hutt and Burkitt; Williams; Davies and Owor; Prates and Torres; Edington and Maclean). They are also rare in Asia (Ahluwalia and Duguid; Akasaka et al.; Reddy and Ranganayakamma), in Finland (Teppo), and New Zealand (Howden).

SPONTANEOUS TESTIS TUMOR IN OTHER ANIMALS. Tumors of the testis are extremely rare in primates other than man. Voronoff reported a seminoma of the testis of an orangutan and a testicular adenocarcinoma in a Cynocephalic hamadryas. More recently, Maruffo and Malinow found a seminoma in a howler monkey (Alquatta caraya).

In dogs, testicular tumors are the fourth most common tumor. Goodpasture reported finding them in 57 percent of his old dogs, and Garner found 73 among 1,512 male sentinel dogs, many of which were relatively young. While statistics vary, seminoma seems to be the most frequent tumor. Histologically, the
tumor is identical to the classic seminoma seen in man; however, it is usually benign. We have seen only one instance of metastasizing seminoma in a dog. Teratoma, choriocarcinoma, or embryonal carcinoma have not been reported in dogs. Teratoma is the most frequent testis tumor in horses; it occurs in colts and is usually benign. A few cases of seminoma have also been described. No germinal testis tumors have been reported in domestic cats, goats, or sheep, but we have seen seminoma in a jungle cat.

Testicular tumors are rarely found in cattle in the Western hemisphere, since these animals are frequently castrated early. However, both seminoma and adenoscarcinoma have been reported. Seminoma has been found in birds.

Leydig cell tumors are common in old rats and mice and can be induced in mice with estrogens. Stevens found embryonal carcinoma in strain 129 mice which differentiates into teratoma. Nigrelli and Jakowska reported a spermatocytic seminoma in a fish from the New York Zoological Gardens.

**ETIOLOGY**

The etiology of testis tumors is unknown. Several factors, however, suggest an etiologic relationship.

**GENETIC FACTORS.** Genetic factors apparently play a role in the high incidence of testis tumors reported in brothers, identical twins, monozygous twins, and members of the same family (Stewart and Bagshaw; Willis; Villani; Salingier; Riches). Müller reported a history of malignant disease in the next of kin in about 16 percent of cases in which sufficient information was available. There was also a high incidence of development of a second testis tumor in patients with one testis tumor.

**MALDESCENT.** There is no agreement on the frequency of the relationship of testis tumor to maldescent. In 2,000 testis tumors, we found that 72 occurred in undescended testes, an incidence of 3.6 percent of maldescent in this group. These figures are based solely on data reported on surgical pathology forms. But from these figures and knowing that cryptorchidism is present in about 0.25 percent of selectees, one can calculate that the chances of a tumor developing in an undescended testis is at least 14 times that of a scrotal testis.

Gilbert and Hamilton, and Sauer and associates reported the frequency of testis tumors in ectopic testes to be 48 times that in scrotal testes, and tumors in abdominal testes were four times more frequent than in testes located in the inguinal region. These studies suggest that as many as one in 80 inguinal testes and one in 20 abdominal testes develop malignant tumors. Miller and Seljelid reported that malignant tumor in undescended testes is 10 times more frequent than in normally descended testes. Since all these studies were from selected cases, it is not known whether they apply to the general population. We have seen one instance of testis tumor in the normally descended testis of a patient with a contra-lateral undescended testis.

Four factors may influence the increased incidence of testicular tumor in a cryptorchid testis: abnormal germ cells; interference with blood supply; endocrine disturbances; and gonadal dysgenesis.

Functional maturation of the germ cell is never attained in an undescended testis, and despite successful orchiopexy about 50 percent eventually fail to develop spermatogenesis. Undifferentiated testicular tissue is observed in both the undescended and the normally descended testis of infants from birth to five years of age (Engle). In contrast to the normally descended testis, all elements
do not usually mature in an undescended testis, and neoplasia may conceivably evolve.

The presence of peritubular fibrosis and hyalinization and thickened vessels suggests that longstanding ischemia may play a role in the occurrence of testicular tumor, but no confirmatory evidence has yet been presented.

ABNORMAL TESTIS. Is the tumor-bearing testis genetically abnormal? Sohval reported a high incidence of imperfect development of seminiferous tubules and suggested this may be an important etiologic factor. Ashley and Mostofi, however, could find no evidence of dysgenesis in the non-tumorous portion of tumor-bearing testes. Immature tubules were found in 3 percent of cases, fertility was unimpaired, and the nuclear sex was male. The maturation arrest seemed to be related to the preoperative duration of the tumor and was interpreted to be due to the increased blood supply and the higher temperature. More recent reports of the high incidence of dysgenetic testis and abnormalities of chromosomes in testis tumors include those of Adachi and associates; Melicow; Taylor and associates; Rigby; Polani; Martineau; Gutiérrez and associates; Galton and associates; and Ferrier and associates.

SITE OF ORIGIN. Routine autopsy examination does not usually disclose an incidental testicular tumor, because this tumor is rare and the testis is seldom minutely examined. Painstaking examination of testes in fetuses, infants, children, adolescents, and young adults, similar to that made by Stevens in mice, would be desirable.

Intratubular seminoma (fig. 6) has long been recognized as an early stage in the development of testicular tumor, both in man and in the dog. We have also seen intratubular embryonal carcinoma (figs. 72, 73) and syncitial trophoblastic cells (pl. II-A). There is no record of such an early stage of teratoma in man.

AGE. Germinial and other testicular tumors tend to occur in particular age periods. Histologic and behavioral characteristics of the tumors differ with each period.

Seminoma has never been reported in an infant. Testicular embryonal carcinoma and teratoma in infants and children are morphologically different, and the prognosis is much more favorable than for adults. Teratoma, embryonal carcinoma, and choriocarcinoma occur predominantly in young adults, while seminoma is found more frequently in 30 to 50 year old patients. Spermatocytic seminoma, adnexal sarcoma, and secondary tumors are seen predominantly in older men. In view of the restricted time interval during which testicular germ cell tumors can be induced in experimental animals (Stevens, 1970), there may be a similar critical intra-uterine period in human testicular oncogenesis.

ENDOCRINE ABNORMALITIES. The following observations suggest some relationship between the endocrine glands and testicular oncogenesis: (1) The induction of testis tumor in fowl by injection of zinc salts occurs only during periods of maximal pituitary gonadotropin secretion; (2) in man, the peak incidence of testicular tumor is during the period of highest androgenic activity; (3) chorionic gonadotropins and/or estrogens are produced by a number of testis tumors; (4) some patients with testis tumor show an elevation of pituitary gonadotropins, which may persist after orchietomy, that is unrelated to the existence of metastasis and may not be detected in extracts of the primary tumor or the metastasis (Hamburger); (5) in tissue culture, androsterone accelerates the growth of certain testis tumors; and (6) the type of tumor encountered varies with the state of maturation of the testis.
Volpe and associates attribute the high incidence of testicular tumor in cryptorchids to disturbances of endocrine function. The pituitary and other tissues seem insensitive to circulating androgens from an undescended testis and this results in excess secretion of pituitary gonadotropins, chronic over-stimulation of the gonads, and perhaps development of seminoma. Absence of feedback from such a testis may also lead to over-activity of the pituitary gland.

Henriet reported a seminoma in a patient who had received hormone treatment for three years for sterility and a small testis.

INFECTION. Many patients with testicular tumor report a history of some type of orchitis, particularly mumps orchitis. It is quite possible that viral infection of the germ cell or changes in the environment of the germ cell secondary to infection may trigger carcinogenesis. Indeed, viral inclusions have been reported in Leydig cell tumors (Stephens et al.).

TRAUMA. Testicular trauma is a common occurrence and is reported in many patients. Eleven percent of 527 patients with testis tumor reported by Fergusson had a history of trauma. Experimental evidence also suggests the relationship of trauma to tumor. About 5 percent of male mice strain 129 show degenerative changes, ranging from slight to extreme, in the left testis which is smaller and has a higher incidence of teratoma. In spontaneous murine testicular tumor, Stevens observed that hemorrhage and necrosis signaled the site of embryonal carcinoma and preceded teratogenesis. Trauma is considered a factor in zinc or copper-induced fowl testicular tumor. Sobin reported that local physicians consider horseback riding as a cause of testicular tumor in patients in northern regions of Afghanistan, but no definite evidence has been presented to establish that testicular tumor in man results from trauma. A heavy, dragging, tumorous testis may be more susceptible to trauma, and aggravation of a preexisting tumor by trauma may facilitate dissemination, but to date there have been no reports of the influence of trauma on prognosis.

EXPERIMENTAL INDUCTION OF TESTICULAR TUMORS. Russian scientists reported the first induction of teratoma in the testis of fowl following injection of zinc chloride and later by injection of copper sulfate (Michalowsky; Bagg; Falin). They observed that induction was confined to the three springtime months. Carleton and associates produced testicular tumors in 11 of 43 white Leghorns 10 weeks after intratesticular injection of zinc chloride. These avian teratomas contained feathers, skin, respiratory and alimentary glands, cartilage, bone, muscle, and nerve.

Sarcoma of various types has been induced by carcinogenic hydrocarbons injected into the testis. Tumor of germ cell origin has been experimentally produced only in albino rats by Dvizhkov and Potapova, who reported seminoma and Leydig cell tumor 18 to 24 months after injection of zinc powder and zinc chloride. Mount and Stevens produced embryonal carcinoma and testicular teratoma in strain 129 mice by transplantation of the genital ridge of a 12½-day embryo of the same strain, thus providing a reliable and reproducible experimental model for study of testicular teratoma.

CLINICAL MANIFESTATIONS

There are no early symptoms of primary testicular tumor other than slight changes in testicular size and consistency, which are rarely observed. Gradual enlargement of the testis and pain are the most frequent symptoms. Some patients complain of a lump,
nodule, or hardness, with or without pain. Less frequently, there may be a heavy sensation in the lower abdomen, the groin, or the scrotum or a dull ache in the lower abdomen or inguinal region due to drag on the spermatic cord by a heavy testis. There is a tendency to attribute most of the symptoms to accidental trauma or strain. In about 10 percent of cases, there are symptoms of acute pain simulating epididymitis, torsion, or infarction. Rarely, presenting symptoms consist of nausea, vomiting, fever, and scrotal redness.

In all our patients with pure choriocarcinoma, presenting symptoms were referable to metastasis—hemoptysis or gastrointestinal bleeding. Overall, in about 10 to 20 percent of primary testicular tumors, presenting symptoms are referable to metastasis, including a mass in the supraclavicular region, pulmonary involvement, gastrointestinal disturbances due to pressure of enlarged lymph nodes, or lumbar pain secondary to involvement of the retroperitoneal lymph nodes.

Enlargement of an inguinal testis is generally detected early, but discovery of an abdominal testis tumor is usually delayed, and it may take one of two courses: (1) indefinite abdominal complaints, an enlarging lower abdominal mass, and back pain, or (2) symptoms of widespread metastases. Indefinite abdominal symptoms in a patient with an undescended testis should arouse suspicion of a tumor.

HORMONAL ACTIVITIES

Determination of preorchietomy urinary and blood hormone levels is essential for the proper evaluation of subsequent therapy and prognosis. Repeat assays after orchietomy are valuable as an index of response to therapy and the course of the disease.

Many patients with seminoma demonstrate elevation of follicle stimulating hormone (FSH), but it must be remembered that patients with castration or radiation to the testis also show an elevation of FSH. However, the level is rarely over 1,000 i.u./24 hours. The source of FSH has not been determined. Several possible sources include: true rise in FSH due to the marked decrease in androgen output by Leydig cells (Hamburger); synthesis of gonadotropin-like hormones by seminoma analogous to the situation in oat cell carcinoma of the lung; or augmentation of normal FSH activity due to subliminal amounts of chorionic gonadotropins (Paulsen). Hamburger and Godtfredsen, and Albert and Derner recommend careful determination of gonadotropic dose-response curves to resolve the question, but actual separation of the two hormones is preferable.

Bartsch and Hennen reported thyroid stimulating hormone-like activity in a patient with choriocarcinoma of the testis with no evidence of hyperthyroidism. Currie and associates reported a growth hormone-like factor in a patient with a testis tumor that was either choriocarcinoma or had choriocarcinomatous elements. However, this factor was not present in five seminomas, one undifferentiated carcinoma, and one "malignant teratoma" without any foci of choriocarcinoma.

Chorionic gonadotropins are elevated in all patients with choriocarcinoma. One possible exception has been described by Hobson, but the histologic characteristics of that tumor have not been recorded. By bioassay (Hamburger), hemagglutination inhibition (Wide and Gemzell), immunoelectrophoresis (Wilde and Bagshawe), and radioimmunoassay (Bagshawe et al.), the excreted chorionic gonadotropin has been shown to be
identical to the placental chorionic gonadotropin. As in placenta, it is directly related to the amount of viable tumor tissue. Pierce and associates have shown that syncytiotrophoblastic cells are the site of origin of the hormone.

Seminoma, embryonal carcinoma, and teratoma also show elevated chorionic gonadotropins (Hamburger; Hobson and Wide; Hamashige et al.; Hobson; Gangai). Hobson reported elevation in 8 of 115 seminomas, 4 of 19 embryonal carcinomas, 24 of 83 teratocarcinomas, and in two tumors containing mixtures of these types. Kurohara and associates found positive Aschheim-Zondek tests in 14 of 72 seminomas, 9 of 56 embryonal carcinomas, and 8 of 45 teratocarcinomas. Chorionic gonadotropin elevation is usually between 3,000 and 30,000 i.u. per liter; rarely, it reaches 450,000 i.u. per liter. One should strongly suspect foci of choriocarcinoma with such levels (Golding et al.).

The source of elevated chorionic gonadotropins has not been established in germ cell tumors other than choriocarcinoma. There may be three explanations: elevation has not been confirmed or properly identified as chorionic gonadotropins, foci of chorionic gonadotropin-producing cells have been missed, or certain primitive neoplastic germ cells are capable of producing the hormone.

There have been reports that other hormones such as 17-ketosteroids (dehydroepiandrosterone, androsterone, etiocholanolones), estrogens (estriol, esterone, estradiol), and pregnenediol have been elevated in patients with embryonal carcinoma and teratoma (Daly et al.; Kashiwagi et al.). Elevation of 17-ketosteroids in a seminoma has been reported by Hamburger, and by Andreasik and Kober-Kulesza. An increase in urinary estrogens in patients with choriocarcinoma, pure or mixed with other types, has been attributed to choriocarcinomatous elements or to stimulation of Leydig cells by the circulating chorionic gonadotropins. Elevation of corticosteroid has been reported in four patients with seminoma (Bawden et al.) and in one patient with teratoma (Bawden et al.; Dorfman and Shipley).

**ROENTGENOGRAPHIC STUDIES AND CLINICAL STAGING**

On the basis of clinical examination and x-ray findings, the urologist must determine if the tumor is localized to the parenchyma of the testis or has already metastasized.

Chest x-rays and pyelography should be utilized for patients with suspected testicular tumor. In recent years, lymphangiography has received considerable attention; in experienced hands, it is considered especially valuable in the staging of tumors. Phlebography and cavagraphy, either before or after orchiectomy, may also prove very helpful.

The following is a simple, practical system of clinical staging.

The **earliest tumors** are those confined to the testicular parenchyma, with no evidence of spread beyond the testis proper and with negative radiologic studies. **Local spread** is manifested by invasion of the adnexa or the tunica, observed clinically before orchiectomy or detected pathologically. **Further spread** of the tumor, detected by clinical or radiologic examination, is usually to the retroperitoneal, iliac, periaortic, inguinal, and femoral lymph nodes. Such metastases may also be found pathologically in tissue removed by retroperitoneal dissection from a patient with no preoperative evidence of lymph node metastases. Whether detected clinically or pathologically, the stage
of the disease correlates with the prognosis. Clinical, radiographic, or pathologic evidence of metastasis above the diaphragm, or to sites other than lymph nodes previously mentioned, probably constitutes further progression of the disease.

REMOVAL OF TISSUE FOR PATHOLOGIC EXAMINATION

The histologic type of a tumor in many areas of the body is generally determined by biopsy, a procedure definitely contraindicated for suspected testicular tumor. Orchietomy is the universally accepted method for biopsy. If a hydrocele is present, careful diagnostic tapping of the sac without trauma to the tunica may be initially performed.

In unusual circumstances when the testis is to be retained, if palpation is negative after exploration of the scrotal sac for suspected tumor, some urologists advocate visual inspection of the parenchyma and frozen section. Many feel, however, that the high risk of local recurrence and metastatic spread resulting from biopsy justifies removal of a suspiciously malignant testis.

Biopsy of the left supraclavicular lymph node has been recommended as an aid to clinical staging.

It is essential in the pathologic classification of germ cell tumors (see Table I) to realize that they represent a developmental system ranging from highly undifferentiated or primitive immature stem cells at one extreme, through all the intermediate stages, to partly or fully differentiated or mature progeny at the other. The primitive stem cell may develop into seminoma or embryonal carcinoma, and the neoplastic process may proceed along either or both lines. These types may represent the final stage in oncogenesis, or the primitive stem cell may develop into teratoma, choriocarcinoma, or infantile embryonal carcinoma representing further differentiation to embryonic and somatic or trophoblastic and extra embryonic (yolk sac) elements.

It is necessary to identify and designate the cell type and determine whether it is the sole component or if other elements exist. All components and their relative proportions should be recorded. Single cell type tumors constitute 60 percent of testicular tumors and tumors in which more than one component is present, 40 percent.

HISTOGENESIS AND CLASSIFICATION OF GERM CELL TUMORS

HISTOGENESIS. The most common tumor of an organ is usually derived from the principal parenchymal cell of that organ. In the testis, the principal cell is the germ cell lining the seminiferous tubules. Normally, it is a dynamic, constantly maturing cell. When given certain environmental conditions following maturation, such as penetrating into an ovum, it may develop into embryonic tissue—normal or abnormal. It would seem logical, therefore, to relate certain groups of testicular tumors to the germ cell, since the germ cell has the capability to develop a host of cells, tissues, and organs and since certain testicular tumors do manifest such differentiation.

With one exception, there has been general agreement that seminoma arises from germ cells. In 1946, Masson questioned the germinal origin of the typical seminoma, which he maintained for the spermatocytic seminoma.

In many seminomas there are areas where the tumor cells are confined to
Tumors of the Testis

seminiferous tubules. Ultrastructurally, Pierce (1966) demonstrated that undifferentiated seminoma cells resemble primordial germ cells. Seminoma has a male sex chromatin pattern and karyograms of seminoma have approximately the euploid number of chromosomes (Theiss et al.). These findings, therefore, indicate that seminoma must arise from the primordial germ cell and/or spermatogonia and spermatocyte before haploid division.

The cell of origin of primary testis tumors, other than seminoma, has provoked considerable discussion. In 1907, Askanazy first advanced the theory of teratogenesis by metamorphosis of undifferentiated cells. Teratoma could develop and differentiate either from a single cell or group of totipotential cells. The cells could remain dormant for years and then grow and differentiate. He rejected parthenogenesis for these tumors. In 1926, Budde postulated that teratoma probably represented misdirection of action of primary embryonic organizers of the host, and that teratoma originated from cells that had been released from normal developmental control at the primitive stalk stage. Needham, Willis, and Nicholson accepted Askanazy's concept that differentiated elements developed from embryonic cells, but they rejected the germ layer or fetiform origin of teratoma. Willis rejected the concept of parthenogenetic proliferation of a distorted fetus. He favored the origin of teratoma from blastomeres displaced in early embryonic development, which had escaped the influence of organizers, a concept also favored by Collins and Pugh.

Opposed to this dual origin of testis tumors—seminoma from germ cells and embryonal carcinoma, teratoma, and choriocarcinoma from blastomeres displaced in early embryonic life and free of the influence of organizers—has been the holistic approach of other investigators who maintained that all tumors of the testis arise from germ cells; i.e., seminoma, embryonal carcinoma of adult type, infantile embryonal carcinoma, teratoma, and choriocarcinoma. Friedman and Moore, and Dixon and Moore not only favored this concept, but also considered primitive embryonal carcinoma as a tumor of totipotential cells with the capability of giving rise to cytotrophoblastic cells (precursor of choriocarcinoma), ectoderm, mesoderm, and entoderm (precursors of teratoma).

In the absence of an experimental model of testicular tumors, the discussion of the origin and relationship of these testicular tumors remained academic. The exact origin of experimental teratomas of fowl testis produced by Michalowsky and by Bagg has not been determined; moreover, the tumors are different from human testicular tumors.

Tremendous advances have been made during the past 15 years. The most important contribution has been that of Stevens, who found an 8 percent incidence of spontaneous teratomas of the testis in strain 129 mice. The earliest tumor occurred in 15 day old fetuses; it consisted of a nest of undifferentiated embryonal cells in continuity with germinal epithelium of the testis (pl. A-1, 2). In other tumors in newborn mice, epithelial vesicles enclosed pools of blood and products of cellular degeneration. The epithelium rapidly became transformed into two different types; one resembled ectoderm and the other entoderm (pl. A-3, 4).

Stevens also succeeded in inducing these tumors. He found that transplantation of the genital ridge of a 12½ day old embryo to the testis of an adult mouse of the same species resulted in teratoma in 85 to 90 percent of the transplants. He amply demonstrated that both spontaneous and induced tumors arose in the seminiferous tubules (pl.
Figure 1
EMBRYONAL CARCINOMA IN MOUSE
A nest of small undifferentiated embryonal cells is seen in a seminiferous tubule of a 16 day old murine fetus. Three other similar areas were present in the same testis. X525. (Courtesy of Dr. L. C. Stevens, Jr., Bar Harbor, Me.)

Figure 2
EMBRYONAL CARCINOMA IN MOUSE
The normal population of the seminiferous tubule of a 19 day old murine fetus is replaced by small undifferentiated embryonal carcinoma cells. Note the mitotic figure. X450. (Courtesy of Dr. L. C. Stevens, Bar Harbor, Me.)

Figure 3
TERATOMA IN MOUSE
The testis of a 6 day old mouse is mostly replaced by a teratoma which consists primarily of neuroectodermal and mesangial tissue. X160. (Courtesy of Dr. L. C. Stevens, Jr., Bar Harbor, Me.)

Figure 4
TERATOMA IN MOUSE
Several tubular and cystic structures are seen in this 18 day old mouse testis, some of which are lined by columnar epithelium. Three areas of undifferentiated mesangial tissue are present and two nests of primitive cartilage. The tumor replaces most of the testis. X20. (Courtesy of Dr. L. C. Stevens, Bar Harbor, Me.)
PLATE B

Figure 1
MURINE INTRAPERITONEAL EMBRYOID BODIES
The peritoneum is filled with many small and large, clear vesicles. These developed in the peritoneum of a mouse which had been given an intraperitoneal injection of a suspension of murine testicular embryonal carcinoma cells. (Courtesy of Dr. G. B. Pierce, Denver, Colo.) *

Figure 2
EMBRYOID BODIES IN PERITONEUM OF MOUSE
This is a section of one of the peritoneal vesicles of the type seen in figure 1 which shows a typical embryoid body. X240 (Courtesy of Dr. G. B. Pierce, Denver, Colo.) *

Figure 3
TRANSPLANTED TERATOMA IN SUBCUTANEOUS TISSUE OF MOUSE
This illustrates a murine teratoma developing in the subcutaneous tissue of a mouse after injection of embryoid bodies from a peritoneal transplant similar to that seen in figure 2. The section shows predominantly differentiating neural tissue. X60. (Courtesy of Dr. G. B. Pierce, Denver, Colo.) *

A-1). By serial studies of testicular transplants of the genital ridge, Stevens followed the growth and development of teratomas in his animals. Direct continuity between the seminiferous epithelium and neoplastic elements was seen in many early tumors, often in more than one focus. Since many of the tumor-bearing seminiferous tubules were ruptured, it was possible that the tumors arose in the interstitium; however, no tumors were found in the interstitium without tumors in seminiferous tubules.

Stevens observed an undifferentiated carcinoma which was demonstrated by Pierce and associates in 1970 to be a parietal yolk sac carcinoma. Pierce and Beals compared the ultrastructure of murine embryonal carcinoma cells and the multipotential stem cell of teratocarcinoma with the constituents of the primordial testicular tubules in which they arose. They could rule out any relationship to Sertoli cells, and found that the ultrastructure of primordial germinal cells of a 15 day old fetal mouse bore a striking resemblance to embryonal carcinoma cells. Studies of human testis tumors by Pierce and others have conclusively verified the common origin of all germinal testicular tumors. In fact, most recent publications on testis tumors accept this holistic view. While it is possible that the germ cell may have escaped the influence of the organizers to develop into a malignant cell—as may happen in any neoplasia—and that under specific conditions in other parts of the body, certain tumors may arise from totipotential cells that have escaped the influence of the organizer, the germ cell origin of testis tumor is now so well documented that further discussion of the genesis of these tumors seems superfluous.

It is not yet known whether the mechanism of origin of infantile testicular teratoma is identical to that in adults, but certainly its biologic behavior is different.

CLASSIFICATION. The two distinct concepts of histogenesis have led to differences in classification. Our classification is based on the origin of both seminoma and nonseminomatous tumors from germ cells. Willis considered seminomas as of germ cell origin and nonseminomatous tumors as teratomas, but stated that monocellular testicular teratoma could best be designated as embryonal carcinoma. Collins and Pugh and their associates (1964) amplified Willis's classification of teratoma. They divided teratoma into differentiated and malignant teratoma, and further subdivided the latter into malignant teratoma, anaplastic, intermediate A (MTIA), intermediate B (MTIB), and trophoblastic (MTT). Tumors which contained any of the foregoing components and seminoma were classified as combined tumors. Pugh (1971) proposed the term malignant teratoma, undifferentiated to include malignant teratoma, anaplastic and malignant teratoma, intermediate B.

The term malignant teratoma implies that the differentiated teratoma is benign. Malignant teratoma is not an acceptable term for a tumor that is a definite carcinoma, nor is the term malignant teratoma, trophoblastic acceptable for choriocarcinoma. The classification is inconsistent because it sometimes designates the tumor on the basis of its most differentiated elements (MTIA) and sometimes on the basis of its most malignant components (MTT). There is no provision for indicating specific cell types nor relative proportions of each component present. There is difficulty in correlating this classification with our own; e.g., embryonal carcinoma may be present in malignant teratoma, intermediate A; malignant teratoma, intermediate B; malignant teratoma, trophoblastic; and combined tumors. Malignant teratoma, trophoblastic includes pure chorio-
carcinoma and tumors which consist of a focus of choriocarcinoma and one or more other types.

Teilum (1971), whose studies of ovarian and testicular tumors span a period of 30 years, classifies the tumors as seminoma, embryonal carcinoma, entodermal sinus tumor, teratoma, teratocarcinoma, and choriocarcinoma. Gaillard designates the tumors as follows: seminoma; dysembryoma, immature complex type (embryonal carcinoma, with or without embryoid bodies), and immature simple type (ectoblastic, mesoblastic, trophoblastic, or pure trophoblastoma); adult teratoma; and mixed tumor (teratocarcinoma).

The World Health Organization Panel on Testicular Tumors has more recently proposed a tentative classification similar to the one presented in this fascicle.

Table I

<table>
<thead>
<tr>
<th>PATHOLOGIC CLASSIFICATION</th>
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<tbody>
<tr>
<td><strong>GERM CELL TUMORS</strong></td>
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<tr>
<td>Tumors showing one histologic pattern</td>
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<tr>
<td>Seminoma</td>
</tr>
<tr>
<td>Typical seminoma</td>
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<tr>
<td>Anaplastic seminoma</td>
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<tr>
<td>Spermatocytic seminoma</td>
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<tr>
<td>Embryonal carcinoma</td>
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<tr>
<td>Embryonal carcinoma—adult</td>
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<tr>
<td>Polymorphous</td>
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<tr>
<td>Embryonal carcinoma—infantile</td>
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<tr>
<td>Choriocarcinoma</td>
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<tr>
<td>Teratoma</td>
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<tr>
<td>Mature</td>
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<tr>
<td>Immature</td>
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<tr>
<td>Tumors showing more than one histologic pattern</td>
</tr>
<tr>
<td>Embryonal carcinoma and teratoma (teratocarcinoma)</td>
</tr>
<tr>
<td>Others</td>
</tr>
</tbody>
</table>

References


garner, F. M. Personal communication, 1971.


Pugh, R. C. B. Personal communication, 1971.


Sobin, L. Personal communication, 1971.


———. The development of transplantable teratocarcinomas from intratesticular grafts of pre-


GERM CELL TUMORS SHOWING ONE HISTOLOGIC PATTERN

SEMINOMA*

SYNONYMS AND RELATED TERMS: Disgerminoma; dysgerminoma; germinoma; seminal carcinoma; spermatoblastoma; spermatocytoma.

DEFINITION. Seminoma is a germ cell tumor composed of characteristic, large, uniform cells with clear cytoplasm that resemble primordial germ cells and are supported by varying amounts of lymphoid and/or granulomatous stroma. It is a relatively low grade malignant tumor and is highly radiosensitive.

INCIDENCE. Seminomas comprise from 35 to 71 percent of the primary germinal tumors of the testis depending largely upon the source of the hospital population from which the statistics are reported. Seminoma is more commonly found in patients from rural areas (Lipworth and Dayan), in older men, and in cryptorchid testes.

CLINICAL FEATURES. Seminoma occurs most often during the fourth and fifth decades of life, although we have observed this tumor in a 10 year old child. Enlargement of the testis, with or without pain, is the most common symptom. In almost 10 percent of cases, metastases are noted at the initial examination. Of all the germinal tumors, seminoma occurs most commonly in a pure form and metastasizes in this state. Orchiectomy and radiotherapy or chemotherapy are the accepted modes of treatment. The prognosis is fairly good for seminoma which is confined to the testis and has been properly treated.

Histologically, three subtypes of seminoma are recognized: typical seminoma, anaplastic seminoma, and spermatocytic seminoma. Differences in their clinical, gross, and microscopic appearance justify a more detailed discussion.

Typical Seminoma

GROSS. The right testis is involved slightly more frequently than the left by a ratio of 5 to 4. In 85 percent of patients, the testis is enlarged, sometimes reaching 10 times normal size. In 15 percent of patients, the testis is normal or decreased in size. Usually, the enlargement is diffuse, but occasionally it may be nodular. The external surface of the tunica albuginea may be smooth and glistening; if there is a preexisting hydrocele, it may be rough and dull, fibrinous, or thick. There may be occasional dilated venous channels.

Cut surfaces show a bulging, grayish white, lobulated, rather homogeneous, glistening tissue (fig. 1). The consistency is generally soft but may be hard, if there is a moderate amount of fibrous stroma. Areas of

Figure 1
SEMINOMA

On section, discrete spherical tumor nodules show bulging, homogeneous, white soft surfaces. Necrosis of tumor is not common in small tumors such as this. Testicular parenchyma is seen superiorly and laterally in each cut surface. Tunica albuginea appears intact over the surface of the tumor. (Fig. 32 from Fascicles 31b and 32, First Series.)
necrosis and hemorrhage are usually inconspicuous except in large tumors (fig. 2). The tumor is not encapsulated, but is often demarcated from the testicular tissue which may form a rim of varying thickness. In about 50 percent of patients, the testis is replaced by tumor. Extension beyond the capsule to the scrotal sac, the epididymis, or the spermatic cord occurs in 8 percent of cases.

MICROSCOPIC. Typical seminoma is composed of uniform cells supported by a delicate connective tissue stroma (figs. 3, 4). Characteristically, the seminoma cell is large, polyhedral, or round with a distinct cell border. It has clear or granular cytoplasm and a large centrally located, spherical hyperchromatic nucleus with an irregular nuclear membrane, distinct and granular chromatin distribution, and one or two basophilic nucleoli (fig. 5). Occasionally, the nuclei may be small or elongated and nucleoli may be absent. The cytoplasm contains varying amounts of glycogen, and rarely lobules of lipid material. Mitoses are usually infrequent and there is little variation in size and shape of the cells.

The cells occur in loose-appearing sheets and lobules, but may be in columns or even rows due to stromal segregation. Except where they are distinctly within the seminiferous tubules, there is no evidence of acinar, tubular, or papillary formation.
Seminoma

Figure 3
SEMINOMA
This seminoma shows uniform tumor cells and relatively regular, fine branching, supporting stroma with a few scattered lymphocytes. X155. (Fig. 34 from Fascicles 31b and 32, First Series.)

Figure 4
SEMINOMA
Note the regularity of the supporting stroma that divides the tumor into lobules. Cytoplasm of these tumor cells takes little or no stain. X180. (Fig. 35 from Fascicles 31b and 32, First Series.)
In a number of cases, the tumor appears to be confined to the seminiferous tubules (fig. 6), sometimes posing a problem of differentiation from tangentially cut seminiferous tubules that are in a normal or delayed stage of maturation. In intratubular seminoma, the cells are of uniform size and appearance, while in normal seminiferous tubules or those with delayed maturation, the cells are considerably polymorphic. Intratubular seminoma is often associated with a group of atrophic seminiferous tubules with thickened basement membranes that contain dark-staining cells; the interstitium includes focal aggregates of Leydig cells.

Tumor giant cells (fig. 7) may be seen and also two additional types of giant cells may be encountered: (1) **Syncytiotrophoblastic cells** are morphologically identical to those seen in placenta. They are usually multinucleated giant cells with dark-staining nuclei and eosinophilic cytoplasm with vacuoles of varying size (fig. 8). These cells are frequently in close proximity to capillaries. At times, they are elongated with one or more hyperchromatic nuclei, resembling those seen in late stages of placental involution, and (2) **Stromal giant cells** consist of foreign body type giant cells. The stroma varies greatly (figs. 9, 10); sometimes it is quite scant and other times it is extensive. It usually consists of a delicate fibrovascular tissue which divides the tumor cells into lobules of varying size.
Seminoma

Figure 6
INTRATUBULAR TUMOR GROWTH
Intratubular tumor growth is seen in 24 percent of seminomas. The tubules in the center of this photomicrograph are distended with typical seminoma cells and stand out in contrast to the adjacent atrophic seminiferous tubules. In some instances, seminomas may be entirely intratubular without invasion, an example of carcinoma in situ. X105. (Fig. 42 from Fascicles 31b and 32, First Series.)

Figure 7
SEMINOMA
Two giant cells with abnormal nuclei are seen in this photomicrograph. X450.
Figure 8
SYNCYTIAL TROPHOBLASTIC GIANT CELLS IN SEMINOMA
Large spaces within these giant cells appear to be true vascular channels filled with blood. There is intra-vascular tumor growth in the small vessel in the upper left corner. X205. (Fig. 41 from Fascicles 31b and 32, First Series.)

Figure 9
GRANULOMATOUS STROMAL RESPONSE IN SEMINOMA
Cellular response is chiefly lymphoid and histiocytic with some fibroblastic proliferation in this seminoma. Stroma appears to encroach on the tumor cells. X240.
Tumors of the Testis

Two features of the stroma that merit attention are lymphocytic infiltration and granulomatous reaction. Varying amounts of lymphocytic infiltrate are observed in almost all seminomas; it is prominent in about 80 percent of cases and marked in about 20 percent of these. The cells are small mature lymphocytes which are usually scattered in the stroma and between the seminoma cells (fig. 11). They may appear in aggregates, but are rarely follicular.

Granulomatous reaction is observed in about half the cases, but is marked in about 20 percent and consists of fibroblastic and histiocyte reaction. There are varying numbers of lymphocytes (fig. 12) and foreign body giant cells with peripherally arranged small nuclei, and an eosinophilic, centrally located cytoplasm which may contain inclusions of nuclear debris.

The lymphoid stroma and granulomatous reaction may indicate response of the
host to the tumor. Indeed, granulomatous reaction is quite reminiscent of granulomatous orchitis, but it is not observed in all tumors nor in all parts of the same tumor. Dixon and Moore demonstrated a favorable prognostic significance of these stromal reactions.

At times, stromal reaction consists of collagenous, scirrhous, hyalinized, connective tissue, obviously representing a later stage (fig.10). Usually, some lymphocytic infiltration is present in such hyalinized areas. Stromal reaction, whether lymphocytic, granulomatous, or scirrhous, may be so advanced as to mask the presence of a tumor (fig. 12). Lymphocytic infiltration may suggest idiopathic or infectious granuloma, especially when there are central areas of necrosis. The most important differentiating feature is the presence of single tumor cells or small groups of tumor cells with densely staining nuclei and little or no cytoplasm. The cytoplasm of the cells stains with the PAS reaction which is most helpful in identifying seminoma. Where the central area of necrosis is surrounded by a granulomatous reaction, the ghosts of necrotic seminoma cells are readily identifiable, especially with Mallory's iron hematoxylin or reticulum stains.

Two types of necrosis may be encountered: simple necrosis with pyknosis of individual cells or small groups of cells, or coagulation necrosis with ghosts of seminoma cells in various stages of disintegration. Depending upon the size of the tumor and the state of its blood supply, areas of necrosis may be small or large; massive necrosis occurs in about 25 percent of cases.

Invasion of the rete testis produces a characteristic microscopic picture (fig. 13) which is occasionally misdiagnosed as carcinoma of the rete.
ULTRASTRUCTURE. Pierce and Beals have described the ultrastructure of seminoma. The lobules of seminoma are composed of a variety of cells which vary in degree of differentiation. Some are extremely undifferentiated, whereas others have complex cytoplasm with well developed organelles. The large irregular nuclei have multiple bizarre-shaped nucleoli and appear the same, irrespective of the degree of cytoplasmic differentiation.

Undifferentiated seminoma cells, representing the least common stage of differentiation present in the tumor, resemble embryonal carcinoma cells, primordial germ cells, spermatogonia, and spermatocytes (fig. 14). Other cells present a more complex structure. Although aggregated mitochondria are numerous, the most notable feature is the degree of development of cytoplasmic cisternae. Mostly, they are irregular and distended; some profiles contain a moderately electron-dense, finely granular material, whereas others appear empty. Spherical membrane-bound granules are seen in the cytoplasm, apparently derived from the cisternae. Glycogen is scattered throughout the cytoplasm. The most differentiated cells in the lobules contain many membrane-bound aggregates of coarse electron-dense granules (fig. 15). These are apparently derived from cisternae, and their numbers
are in inverse proportion to the numbers of cisternae present. Mitochondria are also present in large numbers and have distorted configurations. The cell membranes of seminoma cells are often exceedingly complex, but lack desmosomes. Cytoplasmic communications which have been described between primordial germ cells and in later stages of spermatogenesis have not been observed between seminoma cells.

Figure 14
SEMINOMA

These are portions of cells from seminoma M-10 (s) to illustrate the lack of development of endoplasmic reticulum and Golgi complexes characteristic of seminoma stem cells. Mitochondria are not well preserved. The cell membranes lack desmosomes. At the bottom, the margin of two well differentiated cells may be seen. X16,000. (Fig. 3 from Pierce, G. B., Jr. Ultrastructure of human testicular tumors. Cancer 19:1963-1988, 1966.)
Anaplastic or Aggressive Seminoma

Some degree of anaplasia is encountered in many tumors, but in about 10 percent of seminomas the bulk of the tumor is anaplastic. No gross characteristics distinguish it from other seminomas. Cellular irregularity with variation in size, shape, and staining of nuclei is present, but often difficult to evaluate since fixation has a considerable effect on the appearance of the cell.
The nuclei may be larger and more vesicular than in typical seminoma; however, increased mitotic activity is the most important and easily recognizable feature. An average of three or more mitotic figures per high power field would certainly indicate a rapidly growing tumor, and such a finding would justify the designation of anaplasia (fig. 16).

Anaplastic seminoma may be differentiated from solid embryonal carcinoma by the larger cells, less distinct cell borders, and more hyperchromatic nuclei in the latter. The lobular pattern is maintained and there is usually some lymphocytic infiltration in anaplastic seminoma. Marked lymphocytic infiltration or granulomatous reaction is usually absent.

The distinction between typical and anaplastic seminoma has good clinical justification because most of the metastasizing seminomas consist of anaplastic seminomas, and the prognosis for this group is distinctly less favorable than that for typical seminomas (table II; Maier et al.).

Table II
COMPARISON OF 10-YEAR SURVIVAL OF TYPICAL AND ANAPLASTIC SEMINOMA

<table>
<thead>
<tr>
<th>Type</th>
<th>Survival Rate</th>
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<tbody>
<tr>
<td>All seminomas</td>
<td>91 percent</td>
</tr>
<tr>
<td>Typical seminomas</td>
<td>93 percent</td>
</tr>
<tr>
<td>Anaplastic seminomas</td>
<td>70 percent</td>
</tr>
</tbody>
</table>

Figure 16
ANAPLASTIC SEMINOMA

Note at least three mitoses in this photomicrograph. In spite of cellular irregularity and considerable mitotic activity, the overall homogeneity and characteristic stromal component make diagnosis certain. X500. (Fig. 37 from Fascicles 31b and 32, First Series.)
Spermatocytic Seminoma

Spermatocytic seminoma was first recognized by Masson in 1946; it is quite different grossly, microscopically, and clinically from typical and anaplastic seminoma. It may be regarded as a separate entity, but is classified under seminoma because of usage. Spermatocytic seminoma comprises about 9 percent of seminomas. Clinically, it occurs most often in those over 40 years of age, although we have seen such a tumor in a young boy. It is usually present for a longer period and is less symptomatic than seminoma. The prognosis for this radiosensitive tumor is good.

GROSS. The tumor tends to be more yellowish, softer, and slightly more mucoid than seminoma and is usually large (pl. I-A). Spongy and/or cystic areas with ragged edges are rather common, but areas of true necrosis and hemorrhage are usually small.

MICROSCOPIC. In contrast to typical and anaplastic seminoma, three types of cells can be recognized in spermatocytic seminoma (figs. 17—19). The main population consists of medium-sized cells with a round nucleus and considerable amount of eosinophilic cytoplasm. Intermixed in this "sea" are two other types: cells resembling secondary spermatocytes after reduction division, and huge, usually mononuclear cells. The small cells have a round, basophilic, glassy nucleus surrounded by a distinct rim of eosinophilic cytoplasm. The giant cells are usually mononuclear, but occasionally may be binuclear or trinuclear. The nuclei are round, oval, or indented and surrounded by a considerable amount of eosinophilic cytoplasm, devoid of glycogen.

Figure 17

SPERMATOCYTIC SEMINOMA
Polymorphism of cells is seen, ranging from small lymphocyte-like cells to large multinucleated or mononucleated cells. X250.
Figure 18
SPERMATOCYTIC SEMINOMA
Pleomorphism of cells is evident. Note the chromatin distribution of the nuclei. X210.

Figure 19
SPERMATOCYTIC SEMINOMA
Note the spireme arrangement of the nuclear chromatin. X920.
The character of the nucleus in the intermediate and the large cells differentiates this tumor from other seminomas. Masson called attention to filamentous "spireme-like" chromatin distribution, similar to the meiotic phase of normal primary spermatocytes (fig. 19). The chromatin occurs in regular clumps, and the nuclear membrane is irregularly thickened. An occasional single, large, basophilic nucleolus is present. A moderate number of mitoses may be seen in some fields and none in others; some of the mitoses are abnormal.

The tumor usually occurs in sheets, occasionally with large or small lakes which contain an eosinophilic precipitate and some cell debris. The stroma is scant, and lymphocytic and granulomatous reactions are absent.

**ULTRASTRUCTURE.** Rosai and associates described the ultrastructure of this tumor as seen in two of their patients (figs. 20—23). Important ultrastructural features included: prominent nucleolus with dispersed nucleolonema; occasional nuclei with the chromosomal configuration of the leptotene stage of meiotic prophase; marked development of the Golgi apparatus, with formation of a dense secretory product; basal bodies and ciliary rootlets; "lamellar bodies"; specialized cell junctions of the zonula adherens type; true intercellular bridges identical to those normally found between spermatocytes and between spermatids; syncytial formations; and basal laminae (basement membranes). Comparison of these findings with those of typical seminoma suggests an origin from the same cell type;

![Image of spermatocytic seminoma](image_url)

**Figure 20**

**SPERMATOCYTIC SEMINOMA**

(Figures 20—23 from same case)

The nucleus shows elongated threads in longitudinal cross sections consistent with leptotene chromosomes. X6500. (Fig. 2 from Rosai, J., Khodadoust, K., and Silber, I. Spermatocytic seminoma. II. Ultrastructural study. Cancer 24:103-116, 1969.)
but it also indicates that spermatocytic seminoma is a tumor distinct from the former by virtue of its greater differentiation and production of secondary spermatocytes and possibly spermatids.

DIFFERENTIAL DIAGNOSIS. Spermatocytic seminoma must be differentiated from typical and anaplastic seminoma on the one hand, and from malignant lymphoma on the other. In typical seminoma, the cells stain fairly uniformly although they are less regular in shape. There is considerable cytoplasm which is usually clear with a distinct cell membrane. It may be ground-glass and eosinophilic, but rich in glycogen. Lymphocytic infiltration is almost invariably present, and granulomatous reaction is not infrequent. Giant cells may be tumor giant cells, or syncytiotrophoblastic, or Langhans' multinucleated type of giant cells. The hallmark of anaplastic seminoma is its anaplasia, increased mitotic activity, and decreased lymphocytic infiltration. Otherwise, typical and anaplastic seminoma are similar. On the other hand, in spermatocytic seminoma, the neoplastic process is characterized by the three cell types, the absence of glycogen, lakes of eosinophilic precipitate, and absence of lymphocytic stromal involvement.

The manner of infiltration is said to be different in that seminoma infiltrates interstitially while spermatocytic seminoma extends intratubularly. We consider intratubular location an indication of early neoplasia and have seen it in both typical seminoma and spermatocytic seminoma. The mode of local spread in each type is interstitial. In about 60 reported cases, some of
which are questionable, there was no association with any teratoid structures. However, we have seen a large testicular tumor consisting mostly of primitive teratoid tissue that revealed spermatocytic seminoma in some areas (see pages 70 and 71).

METASTASIS. Typical and anaplastic seminoma metastasizes as seminoma in 65 percent of cases; in 26 percent of cases metastasis consists of embryonal carcinoma and in 4 percent, teratoma. Although two of Masson’s cases of spermatocytic seminoma terminated fatally, none of the patients in our studies have died from this tumor. Four of the five patients reported by Jackson and Magner died, but we concur with Rosai and associates who believed that these patients had reticulum cell sarcoma rather than spermatocytic seminoma.

The most frequent method of spread in
Seminoma is by the lymphatic route. Autopsy has revealed that paraaortic and iliac lymph nodes are involved in 71 percent of cases; liver, 54 percent; right and left lung, each 37 percent; left kidney, 37 percent; right kidney, 6 percent; left adrenal, 35 percent; right adrenal, 9 percent; pancreas, 21 percent; peritoneum, 22 percent; and pleura, 17 percent.

PROGNOSIS. Seminoma has the most favorable outlook of the germ cell tumors. The 2-year mortality in the Dixon and Moore series was about 8 percent, and even 17 years after treatment 75 percent of the patients were still alive (Nefzger and Mostofi). The occurrence of seminomatous areas in other germ cell tumors does not affect the prognosis of those tumors. See Tables III and IV on pages 77 and 78.
EMBRYONAL CARCINOMA

SYNONYMS AND RELATED TERMS: Adenocarcinoma; germ cell carcinoma; cytotrophoblastic carcinoma; embryoma; embryonic carcinoma; embryoplastic carcinoma; cytotrophoblastoma; teratocarcinoma; teratoid carcinoma; embryonal teratoma; teratoblastoma; malignant teratoma; malignant teratoma, anaplastic; malignant teratoma, undifferentiated; malignant teratoma, intermediate; juvenile embryonal carcinoma, endodermal sinus tumor; yolk sac tumor.

DEFINITION. Embryonal carcinoma is a primary germ cell tumor of the testis with cells which have an embryonic and anaplastic epithelial appearance, and a variable pattern of acinar, tubular, papillary, or solid and reticular structure, sometimes with areas that have an embryonal mesenchymal appearance.

Three distinct types of embryonal carcinoma include: Adult type which occurs only in adults and may present with any of the foregoing patterns. This is a highly malignant tumor with a relatively low radiosensitivity; it corresponds to the rare ovarian embryonal carcinoma. Polyembryoma, which consists of embryoid bodies as the sole distinguishing feature. Embryoid bodies frequently accompany many adult embryonal carcinomas and teratomas, but their presence in such testicular tumors does not justify the designation polyembryoma. This term should be reserved for the extremely rare tumor that consists of myriads of embryoid bodies, corresponding to its ovarian counterpart. Infantile* embryonal carcinoma occurs predominantly in infants and children, and constitutes the most common testicular tumor of this age group; it has a relatively low degree of malignancy. This tumor also occurs in adults, usually with one or more of the other germ cell tumors, has a relatively low degree of malignancy, and corresponds to the endodermal sinus yolk sac tumor of the adult ovary (for details see page 121).

INCIDENCE. The incidence of embryonal carcinoma of adult type was 20 percent in our material, but other reports range from 4.2 to 37 percent of primary germ cell tumors.

CLINICAL FEATURES. Embryonal carcinoma of adult type occurs most often during the third decade, and less frequently during the latter part of the second decade and in older patients. Gradual swelling, with or without pain, is the most common symptom. About one third of the patients show clinical evidence of metastases at the time of hospital admission. Orchiectomy, followed by retroperitoneal lymphadenectomy or radiation, with or without chemotherapy, is generally the mode of treatment.

GROSS. Embryonal carcinoma is usually the smallest of the germinal testicular tumors, averaging about 49 cc.; 40 percent are less than 20 cc. in size. It replaces part or

*The predominant incidence is infantile rather than "juvenile", a term sometimes applied to this tumor.
all of the testis with distortion of the capsular surface (fig. 24). Ten to 20 percent of these tumors invade the epididymis or cord. Cut surfaces show a variegated appearance with grayish white, granular or smooth, bulging soft tissue containing extensive areas of hemorrhage and necrosis, with little, if any, evidence of encapsulation (fig. 25).
MICROSCOPIC. The characteristic feature of this tumor is that the cells resemble epithelial cells and are distinctly malignant and embryonal in appearance. There is considerable variation in their size, shape, and arrangement. They may be large and pleomorphic without distinct cell borders. The cytoplasm may be homogeneously amphophilic or vacuolated. Their nuclei are irregularly oval or round, with an irregular and coarse nuclear membrane, one or more large nucleoli, and varying degrees of nuclear vacuolization. Mitotic figures and mononuclear or multinuclear giant cells are frequent.

The cells may occur as solid sheets simulating seminoma (fig. 27); however, the lobular pattern of seminoma and lymphocytic stroma are usually, but not always missing (fig. 26). The carcinoma cells are usually larger, more epithelial with more abundant and denser cytoplasm, and more varied in size, shape, and staining (fig. 28). Mitoses are more frequent and cell membranes less distinct than in seminoma.

More frequently, small or large acinar, tubular, and/or papillary structures are formed (fig. 28). The cells may be regularly or irregularly arranged around the lumen; they may be cuboidal or columnar and may be arranged in a single layer or piled up (figs. 29, 30, 33). The lumen may be partly or completely filled by cells.

Reticular (fig. 32) and papillary (figs. 30, 31) tubular and acinar patterns are more frequently encountered in infants and children (see page 121), but also may be seen in adults. While a single pattern may predominate in a tumor, more than one pattern is generally observed.

The stroma in embryonal carcinoma varies considerably; it may be scanty, loose, edematous, fibrous and hyalinized, or very cellular, suggesting a sarcoma. Areas of hemorrhage and necrosis are frequent.

The tumor forms solid sheets. X230.

The presence of primitive neoplastic mesenchyme in some tumors has led to confusion in terminology. While recognizing the primitive neoplastic mesenchyme, it seems justified to classify this tumor as embryonal carcinoma (fig. 34), since Pierce and associates demonstrated that such mesenchyme, including contractile muscle elements, originates from embryonal carcinoma.

Some embryonal carcinomas may contain syncytiotrophoblastic cells. It seems desirable to note their presence, but, unless distinct choriocarcinoma is seen, the tumor is reported as embryonal carcinoma with syncytiotrophoblastic cells.

ULTRASTRUCTURE. According to Pierce and Beals, ultrastructurally, poorly differentiated embryonal carcinoma cells are discrete with intact cell membranes (fig. 35).
**Figure 27**

**EMBRYONAL CARCINOMA, SOLID TYPE**

Cellular irregularity, presence of flattened dark cells near the periphery of the tumor lobules, invasion of the stroma, and absence of a definite stromal response are characteristic. X115. (Fig. 48 from Fascicles 31b and 32, First Series.)

**Figure 28**

**EMBRYONAL CARCINOMA AND SEMINOMA**

The right portion of the field shows a seminoma. The cells are arranged in a mosaic. The cytoplasm is vacuolated. A few lymphocytes are present in the upper right. The upper and left portions of the field show an embryonal carcinoma. The nuclei are larger. They are more vesicular with a large nucleolus surrounded by considerable amounts of amphophilic cytoplasm and the cells form glandular structures. X210.
Figure 29

EMBRYONAL CARCINOMA
The tumor forms anastomosing glands and ducts. X155. (Fig. 54 from Fascicles 31b and 32, First Series.)

Figure 30

EMBRYONAL CARCINOMA
The tumor forms glands and papillary projections. This picture is usually seen in infantile tumors. X145.
Figure 31
EMBRYONAL CARCINOMA
Papillary projections are covered by two distinct cell layers separated from each other by a delicate fluorovascular stroma simulating a developing yolk sac. X115.

Figure 32
EMBRYONAL CARCINOMA
The tumor has a reticular pattern. This is the picture usually seen in infantile embryonal carcinoma, but may be seen in adults as well. X605. (Fig. 51 from Fascicles 31b and 32, First Series.)
Cell membranes, which are regular in contour, impart a tilelike pattern to the tissue. A few microvilli are present, but these appear rudimentary. The nucleocytoplasmic ratio is large. The nuclei are irregular in shape, with numerous deep indentations. Nucleoli of irregular configuration are numerous and large, with as many as three nucleoli in a nucleus. Other than masses of free ribosomes and polysomes which impart the amphophilic cytoplasm seen in light microscopy, the cytoplasm of these undifferentiated cells contains few organelles. The mitochondria are often variable in size and shape. The cristae, which are distorted in arrangement, often run parallel to the long axis of the organelle. The endoplasmic reticulum is scant and lamellar. Golgi complexes are rare. In addition to frequent small lipoidal inclusions, larger membrane-bound inclusions are often present; the largest, about one-half the size of a cell, are composed of masses of membranes and distorted nuclei. Smaller ones are composed of lightly packed membranes and debris; they appear to be later stages of degradation of larger inclusions. Carcinoma cells have profusely developed endoplasmic reticulum, many Golgi bodies, and orderly microvilli; they resemble epithelial cells. Primitive cells intermingle with more mature cells.

METASTASIS. Autopsy studies reveal that metastases from pure embryonal carcinoma consist of embryonal carcinoma in 96
Embryonal Carcinoma

Figure 35

EMBRYONAL CARCINOMA

This is a heterotransplant of human embryonal carcinoma, PITT 61, in the cheek pouch of a cortisone-treated hamster. The cell is undifferentiated; the tumor stromal junction is illustrated to show the basement membrane (arrow). The nuclei are large and irregular in shape, with large nucleoli. The cytoplasm contains mitochondria, a few lipoidal inclusions, and many ribosomes. Rough endoplasmic reticulum is sparse, imparting the impression that this is an undifferentiated stem cell. X7,200. Fig. 13 from Pierce, G. B., Jr. Ultrastructure of human testicular tumors. Cancer 19:1963-1988, 1966.)

percent of cases; teratoma, in 8 percent; and choriocarcinoma, in 5 percent of cases with the following distribution: periaortic and iliac lymph nodes, 96 percent (fig. 124); each lung, 84 percent (fig. 37); liver, 80 percent; pleura, 46 percent; bones of trunk, 21 percent; and gastrointestinal tract, 18 percent.

DISCUSSION. Many embryonal carcinomas have tubular and acinar patterns. These have been regarded as indicating
Tumors of the Testis

Figure 36
PERIAORTIC METASTASIS FROM EMBRYONAL CARCINOMA
Metastatic spread by way of the lymphatics to the regional nodes along the aorta up to the renal pedicles is the most common route of dissemination of testicular tumors. A large mass of tumor surrounds the aorta and renal pedicle. (Fig. 46 from Fascicles 31b and 32, First Series.)

Figure 37
MEDIASTINAL AND PULMONARY METASTASES FROM EMBRYONAL CARCINOMA
(Figures 37 and 55 from same case)
Once the abdominal lymphatics and lymph nodes are saturated with metastatic tumor, spread to the mediastinum is frequent. Pulmonary involvement by tumor is probably blood-borne, although retrograde lymphatic spread from the mediastinum is possible. (Fig. 47 from Fascicles 31b and 32, First Series.)
differentiation of the tumor, somatic or otherwise. The use of the term differentiation in such a context is confusing, because it implies stages in the development of some structure in the testis or in a teratoma.

Friedman and Moore, and Dixon and Moore regarded embryonal carcinoma as the primitive tumor of totipotential cells which, under certain conditions, may undergo trophoblastic or somatic differentiation, or both. Their observations were based on the frequent association of embryonal carcinoma with teratoma or choriocarcinoma, and the presence of these latter elements in metastases from embryonal carcinoma. Experimental work of Stevens and associates and ultrastructural studies of Pierce and his coworkers with human and experimental tumors, support the concept of the origin of teratoma from a primitive totipotential cell, which they categorized as embryonal carcinoma.

Embryoid Bodies—Polyembryoma

In a number of embryonal carcinomas and teratomas, organoid structures are formed which simulate embryoid bodies (figs. 38—42. Very rarely, the tumor consists entirely of such bodies, which Evans described in detail. Fully developed embryoid bodies are easily recognizable. They measure less than 1 mm. in diameter and may be spheroid, globular, or cylindroid. Embryoid bodies consist of a disk, a cavity, and a tubular form, surrounded by loose mesenchyme in which syncytiotrophoblastic and cytotrophoblastic cells may be seen. The disk is comprised of single or multilayered, undifferentiated, large, epithelial-like cells; the cavity is lined by flattened epithelial cells and simulates an amniotic cavity. The tubular structure resembles entoderm (fig. 40). Thus, the complex structure designated as embryoid body resembles an embryo of one to two weeks' gestation. More often, however, as beautifully illustrated by Evans, many variations are seen; the most common is a nest or sheet of cells partly lining a cavity with no organoid arrangement.

Stevens has never encountered an embryoid body in spontaneous or induced murine testicular tumor. But Pierce and Midgely found that when a highly pleomorphic testicular murine embryonal carcinoma was injected intraperitoneally and maintained as a peritoneal ascitic tumor, thousands of embryonal bodies were produced (pl. B-1). They consisted of tiny cysts. These murine embryoid bodies had a histogenetic potency, as well as a morphologic similarity to normal mouse embryos 5 to 6 days of age.
When the cysts were washed and transplanted to subcutaneous tissue of strain 129 mice, fully differentiated teratocarcinoma developed which was indistinguishable from control tumors (pl. B-2). Subsequent intraperitoneal grafts of washed cysts eventually gave rise to implants of an anaplastic carcinoma with hyaline stroma and hemorrhagic ascites, but no cysts. These granules were composed of a central core of embryonal carcinoma invested with a layer of visceral yolk sac, but no mesenchyme. Pierce and his associates concluded that embryoid bodies consisting of three germ layers were derived from the release of embryonal carcinoma cells into the ascitic fluid.

Figure 39
EMBRYONAL CARCINOMA
The tumor shows structures resembling an embryonic disk of 1 to 2 weeks. The giant cell at the right suggests a syncytiotrophoblast. The structures are usually seen in association with embryonal carcinoma and teratoma, but occasionally occur alone. X280. (Fig. 56 from Fascicles 31b and 32, First Series.)
Figure 40

EMBRYONAL CARCINOMA
This embryoid-like disk shows amnion above and entoderm below. X805. (Fig. 57 from Fascicles 31b and 32, First Series.)

Figure 41

EMBRYONAL CARCINOMA
(Figures 38, 41, and 42 from same case)
A nest of carcinoma cells is seen in a space surrounded in part by a layer of low cuboidal cells. X165.
Therefore, it is preferable to recognize the structure and malignant potential of embryoid bodies and designate the area as embryonal carcinoma, because embryoid bodies represent a stage in the development of embryonal carcinoma and have a wide morphologic range. If the tumor consists solely or predominantly of embryoid bodies, it may be justifiably designated as polyembryoma, corresponding to its ovarian counterpart (Serov et al.).

PROGNOSIS. The 5-year mortality rate of 64.5 percent for embryonal carcinoma is unaffected by the presence of areas of seminoma, but is somewhat ameliorated if associated with teratoma. Even if the teratomatous component is completely differentiated and benign appearing, the tumor may have previously metastasized accounting for the 40 percent mortality (see Tables III and IV on pages 77 and 78).
CHORIOCARCINOMA*

SYNONYMS AND RELATED TERMS: Carcinoma syncytiale; chorioma (ectodermale); chorio(n) epithelioma (malignum); chorionic carcinoma; malignant teratoma trophoblastic.

DEFINITION. Choriocarcinoma is a highly malignant testis tumor, similar to that in the uterus, composed solely of cytotrophoblastic and syncytiotrophoblastic cells. The syncytiotrophoblastic cells often cap or otherwise constitute the advancing edge of the tumor which may be suggestive of villous-like structures, but lack the true villous formation as seen in hydatiform moles in the female.

INCIDENCE. Pure choriocarcinoma of the testis—a tumor that shows no elements other than syncytiotrophoblastic and cytotrophoblastic cells—is extremely rare. Collins and Pugh reported none among 1,050 cases. There are 18 cases of pure choriocarcinoma among the 6,000 testis tumors listed in the files of the American Testicular Tumor Registry at the Armed Forces Institute of Pathology. Ganina, in Kiev, reported choriocarcinoma in 18 of 138 patients; however, her photomicrographs appear to be embryonal carcinoma suggesting that the term choriocarcinoma was used synonymously with cytotrophoblastoma, a term occasionally used for embryonal carcinoma.

CLINICAL COURSE. In its pure form, the tumor is rare and occurs almost exclusively during the second and third decades. We have observed one case in a 50 year old man. Presenting symptoms are usually referable to metastases, since there is only slight enlargement of the testis and little pain.

GROSS. The testis is usually small or normal, with or without a nodule. It may be enlarged and firm, depending upon the extent of hemorrhage which invariably accompanies choriocarcinoma. In pure form, the tumor presents as a hemorrhagic mass with some grayish white viable tissue identifiable at the periphery (pl. I-B). When choriocarcinoma occurs with other cell types, the area usually appears as a hemorrhagic focus in a cystic or solid tumor in an enlarged testis. Simple necrotic areas, unassociated with hemorrhage, are usually not indicative of choriocarcinoma, but any hemorrhagic area in a testicular tumor must be viewed with suspicion.

MICROSCOPIC. Choriocarcinoma consists essentially of two distinct cell types—syncytiotrophoblastic and cytotrophoblastic (figs. 43, 44). The typical syncytiotrophoblastic cell is readily recognizable; it is large and multinucleated with many hyperchromatic, irregular nuclei in a cytoplasm that is usually eosinophilic or occasionally amphophilic but contains many vacuoles of various sizes. Histologically, the vacuoles contain a slightly eosinophilic staining precipitate, but occasionally red blood cells are present. Other syncytiotrophoblastic cells may be spindle-shaped with one large, irregularly hyperchromatic nucleus. In essence, all stages of syncytiotrophoblastic cells are encountered, similar to those seen in the involution of placenta or in uterine choriocarcinoma.

Cytotrophoblastic cells are fairly uniform; they are medium-sized and closely packed with clear cytoplasm, distinct cell borders, and a single, uniform, rather moderate-sized vesicular nucleus.

Ultrastructurally, cytotrophoblastic cells closely resemble those in embryonal carcinoma (fig. 45); each cell lacks rough endoplasmic reticulum and Golgi complexes. The cytoplasm is composed largely of polysomes and free ribosomes, a configuration characteristic of cells whose primary function is rapid proliferation. The syncytial nature of the syncytiotrophoblastic cell is well demonstrated by electron microscopy (fig. 46). Two
Cytotrophoblast is made up of characteristic uniform cells with clear cytoplasm, and forms villus-like masses, the surfaces of which are covered by syncytiotrophoblastic cells with dark eosinophilic cytoplasm X125. (Fig. 69 from Fascicles 31b and 32, First Series.)

This high power view shows detail of cytotrophoblastic cells and syncytiotrophoblastic cells. X235. (Fig. 70 from Fascicles 31b and 32, First Series.)
Figure 45

CYTOTROPHOBLASTIC CELLS

Portions of two cytotrophoblastic cells are identified by light microscopy in a thick section. A nucleus (n) is present in the upper left. The cell membrane (cm) is seen on the right. PITT 89 (testicular chorionicarcinoma). A few profiles of the endoplasmic reticulum (er) and mitochondria (m) stand out in relief against the background of free ribosomes which dominate the cytoplasm. An occasional desmosome is present. This type of cell is extremely undifferentiated from an ultrastructural standpoint. X16,200. (Fig. 3 from Pierce, G. B., Jr., and Midgley, A. R., Jr. The origin and function of human syncytiotrophoblastic giant cells. Am. J. Pathol. 43:153-173, 1963.)
Figure 46
SYNCYTIOTROPHOBLASTIC GIANT CELL

A syncytiotrophoblastic giant cell is identified by light microscopy from an adjacent thick section PITT 146. The cell is truly syncytial since two nuclei (n) lie in a common cytoplasm. There are numerous profiles of a cisternal type of endoplasmic reticulum (er) which honeycomb the cytoplasm. Some of the mitochondria are swollen (m). Interdigitating microvilli of the cell membranes may be seen at arrows. Similar microvilli form the brush border of a "maternal sinusoid" (s) and are embedded in fibrin. X9,000. (Fig. 2-A from Pierce, G. B., Jr., and Midgley, A. R., Jr. The origin and function of human syncytiotrophoblastic giant cells. Am. J. Pathol. 43:153-173, 1963.)
or more nuclei are seen in a common cytoplasm. Many profiles of a cisternal type of endoplasmic reticulum honeycomb the cytoplasm. Occasional nuclear pores are seen. Mitochondria may be swollen. The free surface has many microvilli which may interdigitate. Similar microvilli form the brush border of the host sinusoids.

As in placental and uterine choriocarcinoma, the advancing edge of the growth, whether in relation to vascular spaces or surrounding tissue, is usually covered by syncytiotrophoblastic cells that cap the cytotrophoblastic cells. Such an arrangement suggests a villous-like formation. True villi, however, as seen in the mature placenta with a core of loose, fibrovascular tissue covered by elongated, hyperchromatic, syncytiotrophoblastic cells, have not been observed. More often, the appearance is reminiscent of early villi, with a mass of cytotrophoblastic cells and a few syncytiotrophoblastic cells at the periphery. While testicular choriocarcinoma in its pure form is indistinguishable from uterine choriocarcinoma, no true villous formation nor hydatid moles have been reported in males.

METASTASIS. Of the 18 pure choriocarcinomas of the testis studied, we found all had metastasized as choriocarcinoma. Metastases were principally hematogenous, but also lymphatic, to the periaortic and iliac nodes and each lung in 100 percent of cases; liver, 86 percent; intestines, 71 percent; and spleen, adrenals, and brain, 56 percent of cases.

DIFFERENTIAL DIAGNOSIS. Pure choriocarcinoma must be distinguished from tumors in which choriocarcinomatous areas occur in association with seminoma, embryonal carcinoma, or teratoma; such tumors should not be diagnosed solely as choriocarcinoma despite the longstanding tradition in pathology that a tumor is designated by its most malignant component. Diagnoses should be based upon the components that are present.

Single or multiple cells resembling syncytiotrophoblastic cells may be found in many seminomas, embryonal carcinomas, and teratomas; however, these should not be diagnosed as choriocarcinoma. Although gonadotropins are elevated in a number of such tumors, such elevation per se without histologic evidence does not justify a diagnosis of choriocarcinoma, since this may be due to castration effect.

The term trophoblastic carcinoma has been employed for certain embryonal carcinomas. Indeed, the cells of some solid embryonal carcinomas are indistinguishable from cytotrophoblastic cells seen in choriocarcinoma. With light microscopy, it is impossible to identify cytotrophoblastic cells with certainty unless accompanied by syncytiotrophoblastic cells (fig. 47). Special microscopy of the tumor and demonstration of high levels of chorionic gonadotropin and estrogens may justifiably lead to a diagnosis of cytotrophoblastoma, but no such reports are available. No correlation of levels of chorionic gonadotropins to the stage of differentiation of choriocarcinoma has been reported in man.

Diagnosis of pure choriocarcinoma should be limited to the classic definition. In embryonal carcinoma and in seminoma, scattered hyperchromatic spindle cells sometimes suggest stages in the involution of syncytiotrophoblastic cells, but we avoid diagnosing such tumors as choriocarcinoma.

The term malignant teratoma trophoblastic has been used by Collins and Pugh to include both pure and mixed types. We consider the term undesirable.

While the precautions and distinctions we have proposed may be regarded as puritanical, we feel they are valid because pure
choriocarcinoma almost always pursues a rapidly fatal course; other types may not. Most, if not all reported cases of surgically cured choriocarcinoma of the testis, and most reported cases of testicular choriocarcinoma treated unsuccessfully by chemotherapy are tumors in the mixed category.

TREATMENT. Radiotherapy following orchiectomy has been of no value in the treatment of choriocarcinoma. Chemotherapy has been unsatisfactory to date, but has not yet been adequately tested.

PROGNOSIS. Prognosis is poor and patients with this tumor usually die within a year (see Table IV on page 78). Prognosis is slightly more favorable if choriocarcinoma occurs with embryonal carcinoma, and even more favorable when associated with seminoma or teratoma.

* * * * *
TERATOMA*

SYNONYMS AND RELATED TERMS: Teratoma, bidermoma; compound tumor; dermoid; dermoid cyst; dysembryoma; embryoma; "mixed teratoid tumor"; monodermoma; "parasitic fetus"; teratoblastoma; teratoid tumor; tridermoma; differentiated teratoma; malignant teratoma, intermediate A, intermediate B.

DEFINITION. Teratoma is a complex tumor with recognizable elements of more than one germ layer in various stages of maturation, often arranged in such a manner as to suggest abortive organ formation. It corresponds to ovarian cystic and solid teratomas, but dermoid cysts are rare.

Generally included under this entity are three rare lesions of the testis: epidermal cyst, carcinoid, and retinal anlage tumor. It has been postulated that these represent one-sided development of teratoma. We believe that these lesions should not be diagnosed as teratoma (monodermal or otherwise), but by their specific histologic composition.

INCIDENCE. Teratoma comprises 4 to 9 percent of testicular tumors.

CLINICAL COURSE. Teratoma occurs in males of any age, but more frequently during the first, second, and third decades. The chief symptom is gradual swelling of the testis, with or without pain; 24 percent of patients show evidence of metastases on hospital admission. Treatment consists of orchectomy, sometimes followed by lymphadenectomy, with or without radiation. There is a 5-year mortality rate of 29 percent. The presence of foci of seminoma does not affect prognosis, while foci of embryonal carcinoma or choriocarcinoma make the prognosis worse. Teratoma occurring in infants and children behaves as a benign neoplasm clinically, although it may be only partly differentiated and show definite areas of histologic malignancy.

GROSS. The testis may be of normal size, but it is usually enlarged. The average volume is 70 cc.; in one third of cases, it is less than 20 cc. and in one fourth, it is over 100 cc. The tunic is irregularly distorted and nodular. The tumor cuts with varying degrees of resistance, and the cut surface reveals cysts of various sizes filled with a clear, gelatinous, or mucinous substance (fig. 48). Varying amounts of solid tissue may be seen between the cysts, and there may be islands of firm, translucent cartilage and spicules of bone. Necrosis and hemorrhage are rare; however, microscopic examination is essential in and around areas of hemorrhage and solid areas that show no cartilage or bone. Extension beyond the capsule occurs in about 6 percent of cases.

MICROSCOPIC. Teratoma is the term used to denote a tumor in which elements are present that are derivable from more than one of three germ layers—ectoderm, entoderm, or mesoderm (figs. 49—55). Ectodermal elements are represented by squamous epithelium, with or without keratinization, and by neuronal tissue; entodermal structures, by gastrointestinal and respiratory tissue and other mucous glands; and mesodermal elements, by bone, cartilage, and muscle.

Histologically, teratoma could be further designated as immature or mature. Embryoid bodies would seem to constitute the most immature teratoma. As stated previously, however, we group embryoid bodies with embryonal carcinoma. The term immature teratoma is reserved for neoplasms composed of primitive neuroectoderm, entoderm, or mesoderm. Next in order is maturation to the tissue level—formation of cartilage, bone, mucous glands, squamous, transitional, or cuboidal epithelial cells, or smooth or skeletal muscle. Organoid or differentiated teratoma is employed to denote tumors or areas that
Figure 48
TERATOMA
Multicystic structure is characteristic of teratomas. Cyst contents are mucinous or caseous, depending upon entodermal or ectodermal character of epithelial lining. Islands of hyaline cartilage can frequently be identified in the tumor stroma. (Fig. 60 from Fascicles 31b and 32, First Series.)

Figure 49
TERATOMA
The complex structure of the tumor is apparent by the presence of cystic and solid areas. X10.
show abortive organ formation. The most frequent of these are neural (figs. 51, 52). Gastrointestinal tissue is common; sometimes a viscus is seen lined by a distinct mucosa, lamina propria with lymphoid tissue, submucosa, and muscularis (fig. 50). Respiratory structures with tracheal or bronchial formation are the next most frequent elements. Abortive eye (fig. 52), pancreas, liver, choroid plexus, and bone marrow are also seen. Several varieties of mesodermal tissue may be found (figs. 54, 55). While a tumor may consist solely of immature, partly mature, or completely mature elements, more frequently both mature (fig. 53) and immature elements are present (figs. 54, 55). Pure immature teratoma is extremely rare.

Testicular teratoma that occurs in infants and children is apt to be principally mature and organoid.

Although no malignant areas may be identified, teratoma should not be designated as benign. In a few teratomas, primitive, undifferentiated, or differentiated sarcomatous tissue may be seen. If the area appears malignant but cannot be recognized as carcinoma, we designate it teratoma with histologically malignant areas. Rarely, the epithelial component (squamous or glandular element) may manifest premalignant or malignant change (fig. 56). If definite carcinoma is identified, we designate it teratoma and carcinoma, specifying the type of carcinoma.

Figure 50

TERATOMA

The teratoma contains structure resembling primitive gut. X100. (Fig. 65 from Fascicles 31b and 32, First Series.)
Tumors of the Testis

Figure 51
TERATOMA
The tumor forms a structure suggesting primitive neuroectodermal tissue. X80.

Figure 52
TERATOMA
The tumor forms a structure with columnar epithelium and melanin reminiscent of retina. X185. (Fig. 67 from Fascicles 31b and 32, First Series.)
Figure 53

TERATOMA

The tumor forms mature cartilage, squamous and enteric cysts. X80.

Figure 54

TERATOMA

The tumor forms striated muscle fibers. Such foci are occasionally encountered in the connective tissue of teratoma. X810. (Fig. 73 from Fascicles 31b and 32, First Series.)
A glandular structure and two nests of cartilage are present. The bulk of the tumor, however, consists of undifferentiated cells. X185. (Fig. 62 from Fascicles 31b and 32, First Series.)
METASTASIS. Metastases observed at autopsy of patients with teratoma consist of teratoma and embryonal carcinoma (63 percent each) and choriocarcinoma (25 percent). The tumor metastasizes most often through the lymphatic vessels to the following sites: preaortic and iliac lymph nodes, 100 percent; liver, 83 percent; each lung, 72 percent; bones of trunk, 36 percent; pleura, 35 percent; and intestines, 25 percent.

PROGNOSIS. The 2-year mortality of teratoma is 28 percent and is unaffected if associated with seminoma; however, association with embryonal carcinoma or choriocarcinoma does have an unfavorable effect on prognosis. See Tables III and IV on pages 77 and 78.

DERMOID CYST

In contrast to the incidence of dermoid cysts in the ovaries, where they are the most common teratomas, these cysts rarely occur in the testis. Grossly and microscopically in both males and females, dermoid cysts consist of hair, sebaceous and keratohyaline material, teeth, and other bony and cartilaginous tissue (fig. 57). The cyst wall consists of keratinizing, stratified, squamous epithelium and skin appendages. In the male, thyroid tissue is rarely present, but pancreatic tissue is seen occasionally. We have never observed metastasis from a pure dermoid cyst of the testis.
LESIONS CONSIDERED AS ONE-SIDED DEVELOPMENT OF TERATOMA

Simple Epidermoid Cyst

As the name indicates, this cyst is lined by keratinizing, stratified, squamous epithelium supported by fibrous tissue (fig. 58). The cyst is filled by keratohyaline material, and there are no skin appendages. About one percent of testicular tumors are simple epidermoid cysts. Price and Mostofi reported that none of the 70 cases in the American Testicular Tumor Registry, including four in children, showed metastases when the tumor consisted only of simple epidermoid cyst without scars or other elements. In all 10 cases studied by Abell and Holtz, the epidermoid cyst had been present since childhood. It was postulated that such lesions develop prior to puberty, reach maturity, then cease to grow. This lesion should not be designated as teratoma, but as an epidermoid cyst.

Carcinoid Tumor

Carcinoid tumor of the testis may be primary or metastatic. It may be functional and give rise to symptoms of “carcinoid syndrome” upon palpation of the testis, or it may be nonfunctional and detected only as a testicular enlargement or nodule. Whether the primary tumor is a one-sided development of teratoma has not been established. Grossly and microscopically, carcinoid tumor of the testis is similar to this tumor encountered elsewhere (figs. 59, 60).

Figure 58
EPIDERMOID CYST
The cyst is lined by keratinizing, stratified, squamous epithelium. X350.
The rather uniform tumor cells occur in sheets and islets separated by a delicate stroma. X160.

Higher magnification of the tumor shows the uniform small cells. X400.

Melanotic Hamartoma
This benign tumor is primarily an adnexal tumor and will be described in that section on page 174, but we have seen two cases presumably originating in the testis.
GERM CELL TUMORS SHOWING MORE THAN ONE HISTOLOGIC PATTERN

More than one histologic pattern is observed in about 40 percent of tumors of the testis. The relationship of these tumors to each other and their designation have caused much confusion in testicular oncology.

The most frequent association is that of teratoma and embryonal carcinoma which occurs in 24 percent of all testicular tumors. Teratoma, embryonal carcinoma, and seminoma are seen in 6.4 percent of cases; embryonal carcinoma and seminoma, in 5 percent; teratoma and seminoma, in about 2 percent; and teratoma, embryonal carcinoma, and choriocarcinoma, in 1 percent (fig. 61). The following combinations comprise about 3 percent of all testicular tumors: teratoma and choriocarcinoma; teratoma, choriocarcinoma, and seminoma; teratoma, seminoma, embryonal carcinoma, and choriocarcinoma; choriocarcinoma and seminoma; choriocarcinoma and embryonal carcinoma; choriocarcinoma, embryonal carcinoma, and seminoma. Rarely, a teratoma may show differentiated sarcoma or malignant primitive elements other than embryonal carcinoma. In such cases, the tumor should be designated as teratoma with malignant areas of the type observed so that the diagnosis reflects the histologic content of the tumor (figs. 62—66).

Figure 61
TERATOMA, EMBRYONAL CARCINOMA, AND CHORIOCARCINOMA
Cut section shows a tumor which is in part cystic, in part solid, and in part hemorrhagic. The hemorrhagic areas of such tumors should be examined for the presence of foci of choriocarcinoma.
Friedman and Moore coined the term teratocarcinoma to designate teratoma with embryonal carcinoma, seminoma, and/or choriocarcinoma as well as that in which teratoma, neuroepithelioma, or sarcoma occurred together. Dixon and Moore designated teratoma with embryonal carcinoma or choriocarcinoma, or both, with or without seminoma as Group IV tumors. It is preferable to identify each component, such as teratoma and embryonal carcinoma, or teratoma, embryonal carcinoma, and seminoma, in their order of predominance. Such definitive designation eliminates much unnecessary confusion and provides the therapist with precise information about the patterns present.

The association of one cell pattern with another usually affects the clinical behavior, treatment, and prognosis of the tumor. Dixon and Moore have shown that seminoma in association with embryonal carcinoma or teratoma has no effect on prognosis although it may affect the mode of therapy. On the other hand, the presence of embryonal carcinoma with teratoma, and the presence of choriocarcinoma with either embryonal carcinoma or seminoma does affect the prognosis.

The most important of these combinations is that in which teratoma occurs with embryonal carcinoma, with or without other elements. Its frequent occurrence justifies a more detailed discussion.

Figure 62
MALIGNANT TUMOR OF TESTIS
(Figures 62—66 from same case)
Cut section of a huge testicular tumor with cystic and necrotic areas. Note the atrophic contralateral testis.
Tumors of the Testis

Figure 63
TERATOMA WITH MALIGNANT AREAS
(Figures 62—66 from same case)
This low power view of the tumor in figure 62 shows sheets of spindle and undifferentiated cells. X90.

Figure 64
TERATOMA WITH MALIGNANT AREAS AND SPERMATOCYTIC SEMINOMA
(Figures 62—66 from same case)
This higher power view shows undifferentiated areas. X450.
Figure 65
TERATOMA WITH MALIGNANT AREAS AND SPERMATOCYTIC SEMINOMA
(Figures 62—66 from same case)
This higher magnification from another area shows spindle-shaped cells. X450.

Figure 66
TERATOMA WITH MALIGNANT AREAS AND SPERMATOCYTIC SEMINOMA
(Figures 62—66 from same case)
Another area of the large tumor represents spermatocytic seminoma. X450.
EMBRYONAL CARCINOMA WITH TERATOMA, WITH OR WITHOUT OTHER ELEMENTS

SYNONYMS AND RELATED TERMS: Teratocarcinoma; Group IV tumor; malignant teratoma, intermediate A or B; malignant teratoma trophoblastic; combined tumor.

DEFINITION. This is a tumor of germ cell origin in which at least two distinct histologic patterns are identified, one of which is embryonal carcinoma and the other teratoma. Areas of seminoma, infantile embryonal carcinoma, and/or choriocarcinoma may also be present. It is preferable to list exact components in their order of predominance.

INCIDENCE. The incidence rate varies from 14 to 32 percent of testicular tumors.

CLINICAL COURSE. The tumor is usually seen during the third decade, but may be observed earlier. Testicular enlargement and pain are the chief symptoms, but about 20 percent of patients present with symptoms referable to metastases.

GROSS. The testis is usually enlarged; this tumor is the largest of all testis tumors at the time of detection and has an average volume of 85 cc. in adults (fig. 61). Cut surfaces show cystic teratoma and solid areas, usually with some hemorrhage and necrosis. The testis is often replaced entirely by the tumor.

MICROSCOPIC. In addition to areas of embryonal carcinoma, there are one or more definite areas of teratoma. This group of tumors is distinguished from teratomas in which definitely malignant, spindle-shaped cells are observed (teratoma with malignant areas), or from the rare teratoma with squamous or mucous adenocarcinoma. Not infrequently, embryoid bodies in some stage of development may be encountered.

METASTASIS. Based upon autopsy studies, these tumors metastasize principally as embryonal carcinoma (80 percent). However, choriocarcinoma and teratoma may be seen in 30 percent and 40 percent of cases, respectively. Metastases are through the lymphatic vessels and the blood stream to the preaortic lymph nodes in 92 percent of cases; each lung, 80 percent; liver, 70 percent; brain, 40 percent; and pleura, 33 percent.

NATURAL HISTORY OF GERM CELL TUMORS

INCIDENTAL AND EARLY TESTICULAR TUMOR IN MAN. Routine autopsy examination rarely discloses an incidental testicular tumor, because this tumor is rare and the testis is seldom minutely examined. Painstaking examination of testes in fetuses, infants, children, adolescents, and young adults, similar to those of Stevens in mice, would be valuable.

Intratubular seminoma (fig. 6) has long been recognized as an early stage in the development of testicular tumor both in man and in the dog. We have also seen intratubular embryonal carcinoma (figs. 72, 73) and one intratubular formation suggesting early syncytiotrophoblastic cells (pl. II-A). No record of such an early stage of teratoma in man has been made.

Some years ago, we described certain cells in the seminiferous tubules of patients with testicular tumors. These cells were basally located. They had hyperchromatic
nuclei, vacuolated cytoplasm, and occasional mitoses (figs. 67, 68). We considered these cells to be the earliest undifferentiated, multipotential, neoplastic germ cells capable of developing into any one of the histologic patterns of germ cells in the primary or the metastatic tumor. These cells have considerable invasive potential; in some cases they may be found in the interstitium and even in the lymphatic and vascular spaces. Bunge and Bradbury confirmed the role these cells may play in the development of testicular seminoma. In a 27 year old man studied for fertility potential, testicular biopsy showed defective spermatogenesis. When the patient returned three years later, there was a left testicular mass and evidence of retroperitoneal lymph node metastases; left orchiectomy revealed a seminoma. Several sections of tumor from the original left testis biopsy showed hyperchromatic cells located in a single seminiferous tubule, extending into the interstitium. We have seen similar cells in relationship to seminoma, embryonal carcinoma (figs. 72, 73), teratoma, and choriocarcinoma (fig. 8).

ROUTE, DISTRIBUTION, AND NATURE OF METASTASES. Based on selected data from autopsies, seminoma tends to have a wider lymphatic distribution, while choriocarcinoma spreads principally through the blood vessels; embryonal carcinoma and teratoma spread both through the lymphatics and the blood vessels.

Sites of metastases in order of most to
least frequent occurrence are: preaortic, iliac, mediastinal, and supraclavicular lymph nodes; liver; lungs; pleura; kidneys; intestinal tract; peritoneum; and bones of the trunk.

The histologic features of the metastatic tumor are usually the same as those of the primary tumor. However, the two may be different and more than one histologic type may be seen (Dixon and Moore).

Pure choriocarcinoma invariably metastasizes as choriocarcinoma. Dixon and Moore reported the following statistics: Embryonal carcinoma usually metastasizes as embryonal carcinoma (96 percent), but occasionally it may metastasize as teratoma and choriocarcinoma (8 and 5 percent, respectively). Seminoma may metastasize as seminoma (65 percent), embryonal carcinoma (25 percent), choriocarcinoma (9 percent), and teratoma (4 percent). Teratoma may metastasize as embryonal carcinoma (63 percent), teratoma (63 percent), and choriocarcinoma (25 percent). Teratocarcinoma may metastasize as embryonal carcinoma (80 percent), teratoma (42 percent), and choriocarcinoma (30 percent). We have not seen any metastatic tumor from simple epidermal cysts.

Tumor with a single cell type in the primary site may show two or more different histologic variants in the metastatic tumor. In the liver, the lungs, and the kidney, metastases may be choriocarcinoma, while in the lymph nodes, they may be teratoma or embryonal carcinoma.

There are three explanations for the discrepancy between the histologic features of the primary tumor and those of the metastatic tumor: (1) Possibly, a small focus was missed in the primary tumor; (2) the primitive, multipotent, malignant germ cell may have developed into one or the other type in the testis, while the same cell type carried to distant sites developed into one or more histologic variants; or (3) the environment may have affected the histologic characteristics of the metastatic tumor. Indeed, Pierce observed that murine embryonal carcinoma transplanted into the peritoneal cavity yielded thousands of embryoid bodies, while in subcutaneous transplants, it developed into teratomatous growth with many types of tissue (Pierce; Stevens). To date, no such correlation of histologic type with the site of growth has been reported in man.

The lymphatic spread of testicular neoplasm is variable, depending upon the side involved. The most common sites of lymphatic drainage from the right testis are to the paraaortic, preaortic, interaortocaval, preaortic, right common iliac, and right external iliac (proximal) nodes. The most common sites of lymphatic drainage of the left testis are to the paraaortic, preaortic, left common iliac, and left external iliac nodes. Metastases were confined to ipsilateral nodes in 85 percent of right side tumors and 80 percent of left side tumors; they were in both ipsilateral and contralateral nodes in 18 percent of right side tumors and 20 percent of left side tumors. Only one right side tumor presented metastasis in the contralateral node (Ray et al.). From retroperitoneal lymph nodes, the spread is to the thoracic nodes, and thence through the thoracic duct to the left supraclavicular node and the subclavian vein. Accessory lymph channels may also deposit tumor cells in the mediastinal lymph nodes (Whitmore).

Inguinal metastases occur most frequently in patients with prior scrotal surgery. Miller and Seljeld, however, reported that 4 of 7 patients with inguinal metastases had no prior surgery, and the inguinal manifestation occurred without involvement of the pre-
TREATMENT

Initial treatment for testicular germ cell tumors is inguinal orchiectomy, with complete removal of the spermatic cord and the contents of the inguinal canal and testis in its intact tunic. This is essential for prevention of local recurrence. Dean reported a 24 percent recurrence in 63 patients who had simple orchiectomy. In our experience, local recurrence has been limited almost entirely to those patients who had biopsy or simple orchiectomy. Orchiectomy is often performed, even when there is clinical evidence of metastases.

Inguinal orchiectomy has resulted in a 5-year survival rate of 56 percent for seminoma and 32 percent for embryonal carcinoma (Whitmore). Regrettably, no technic yet exists to differentiate clinically between the curable tumors and those that have already spread subclinically to become manifest at a later date.

Subsequent therapy is designed to prevent, remove, destroy, or control metastases; ideally, it should be restricted to those tumors which have already metastasized or eventually will metastasize. Since clinically, however, the tumors cannot be accurately or reliably staged, and since all germinal tumors may metastasize to retroperitoneal lymph nodes, almost all patients with testicular germinal tumors are given further prophylactic or curative therapy. The specific treatment is dictated by the clinical stage and histologic characteristics of the tumor. It includes surgery such as retroperitoneal lymph node dissection and/or removal of a single metastasis, radiation therapy, and/or chemotherapy. Retroperitoneal lymphadenectomy is the routine treatment for all germ cell tumors except seminoma and choriocarcinoma. Radiotherapy is the treatment of choice for seminoma, and if metastatic, supplementary chemotherapy is used. Chemotherapy is currently being used for choriocarcinoma, but has not been very successful. For embryonal carcinoma and teratoma, retroperitoneal lymph node dissection is performed; if metastatic tumor is found, chemotherapy is used. For a single metastatic tumor or one which does not respond to radiation, surgical removal is advocated.

COMPLICATIONS OF SURGERY. The most frequent complication from retroperitoneal lymphadenectomy is ejaculatory impotence, which frequently results from removal of L1 sympathetic ganglia on each side or damage to the sacral plexus or nervi erigentes. This problem may be resolved by avoiding the common iliac artery (Leadbetter). Rarely, a vascular accident involving the inferior vena cava or the aorta may complicate the procedure.

COMPLICATIONS OF RADIATION THERAPY. In addition to the usual symptoms manifested by patients treated by prophylactic radiation, other serious complications have been reported. An amazingly high incidence of radiation nephritis has been reported from Manchester, England in patients with seminoma given prophylactic radiation. This complication resulted from inclusion of the kidneys within the radiation field and high doses of radiation (Mostofi).

In the United States, death from radiation nephritis in patients with seminoma is surprisingly rare. In the 17-year follow-up of patients of Dixon and Moore, Nefzger and Mostofi found a high incidence of cardio-
vascular disease, but only six cases of radiation nephritis. Such favorable results have been attributed to exclusion of the kidneys from the radiation field. However, it should be emphasized that many, if not all patients who received radiation treatment for testicular tumor have shown varying degrees of radiation-induced damage to the kidneys even though death may result from other causes (Mostofi). Other complications of radiation are nutritional deficiency (secondary to gastrointestinal and pancreatic fibrosis and cirrhosis of the liver), pulmonary fibrosis, and anemia.

Several osteosarcomas of the soft parts were noted in patients with testicular tumor who were treated prophylactically by radiation. The earliest occurred four years after radiation. We have seen only one case of leukemia, which occurred more than 17 years after exposure. Little information is available on the frequency of impotence in patients treated by radiotherapy.

COMPLICATIONS OF CHEMOTHERAPY. Complications of chemotherapy for germinal testicular tumor are similar to those for other neoplasms. One patient with choriocarcinoma died from massive hepatic necrosis; very little viable tumor could be identified at autopsy.

PROGNOSIS

Spontaneous regression of testicular tumors rarely occurs and has been detected only in those patients with generalized metastases.

The tunica albuginea constitutes a natural barrier to local extension of the tumor. In our experience, local extension occurs in areas in which the vessels, nerve, rete testis, and cord penetrate the tunic; when the integrity of the tunic has been compromised by needle or open biopsy or by orchiopexy; or when there has been simple orchiectomy.

Almost 90 percent of deaths of patients treated for testicular tumor occur within two years after onset; almost all deaths occur within six years. In the 17-year follow up (Table IV) of 834 patients originally reported by Dixon and Moore, Nefzger and Mostofi found that only two patients died of metastases after six years. Fifteen patients died of another (extratesticular) primary tumor; the shortest survival was 4 years, 11 months after orchietomy and the longest was 16 years, 9 months. One patient in this group died 11 years, 2 months postorchiectomy from malignant tumor involving the lungs, lymph nodes, and skeleton; another patient died 16 years, 1 month postorchiectomy from malignant tumor involving the right lower abdomen. We were unable to examine the slides, and although we believe these were independent tumors, it is possible they may have been delayed metastases of 10 to 20 years' duration. Our studies show that 81 percent of patients who survived for two years were still living after 15 years (Nefzger and Mostofi). Rarely, however, a patient, especially one with seminoma, may manifest evidence of metastasis 5, 10, or 20 years after orchietomy. In such patients, the opposite testis should be carefully examined.

A number of clinical and pathologic observations are helpful in prognostication of testicular tumors. The most important of these are: extent of the tumor at the time of first examination, e.g., extension into epididymis or metastases; its histologic structure; location of the tumor in the testis; its hormone secretion; and the mode of therapy. Prognosis is more favorable for those patients whose tumors are: (1) confined to the testis, particularly if they are peripherally located and do not involve the hilum, the rete, or the
epididymis; (2) typical or spermatocytic seminoma, epidermal cyst, or mature teratoma; (3) seminoma that shows lymphoid or granulomatous reaction; and (4) without evidence of hemorrhage or vascular invasion. Prognosis is also better for patients in whom chorionic gonadotropins are negative and the Leydig cells do not show hyperplasia in the uninvolved portion of the testis (Table III).

Good prognosis may be expected for infants and children, for patients with painless enlargement of the testis, and for those with short-term symptoms. A poorer prognosis is associated with rapid onset and progression of symptoms. White children have a more favorable prognosis than Black children. Patients with tumors less than 2 cm. in size (except choriocarcinoma) and those without gynecomastia also have a good prognosis.

Table III

PROGNOSTIC FACTORS IN GERM CELL TUMORS*  
Percent of Patients with Operable Tumors  
Dying within 2 Years of Operation

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Overall mortality</th>
<th>Pain</th>
<th>Metastasis at first examination</th>
<th>Local extension</th>
<th>Preoperative urinary gonadotropins</th>
<th>Lymphoid stroma and/or granulomatous reaction</th>
<th>Vascular invasion</th>
<th>Leydig cell hyperplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seminoma</td>
<td>6.4</td>
<td>10</td>
<td>4</td>
<td>32</td>
<td>6</td>
<td>20</td>
<td>4</td>
<td>15</td>
</tr>
<tr>
<td>Teratoma with or without seminoma</td>
<td>26.1</td>
<td>40</td>
<td>18</td>
<td>93</td>
<td>9</td>
<td>57</td>
<td>15</td>
<td>4</td>
</tr>
<tr>
<td>Teratoma with embryonal carcinoma and/or choriocarcinoma and with or without seminoma</td>
<td>47.9</td>
<td>84</td>
<td>41</td>
<td>70</td>
<td>43</td>
<td>69</td>
<td>47</td>
<td>69</td>
</tr>
<tr>
<td>Embryonal carcinoma with or without seminoma</td>
<td>58.7</td>
<td>68</td>
<td>47</td>
<td>92</td>
<td>46</td>
<td>82</td>
<td>85</td>
<td>50</td>
</tr>
</tbody>
</table>

### Table IV

<table>
<thead>
<tr>
<th>Tumor Type*</th>
<th>Initial Number</th>
<th>Alive 2 years after treatment</th>
<th>Alive 17 years after treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Percent</td>
<td>Number</td>
</tr>
<tr>
<td>Seminoma alone</td>
<td>316</td>
<td>291</td>
<td>92.1</td>
</tr>
<tr>
<td>Teratoma alone (59) or with seminoma (15)</td>
<td>74</td>
<td>53</td>
<td>71.6</td>
</tr>
<tr>
<td>Teratoma with either embryonal carcinoma (199) or choriocarcinoma or both and with or without seminoma</td>
<td>273</td>
<td>137</td>
<td>50.2</td>
</tr>
<tr>
<td>Embryonal carcinoma alone (123) or with seminoma (42)</td>
<td>165</td>
<td>65</td>
<td>39.4</td>
</tr>
<tr>
<td>Choriocarcinoma alone (3) or with either embryonal carcinoma or seminoma or both</td>
<td>6</td>
<td>1</td>
<td>16.7</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>834</strong></td>
<td><strong>547</strong></td>
<td><strong>65.6</strong></td>
</tr>
</tbody>
</table>

*Numbers in parentheses refer to number of cases in each category. Adapted from Table 2 in Nefzger, M. D., and Mostofi, F. K. Survival after surgery for germinal malignancies of the testis. Cancer 30:1225-1232, 1972.*
The effects of therapy are difficult to assess, but it appears that patients who had biopsy or those who had simple orchietomy have a less favorable course than those treated without biopsy or those with inguinal orchietomy. Resection in patients with clinically solitary metastases improves the prognosis.

Patients with seminoma who have granulomatous and/or lymphoid reaction in their tumor, those who have proper radiation treatment, and patients with embryonal carcinoma, teratoma, and teratocarcinoma with metastases who are treated by radical surgery have a better chance of survival than those treated by radiation.

Of course, all the foregoing factors are statistical and it is impossible to give an exact prognosis for individual patients.

**TUMOR IN CRYPTORCHID TESTIS**

We have already discussed the role of incomplete descent of the testis in the development of testicular tumor and the high incidence of testicular tumors in cryptorchid testis, together with their clinical signs and symptoms (see pages 8 and 11).

Seminoma is the most frequent cell type in undescended testicular tumor; however, embryonal carcinoma and teratoma either in pure form or with choriocarcinoma have also been seen.

**BILATERAL GERM CELL TUMORS**

Controversy exists over the frequency of bilateral—simultaneous or successive—testicular tumors. Collins and Pugh found 24 such tumors in their study of 995 testicular tumors; however, 13 were malignant lymphomas initially manifested as testicular tumor which should be excluded in any discussion of bilateral primary testicular tumor. We have found an incidence rate of one percent bilateral tumors in our material. In about one third of the cases, the tumors were simultaneous; in others, they were consecutive with a time interval ranging from 3 to 15 years. In those cases with bilateral tumors, seminoma was present in both testes in 75 percent of cases; in the remainder, seminoma occurred in one testis and embryonal carcinoma with teratoma occurred as the other tumor.

While the possibility of metastasis from one testis to the other cannot be entirely excluded, especially if the tumors are simultaneous, the low incidence of bilateral testis tumor tends to exclude this hypothesis and suggests independent origin of each tumor.

Discussion of the frequent occurrence of bilateral Leydig cell tumors and testicular malignant lymphoma in which there is a much higher incidence of bilateral involvement appears on pages 98 and 131, respectively.

**EXTRAGENITAL GERM CELL TUMORS**

The majority of tumors of the types described in this fascicle as originating from germ cells arise in the genital organs of both sexes. Careful studies have revealed that such tumors do occur in a number of extragenital sites and this forms the subject of another fascicle on Extragenital Teratomas and Related Lesions, in preparation, replacing the former fascicles on the subject which are now out of print.

It is interesting that germ cell tumors do not arise more frequently in extragenital sites. Conceivably, such tumors could arise
from somatic cells, since somatic cells carry
the same complement of genetic information
as germ cells. The tendency for such
extragenital tumors to arise in the midline
suggests that germ cells may have been
detained enroute in their embryologic
journey from the primitive yolk sac to the
germinal region which forms the gonad
(Mintz and Russell).

Such extragenital tumors are more the
exception than the rule and, therefore,
tumors of germ cell type discovered in other
sites are always suspect as metastatic from
the gonad. Certainly a primary source in the
testis or ovary must be excluded.

"BURNED OUT" TESTICULAR TUMOR

Discovery of an apparent extragenital
choriocarcinoma, embryonal carcinoma,
teratoma, or seminoma usually provokes
much discussion and pontification. Careful
and thorough examination of the testis has
revealed that some of these lesions repres-
ent metastases from regressed primary
testicular tumor. The frequency of occur-
rence of these testicular lesions before
metastases are manifest is unknown. Unless
there are secondary manifestations, testi-
cular lesions are likely to be overlooked,
because few testes are carefully examined at
autopsy. Not infrequently, identical lesions
are seen in tumor-bearing testes; we found
none, however, in the testes of patients with
mediastinal teratoid tumor, those with mali-
gnant disease of other types, or those who died
from accidents.

A well defined fibrous scar in the testis
consisting of relatively acellular, usually
dense, but sometimes loose, collagenous
tissue is diagnostic of this lesion; it often con-
tains ghostlike remnants of hyalinized semi-
niferous tubules, hemosiderin deposits (fig.
69), scattered plasma, and mast cells. The
irregular, rounded, elongated, stellate, or
linear scar is usually located near the rete
testis (pl. I-F), but rarely at the pole.

Frequently, peculiar hematoxyphilic
deposits (fig. 70) are present. These occur as
sharply rounded or oval foci, separated from
each other by a basement membrane and
intervening scar tissue. The deposits have an
amorphous, granular, unorganized structure
sometimes appearing as large irregular frag-
ments in a homogeneous matrix.

Histochemical reactions indicate that
hematoxyphilic bodies are composed of a
complex mixture of phospholipids, protein,
and scanty 1-2 glycol groups in combination
with DNA. Some also contain mucino-
caimorphinophilic material and calcium phos-
phate, but calcium per se is not an essential
part of the complex. Hematoxyphilic body-
containing spaces are seminiferous tubules
and not vascular or other spaces (Azzopardi et
al.).

In a few instances, viable malignant neo-
plastic cells are seen within tubules often
associated with hematoxyphilic bodies.
These cells do not have the sharp outline nor
the cytologic characteristics of intratubular
seminoma, but are typical of embryonal carci-
noma (figs. 72, 73).

In addition to scar and hematoxyphilic
bodies that are suggestive of a previous
tumor, two elements are often seen near the
scar. The most frequent is a distinct tera-
tomatous element that consists of epidermal
cysts and mucous and nonmucous epithelial
cysts (fig. 71) with or without smooth muscle
in their walls. Less frequently, seminoma-
tous foci are found that rarely comprise more
than a fraction of a high power field.

We believe that the scar and hematoxy-
philic bodies indicate necrosis of preexisting
germ cell tumor and justify the diagnosis of
"burned out" primary testicular neoplasm.
Figure 69
TESTICULAR SCAR AND OLD HEMORRHAGE
The area of scar in the testis shows a massive deposit of iron representing a burned out testicular tumor. X165.

Figure 70
TESTICULAR SCAR AND SEMINOMA
This photomicrograph reveals hematoxyphilic bodies in some of the seminiferous tubules. The small nest of tubules in the right lower corner is filled by intratubular seminoma. X50.
Tumors of the Testis

Figure 71
TESTICULAR SCAR AND TERATOMA
Note the residual teratoid structures in association with scar and hematoxyphilic bodies. X20.

Figure 72
EARLY TESTIS TUMOR
A single focus in the testis shows a number of seminiferous tubules filled with tumor cells. X80.

Figure 73
EARLY TESTIS TUMOR
This higher magnification shows intratubular embryonal carcinoma cells. X210.

References
Bawden, D., Hockley, A., and Key, H. E. Urinary 17-


Pugh, R. C. B. Personal communication, 1971.


TUMORS OF SPECIALIZED GONADAL STROMA

In the introduction to this fascicle, we theorized that even though there is not total agreement among embryologists that Leydig, Sertoli, granulosa, and theca cells have a common origin, the frequent occurrence of tumors showing combinations of these cell types can best be explained on the basis of their origin from the primitive gonadal stroma or mesenchyme. The terms primitive gonadal stroma and gonadal stromal tumor are used in preference to mesenchyme and mesenchymoma because the latter have been applied to certain tumors of soft tissue.

Oncogenetic potentialities of this cell type may be manifested in either gonad as differentiated Leydig cell tumor, Sertoli cell tumor, granulosa cell tumor, undifferentiated gonadal stromal tumor, or an admixture of any of these types.

Most of the tumor can be readily identified as pure Leydig cell tumor, pure Sertoli cell tumor, or granulosa cell tumor; the remainder consists of spindle-shaped, theca-like cells (the gonadal stromal tumor), or an admixture of two or more of these cell types. Leydig cell tumor will be discussed as a separate entity, but the other rare types will be discussed together because of their clinical similarity (Table V).

Table V

PATHOLOGIC CLASSIFICATION

<table>
<thead>
<tr>
<th>TUMORS OF SPECIALIZED GONADAL STROMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leydig cell tumors</td>
</tr>
<tr>
<td>Sertoli, granulosa-theca cell tumors</td>
</tr>
<tr>
<td>Undifferentiated or primitive tumors</td>
</tr>
<tr>
<td>Combinations of above</td>
</tr>
<tr>
<td>TUMORS SHOWING BOTH GERM CELL AND GONADAL STROMAL ELEMENTS</td>
</tr>
<tr>
<td>Gonadoblastoma</td>
</tr>
</tbody>
</table>
LEYDIG CELL TUMOR

SYNONYMS AND RELATED TERMS: Interstitial cell tumor; interstitial cell adenoma; interstitial cell carcinoma.

DEFINITION. Leydig cell tumor originates from interstitial cells of Leydig and manifests the histologic spectrum of the involution of these cells. It presents variable endocrine symptoms ranging from masculinization in children to feminization or no symptoms in adults.

INCIDENCE. Of 6,000 testicular tumors recorded in the American Testicular Tumor Registry, the incidence of Leydig cell tumor is almost 3 percent. It occurs with almost the same frequency in Caucasians and in Blacks.

SPONTANEOUSLEYDIG CELL TUMOR IN ANIMALS. Spontaneous Leydig cell tumor has been described in dogs; the reported incidence varies from 1 to 100 percent, depending upon the age of the dog and histologic requirements for the diagnosis of the tumor. Most old dogs show hyperplasia, and with advancing age of the dogs the incidence of tumor may reach 80 percent or more. These tumors have also been found in horses, cows, rats, birds, and mice; in the latter, they are transplantable with retention of their hormone activity (Gardner; Dow; Scully and Coffin; Innes; Franks; Narayana et al.).

ETIOLOGY. Why Leydig cell tumor develops is unknown, but the following factors may be involved:

Leydig cells, one of the two normally hormone producing cells in the testis, are under the control of the pituitary, and focal and diffuse hyperplasia and tumors of Leydig cells have been reported in the following endocrine disturbances: Klinefelter's syndrome, Cushing's syndrome, adrenogenital syndrome, and subtotal adrenalectomy—all of which are related to increased pituitary activity—and partial pituitary resection.

While interstitial cell stimulating hormone (ICSH) is elevated in pituitary-induced Leydig cell hyperplasia, ACTH seems to be implicated (Abelson et al.; Hamwi et al.).

Increased levels of human chorionic gonadotropins and estrogens in maternal and fetal blood during pregnancy produce hyperplasia of Leydig cells of the testis in newborn infants. In many germ cell tumors of the testis, marked Leydig cell hyperplasia is attributed to chorionic gonadotropin secretion or to elevated ICSH. At times, hyperplasia is so marked as to simulate a tumor. Atrophy of seminiferous tubules resulting from cryptorchidism, old age, ischemia, infection, trauma, testicular radiation, cirrhosis of the liver, and malnutrition may produce a relative increase in Leydig cells simulating hyperplasia.

In experimental estrogen-induced Leydig cell tumor, evidence supports the hypothesis that the action of estrogens is indirect and mediated through the pituitary.

Of interest is the observation of Pourreau-Schneider and associates who found viral type particles in estrogen-induced and spontaneous Leydig cell tumors in mice.

The high incidence of hyperplasia and tumor of the testis in many old dogs and rats is undoubtedly related to senile endocrine disturbances.

Senility per se results in the development of Leydig cell tumor. Jacobs and Huseby observed Leydig cell tumor in 68 percent of inbred Fisher rats, set aside as nonbreeders, who lived from 495 to 917 days (average 778). Three fourths of the experimentally induced tumors developed bilaterally.

Leydig cell tumor is produced in mice by administration of various estrogenic hormones—estradiol benzoate, stilbestrol, triphenylethylene and tri-p-anisylchloroethylene. For most substances, the response
is strain-limited: A, C, JK, and IFS strains respond, while CBA, C\textsubscript{57}Black, C\textsubscript{3}H, NI, and F strains do not. Tri-p-anisylchloroethylene is almost universally effective (Bonser and Robson; Shimkin et al.; Athias; Gardner and Boddaert).  

Chorionic gonadotropins accelerate the effects of estrogens, and this activity is further enhanced with anterior pituitary-like hormones. Leydig cell nodules develop in monkeys after ICSH administration, and in man after administration of chorionic gonadotropins, pituitary gonadotropins, and pregnant mare serum.

Transplantation of immature testis into the spleen with castration may result in Leydig cell tumor in rats and some mice (Biskind and Biskind; Gardner; Gunn et al.). Radiation also produces Leydig cell tumors in rats as does injection of tissue from leprosy lesions and administration of zinc and cadmium salts.

Metastasis of experimentally induced Leydig cell tumor occurs by way of the lymphatic vessels and the blood vessels and is dependent upon cell type. The more primitive cells are those that may metastasize. The tumor is also transplantable, but its growth is strain and estrogen dependent in males, particularly in the early transplant generations. It grows better in castrated animals. The transplant may persist but remain indolent for from 51 to 204 days and then grow upon administration of estrogens. Once initiated, growth persists after estrogens are discontinued; it persists in hypophysectomized animals, is capable of metastasis, and may kill the host (Hooker and Pfieffer; Shimkin et al.)

CLINICAL SIGNS AND SYMPTOMS. Painless enlargement of the testis or a mass are the most common symptoms in human beings. All children with Leydig cell tumor manifest macrogenitosomia with enlarged penis, pubic hair, deep voice, and hirsutism (fig. 75). Other symptoms include precocious skeletal and muscular development, excessive interest in women, frequent erection without nocturnal emission, and facial acne; in one instance a 2 year old child smoked cigars. Abelson and his associates believe that sexual precocity before puberty is more often associated with congenital adrenogenital hyperplasia and that Leydig cell tumor development is probably due to stimulation with ACTH.

If treatment is delayed until adolescence, premature closure of the epiphysis may occur in children with Leydig cell tumor and result in a short, perhaps dwarfish individual.

In adult patients, 24 to 36 percent have gynecomastia (figs. 74, 76). During the second decade, some young men manifest both macrogenitosomia and gynecomastia, in that order. Other related symptoms include loss of libido and female hair distribution, with or without genital underdevelopment. Reiners and Horn reported a case with increased libido. Interestingly, some patients with malignant Leydig cell tumor and metastasis show an unusual preservation of muscular structure and absence of cachexia.

Symptoms may be present from a few days to five or more years at the time of initial examination; the average duration of 28 months indicates the slow growth of Leydig cell tumor.

ENDOCRINE ACTIVITIES. Information concerning hormonal activity of Leydig cell tumor has been gathered from benign and metastatic tumors in man as well as from experimental and transplantable tumors. Studies have been made of urine and peripheral blood, with or without prior administration of certain hormones, spermatoc vein blood, hormone determination of tissue, and incubation of tumor tissue with various
Figure 74

GYNECOMASTIA

This photomicrograph shows gynecomastia in a fatal case of tumor of the testis. Note the loose, edematous connective tissue within the lobules and hyperplasia of duct epithelium. X100. (Fig. 79 from Fascicles 31b and 32, First Series.)
Macrogenitosomia is seen in a 5 year old boy. Note the large penis. (Fig. 1 from Hertz, R., Cohen, M. I., Lewis, L. G., and Firminger, H. I. Sexual precocity in a 5 year old boy with interstitial-cell tumor of the testis. J. Clin. Endocrinol. Metab. 13:1248-1253, 1953.)

Note enlargement of the breasts.
labeled and unlabeled substances. Spermatic vein blood assays have provided the most reliable data on specific endocrines prior to the effects of peripheral metabolism. Small abnormalities may be detected by this method. Indeed, Smith and associates and Bayer and associates demonstrated androstenedione, 11 beta hydroxyandrostenedione, testosterone, and 17 alpha hydroxyprogesterone in the spermatic vein blood of boys with virilizing testicular tumor which could not be detected in the peripheral blood.

Most studies have been made of the urine or peripheral blood and have shown that 17-ketosteroids are elevated 3 to 6 times normal in primary tumors and 10 to 30 times normal in metastatic tumors (Lipsett et al.; Engel et al.; Wegienka and Kolb; Ward et al.; Baines et al.; Abelson et al.). Individual components that are high include: dehydroepiandrosterone, etiocholanolone, 11 ketoandrosterone, and 11 hydroxyandrostosterone. Elevation of urinary gonadotropins has also been reported.

Direct assays and incubation of homogenates of the tumors with various labeled substances have revealed elevations of tetrahydrocortisone, tetrahydrocortisol, pregnantriol, pregnanediol, 17 hydroxyprogesterone, and estrogens (estril, estrone, and estradiol). The levels decreased after removal of the tumor (Engel et al.; Besch et al.; Inano and Tamaoki; Smith et al.; Baines et al.; Schongut et al.).

These observations have clarified the pathophysiology of Leydig cell tumors and their enzymatic activities. Sometimes, no hormones can be identified; sometimes, only androgenic hormones are found; sometimes androgenic, estrogenic, and progesteronal hormones are found; and, in some tumors, corticosteroids are also demonstrated.

The secretion of corticosteroids and progesterone by a testicular tumor raises serious doubts about the pathologic diagnosis of Leydig cell tumor. Are testicular tumors, which produce progesterone and its derivatives and corticosteroids and their derivatives, truly Leydig cell tumors or are they adrenal rest tumors?

Incubation of transplantable murine Leydig cell tumor—which androgenicity had been demonstrated by the maintenance of secondary sex organs in castrated mice—with various labeled substances has provided strong evidence suggesting that Leydig cell tumor of the testis has the potential to produce not only androgenic and estrogenic hormones but also progesterone and corticosteroids (Abelson et al.; Dominguez and Huseby; Engel et al.; Jacobs and Huseby; Lipsett et al.; Sharma et al.; Schongut et al.; Shin et al.; Besch et al.; Hamwi et al.; Dorfman et al.). In vivo demonstration of such activity is certainly most desirable.

These hormone studies indicate that Leydig cell tumor may possess the following enzyme systems: 11 beta hydroxylase, 17 alpha hydroxylase, 17 beta hydroxysteroid dehydrogenase and 11 beta hydroxysteroid dehydrogenase, cortisol-C11-C20 lyase 4-5 beta hydrogenase, 3 alpha hydroxysteroid dehydrogenase, and 17 alpha hydroxypregnene-C17-C20 lyase (Dominguez and Huseby; Inano et al.; Savard et al.; Smith et al.; Engel et al.; Lipsett et al.; Sharma et al.). The 11 beta hydroxylation of both C19 and C21 steroids seen in human testis tumors is not seen in fetal or adult testes (Engel et al.; Axelrod; Slaunwhite et al.; Acevedo et al.). This is the only instance in testicular tumors in which a neoplasm produces an enzyme not usually present in nonneoplastic tissue. The 11 beta hydroxysteroid dehydrogenase activity is present in cell free homogenates of mouse Leydig cell tumors as shown by conversion of 11 deoxycorticisol to cortisone by way of cortisol (Acevedo et al.; Inano and Tamaoki).
Correlation of diverse histologic patterns in the primary tumor with multiple endocrine manifestations would seem to be rewarding, but all we know for certain is that the spindle cell type probably does not produce any hormones (Shin).

Macrogenitosomia and other masculinizing symptoms in children are readily explained on the basis of androgens produced by the tumor. The absence of such androgenic manifestations in adolescents is explained on the basis of homeostasis. In a few older patients, we have noted maintenance of active sexual activity, but whether this bore any relationship to the tumor could not be determined.

Gynecomastia in adults may be due to estrogen production by tumor cells. Melicow credits Ruben as being the first to show gynecomastia and testicular tumor in his painting of a Kafir. Possibly, androstenedione, which has a low androgenicity, is produced by the tumor and is readily aromatized. It is metabolized to estrogens at the target organ, the breast, which is stimulated, but no increase in blood or urine estrogens are detected (Pierrepoint et al.; Brogard et al.).

Even with exceedingly high steroid secretion, there may be a surprising absence of endocrine symptoms which is perhaps related to the potency of the hormones.

GROSS. Although Leydig cell tumor is usually unilateral, 5 to 9 percent are bilateral. The latter type may be indicative of adrenogenital syndrome. The testis may be diffusely enlarged or may show one or more nodules; both sides are about equally involved. The tumor may vary from less than 1 cm. to more than 10 cm. in size. It is generally soft, but is sometimes quite firm or even hard. It is usually lobulated and may appear encapsulated. Cut surfaces are homogeneously yellow to mahogany-brown and bulging (pl. I-D). Areas of hyalinization and even calcification may be seen, but hemorrhage and necrosis are rare; their presence should increase suspicion of malignant tumor.

MICROSCOPIC. Leydig cell tumor presents a surprising variation in histologic characteristics that can best be understood if one realizes that these neoplasms recapitulate the normal development and evolution of Leydig cells. The histologic features of Leydig cell tumor in man are essentially the same as the spontaneous and induced tumors in animals. Generally, four types of cells can be recognized. The most common are medium-sized hexagonal cells (fig. 77). They have indistinct cell boundaries with eosinophilic or vacuolated cytoplasm surrounding a regular round or oval vesicular nucleus, with a delicate chromatin and one small basophilic

![Figure 77](image_url)

**LEYDIG CELL TUMOR**

The neoplasm consists of fairly uniform cells with ground glass eosinophilic cytoplasm and round nucleus. X250.
nucleolus (fig. 78). Occasional large but regular nucleated cells, binucleated cells, or multinucleated cells are present (fig. 79). Some cells contain brown pigment (lipofuscin).

The cells may occur in cords, fascicles, islands, and nests, but generally they have a distinct endocrine pattern of vascularity (figs. 80, 81). Each cell is often enmeshed in a delicate reticulin. The stroma is usually delicate, but may show varying degrees of hyalinization (fig. 82) and even calcification. Leydig cell tumor is usually encapsulated, but the tumor cells may merge into the surrounding parenchyma.

The histologic features of Leydig cell tumor in man are essentially the same as the spontaneous and induced tumors in animals.

The most pathognomonic feature of Leydig cells is Reinke’s crystals. This cigar-shaped cytoplasmic inclusion of varying size is quite elusive with hematoxylin and eosin stain (pl. II-B); it is best demonstrated by Masson trichrome, PTAH, and Mallory’s iron hematoxylin stain. We have seen Reinke’s crystals in about 40 percent of the tumors. In addition to good fixation and a careful search, luck or chance seem to play an important role in locating them. Although Tillinger and associates related these crystals to the secretion of male sex hormones, no evidence of any functional activity of the crystals, which are believed to be protein, has been presented to date.
Ashbel and Seligman's 17-ketosteroid and estrogen histochemical reactions are sometimes positive; however, the reactions are nonspecific.

Figure 80
LEYDIG CELL TUMOR
(Figures 80 and 81 from same case)
The tumor forms broad sheets of cells which have vacuolated cytoplasm in the center, but cells at the periphery form cords and have dense eosinophilic cytoplasm. X100.

Figure 81
LEYDIG CELL TUMOR
(Figures 80 and 81 from same case)
This is another area of the tumor shown in figure 80. The cells are small and dark staining. X75.

Figure 82
LEYDIG CELL TUMOR
Note extensive hyalinization of the stroma. X75.
While the foregoing describes the histologic features of the most common cell type, three other types may be encountered in Leydig cell tumors. Most frequently, the cells are large, finely or coarsely vacuolated, and contain lipids (fig. 78). Some tumors may consist of small hyperchromatic cells, and still others of elongated spindle-shaped cells with eosinophilic and granular cytoplasm (fig. 83). The nuclei may vary from small to large, round to oval or spindle-shaped, vesicular to pyknotic. At times, very small or slender dark cells may be encountered.

Ultrastructurally, the tumor cells contain abundant SER (fig. 84) and resemble normal cells, except that mitochondria are more frequent (Dadoune et al.).

**DIFFERENTIAL DIAGNOSIS**.

Hyperplasia versus Tumor: Marked hyperplasia may simulate tumor, especially in cases in which the tumor begins as foci of hyperplasia that coalesce to form tumor. Hyperplasia is usually diffuse and not focal, imparting to the testis a mahogany-brown color and increased consistency with no discrete nodules. Microscopically, the hyperplastic cells fill and distend the preexisting intertubular spaces without destroying or displacing the tubules which usually show atrophy (fig. 85).

In advanced stages, the existence of testicular stroma between nodules of Leydig cells, the presence of widely separated tubules in a sea of Leydig cells, and the absence of compressed testicular tissue at the periphery of the nodules are helpful diagnostic aids in distinguishing between hyperplasia and tumor. It is probably a tumor if there is a distinct mass of Leydig cells with no seminiferous tubules in the mass and there is some compression of the tissue at the periphery. At times, the advancing edge of a solid tumor may have the appearance of hyperplasia with tumor cells separating seminiferous tubules.

Benign versus Malignant Tumor: Variation in size, shape, and staining of the cells and nuclei and the appearance of double or multiple nuclei may arouse suspicion of malignancy in Leydig cell tumors. While such features may be evident in many tumors, less than 20 acceptable cases of malignant Leydig cell tumor have been reported. The actual incidence of malignant tumor in our cases is about 10 percent. This corresponds to 15 accepted cases in 150 Leydig cell tumors reported to date. The most reliable local evidence of malignancy is increased mitotic activity (fig. 86), extension to the tunica and appendages, and invasion of vascular spaces.
This cytoplasm of a neoplastic cell is representative of those in virilizing Leydig cell tumor from the testis of a 7 year old boy; Golgi bodies (g) blend with numerous profiles of vesicular smooth endoplasmic reticulum. Many inclusions are scattered throughout the cytoplasm; pleomorphic dense body (p); membrane bound inclusions (arrow); mitochondria (m) with arrangement of cristae typical of steroid secreting cells; nucleus (n). X16,500. (Fig. 87 from Beals, T. F., Pierce, G. B., and Schroeder, C. F. The ultrastructure of human testicular tumors. I. Interstitial cell tumors. J. Urol. 93:64-73, 1965.)

(87). However, since Leydig-like cells are normally present along the spermatic cord (fig. 88), especially in relation to the nerve bundles, their appearance in such locations should not in itself cause suspicion of malignancy. Presence of tumor cells in lymphatics and blood vessels is rare in malignant Leydig cell tumor and their appearance should immediately suggest the possibility of a metastatic carcinoma. Only when this is eliminated, can the diagnosis of malignant Leydig cell tumor be considered. This tumor should be carefully examined for the presence of glandular and acinar structures. A helpful diagnostic aid is the presence of Reinke's crystals (pl. II-B).
HYPERPLASIA OF LEYDIG CELLS

Stroma is uniformly distended by closely packed Leydig cells. The tubular atrophy evident here may be, but is not always associated with hyperplasia of Leydig cells X125. (Fig. 82 from Fascicles 31b and 32, First Series.)

MALIGNANT LEYDIG CELL TUMOR

(Figures 86, 87, and 89 from same case)

This tumor is somewhat more anaplastic than the usual Leydig cell tumor. X350.
Figure 87
MALIGNANT LEYDIG CELL TUMOR
(Figures 86, 87, and 89 from same case)
Note the vascular invasion in this photomicrograph of the tumor shown in figure 86. X40.

Figure 88
EXTRATESTICULAR LEYDIG CELLS IN SPERMATIC CORD
Masses of Leydig cells such as these are frequently incidental findings along nerves and vessels of spermatic cord. The absence of fascicular arrangement of cells and presence of crystalloids aid in differentiation from adrenal cortical rests. X185. (Fig. 83 from Fascicles 31b and 32, First Series.)
Our experience confirms that of Warren and Olshausen, and Masson that the most reliable criterion of malignant Leydig cell tumor is the demonstration of metastasis (fig. 89). Two factors, however, limit this observation: (1) Metastasis usually develops several years after the appearance of the primary tumor, although occasionally this may occur within two years; and (2) the presence of a tumor in the testis and in the retroperitoneal lymph nodes and viscera does not necessarily indicate a malignant Leydig cell tumor inasmuch as a secondary carcinoma can give this picture. Demonstration of Reinke's crystals is helpful, but we have found none in any metastatic tumor. The demonstration of hormonal activity in conjunction with clinical and pathologic findings is the most reliable criterion of metastatic Leydig cell tumor.

Leydig Cell Tumor versus Adrenal Rest Tumor: Histologic differentiation between Leydig cell tumor and adrenal rest tumor may be difficult. Adrenal rests usually occur on the surface of the spermatic cord or in the region of the rete testis, not in the substance of the testis; they are usually encapsulated. Most adrenal rests have tissue orientation into at least two zones; the cells occur in cords, and the nuclear pattern is somewhat different (fig. 90). Adrenal cortical cells are usually smaller. The nuclei vary moderately in size and shape, but the nuclear chromatin distribution is fairly characteristic with a very thin
and delicate nuclear membrane surrounding a vesicular nucleus and two or three fine particles. In contrast, Leydig cell nuclei are less vesicular and usually have one small nucleolus. Demonstration of Reinke’s crystals may provide a more reliable basis for differentiation, but not all Leydig cells show crystals. Baines and associates’ claim that fractionation of urinary 17-ketosteroids can distinguish the two has not been confirmed; the diverse endocrine activity of Leydig cell tumor raises doubts of the practicability of hormone assays.

Tumors occurring in the substance of the testis should generally be considered of Leydig cell origin. However, it should be noted that adrenal cortical cells and Leydig cells have a common cell of origin, a close histologic appearance, and similar endocrine functions—under certain conditions, adrenal cortical cells produce increased androgenic substances, and on occasion, Leydig cells are said to produce corticosteroids.

**Leydig Cell Tumor versus Tumors of Sertoli Cells Simulating Luteinized Cells:** The term “luteinized” is used solely to indicate histologic similarity to the process seen in theca granulosa cells when the cytoplasm assumes a ground-glass eosinophilic character.

Differentiation between these two tumors may be quite difficult. Sertoli cells are usually intratubular. The tumor is usually biphasic or multiphasic, with areas of interlacing spindle cells or distinct Sertoli cells; Reinke’s crystals are absent, and the cells are usually larger than Leydig cells.

**Leydig Cell Tumor versus Metastatic Carcinoma:** Metastatic carcinoma usually involves the interstitium, and tumor cells that have eosinophilic cytoplasm may simulate those of Leydig cell tumor. In our experience, metastatic carcinomas usually are more pleomorphic, form acini or glands, and have a different nuclear pattern. Also, there are usually tumor cells in vascular spaces, in the tunica, and/or in the hilar or adnexal structures. When these features are present, a metastatic carcinoma is the probable diagnosis.

**Leydig Cell Tumor versus Malignant Lymphoma:** Confusion may result if these tumors occupy the interstitium. The cell in lymphoma is usually largely nucleus with a small amount of amphophilic cytoplasm, while the cells in Leydig cell tumor have abundant eosinophilic or vacuolated cytoplasm.

**METASTASIS.** The histologic features of the metastases are the same as the primary tumor, and distribution is essentially the same as in seminoma.

**TREATMENT.** Initially, inguinal orchectomy is the treatment of choice for benign Leydig cell tumor. In most patients especially without any endocrine manifestations, correct diagnosis can be made only after orchietomy. Since 10 percent of the tumors metastasize, further evaluation must be carried out to detect possible spread.

Subsequently, a localized metastatic tumor may be removed surgically, especially in the retroperitoneal area. There are no reports of cures by radiation. Some success has been reported with 2,2-bis-(2-chlorophenyl-4-chlorophenyl) 11,1-dichloroethane alone or in combination with corticosteroids or dexamethasone (Abelson et al.).

**NATURAL HISTORY.** Leydig cell tumor occurs at any age; androgenic manifestations appear in children, and estrogenic or progestational symptoms develop in some men. These tumors are usually benign, but 10 percent metastasize. The shortest period reported before metastasis occurred was four months after orchietomy; the longest period was nine years, but metastases are usually late.
OTHER GONADAL STROMAL TUMORS

SYNONYMS AND RELATED TERMS: Sertoli cell tumor, granulosa cell tumor, theca cell tumor, or combinations; androblastoma.

DEFINITION. These rare tumors are derived from primitive sex stroma or mesenchyme and may consist of pure Sertoli cells, pure granulosa cells, spindle fibroblastic theca-like cells, or an admixture of these, with or without foci of Leydig cells.

When reporting these tumors, it is desirable to specify all cell types present.

INCIDENCE. These tumors comprise less than 2 percent of testicular tumors.

SPONTANEOUS TUMOR IN ANIMALS. The most common histologic pattern in animals is Sertoli cell tumor, commonly seen in older dogs; it may be associated with feminizing symptoms. The tumor has also been reported in horses, jungle cats, parakeets, and rats.

CLINICAL SYMPTOMS. Gonadal stromal tumors occur in all age groups from newborn infants to people in their eighth decade; one-fifth occur during the first 10 years, one-third during the years from 20 to 39, and one-fifth during the years from 40 to 60. Testicular enlargement, with or without pain, is the most frequent symptom; a third of the patients, however, present with symptoms of gynecomastia. Physical examination is usually negative except for an enlarged testis which may be tender, and enlarged breasts when they are affected. There may be decreased libido in a few patients.

ENDOCRINE ACTIVITIES. The endocrine activities of these tumors in man was highlighted in several papers by Teilum, who found gynecomastia in three patients. Gynecomastia has not been present as the predominant symptom in most of the subsequent reports.

Assays of hormone production in man are sparse. Increased urinary excretion of androgens (Fuglsang and Ohlsen), estrogens (Ostergaard; Scully and Parham), and pregnandiol (Lewis and Stockard) have been reported, but normal levels of estrogens (Lewis and Stockard) and androgens (Plunkett and Barr; Lewis and Stockard) have also been reported. The 17-ketosteroids are usually normal as are gonadotropins.

Histologic evidence of the hormone effects of these tumors has been fragmentary. The breasts show mammary hyperplasia with dilatation and hypertrophy of ducts. Atrophy of the testes or depressed spermatogenesis have been reported (Mostofi et al.).

Endocrine studies on canine Sertoli cell tumors have shown little deviation from normal testes. There was no significant difference in the formation of estrone, estradiol 17 beta, and estriol from (4-14C) dehydroepiandrosterone (DHA) and (7 alpha-3H) DHA sulfate in vitro with Sertoli cell tumors from two dogs, nor in the metabolism of radioactive progesterone or testosterone in either homogenate or tissue culture of canine Sertoli cell tumors compared to tissue from a normal dog testis (Pierrepoint; Siegel et al.). Pierrepoint also noted that both Sertoli cell tumor and normal testis metabolized DHA sulfate to DHA, androstenediol, androstenedione, and testosterone. However, he reported "an inversion of the relative production of androstenedione and testosterone from DHA by one of the tumors compared with normal testes (2 percent compared to 22 percent)". He postulated that a low testosterone output in conjunction with normal or low estrogen production may account for alopecia, and that androstenedione may be metabolized in the breast to estrogens which could act there without apparent increase in circulating or urinary estrogen levels.
GROSS. The left testis is twice as frequently involved as the right. Tumors may vary from 1 to 10 cm. in diameter. They are usually firm, but may be cystic, solitary, lobulated, well encapsulated (pl. I-C), and are grayish white to yellow. Necrosis and hemorrhage are rare. The capsule may be involved, but rarely is there extension to the cord.

MICROSCOPIC. Much confusion exists in the interpretation of the histologic features of this group of tumors (figs. 91—101).

Well differentiated Sertoli cell tumors are readily recognizable. The epithelial cells vary in shape from hexagonal to tall columnar. They have a large, round or oval, single vesicular nucleus with a distinct nuclear membrane containing a fine chromatin network and a solitary, small, basophilic nucleolus. The cytoplasm is scanty or abundant with large clear vacuoles, often containing lipid; the staining reaction is either eosinophilic or basophilic (fig. 92). Mitotic figures and giant cells are extremely rare.

The arrangement of the Sertoli cells varies, but in most instances their tubular form resembles seminiferous tubules, the lumina of which are sometimes filled with cells or with cell debris and eosinophilic precipitate (figs. 93, 94).

In some tumors, the cells are smaller, more cuboidal, and have a follicular arrangement closely resembling graafian follicles. Sometimes the structures resemble Call-Exner bodies, but no ova are identified (figs. 99—101).

In about one third of cases, cells with abundant ground-glass, eosinophilic cytoplasm are found which resemble lutein or Leydig cells, but they form tubules or are intermingled with spindle-shaped stromal cells (figs. 93, 94).

The spindle-shaped stromal cell has an elongated nucleus with eosinophilic and sometimes vacuolated cytoplasm (figs. 95, 96, 99). This type of cell usually occurs in bands between the tubules, but on rare occasions it may be the only component. Mitoses (fig. 97) and giant cells are occasionally encountered. Transitions between the epithelial and spindle cells are sometimes seen. Intermingled with spindle cells are occasional lipid-containing epithelial cells and macrophages (fig. 96).

DISCUSSION. The histologic spectrum of these tumors led the senior author to postulate a common cell of origin from the primitive specialized stroma of the gonad. It was suggested that this stromal cell is capable of differentiating into Sertoli and Leydig cells in the male, and theca or granulosa cells in the female. While oncogenic manifestations are usually Sertoli-Leydig cell tumors in the male testis and theca-granulosa cell in the female ovary, either tumor or an admixture may occur in either sex.

Sertoli-Leydig cells in the male and theca-granulosa cells in the female have a common function. They serve as specialized supporting stroma of the germ cells and the gonad. Origin from the primitive stroma of the gonad for these four cell types best explains the common function and the oncogenic manifestations. Embryologists, however, are not entirely in agreement concerning the origin of these cells. Gillman postulated that Sertoli-granulosa cells were derived from the mesothelium of the genital ridge, while Leydig and theca cells originated from the gonadal mesenchyme. Gillman's interpretation, however, was based on sections which were 30 to 40 microns thick, and must be considered unsatisfactory for discriminate observation.

While the term mesenchyme is commonly used by embryologists, we have refrained from employing either it or its neoplastic form—mesenchymoma—in this context for fear of confusion with certain tumors of soft tissues.
**Tumors of the Testis**

**PLATE I**

**SPERMATOCYTIC SEMINOMA**
A. The lesion is lobulated, homogeneously grayish yellow with small and large cystic areas. (Courtesy of Dr. Robert Scully, Boston, Mass.)

**CHORIOCARCINOMA OF TESTIS**
B. Note the large area of hemorrhage. Little viable tissue is seen.

**GONADAL STROMAL TUMOR**
C. Grossly, the tumor presents a homogeneous yellowish, fairly encapsulated appearance.

**LEYDIG CELL TUMOR**
D. The tumor is mahogany tan and fairly well circumscribed.

**INFANTILE EMBRYONAL CARCINOMA**
E. The tumor is grayish white and unencapsulated; it has a bulging, moist, mucinous surface.

**TESTICULAR SCAR AND SEMINOMA**
F. A stellate scar is seen in the hilar region of the testis of a patient who died of generalized embryonal carcinoma and teratoma. Seminoma in the testis was microscopic.
Tumors of the Testis

Figure 91
MIXED GONADAL STROMAL TUMOR
Tubular and stromal components are present in this mixed gonadal stromal tumor. Resemblance to mixed ovarian arrhenoblastoma is striking. X180. (Fig. 86 from Fascicles 31b and 32, First Series.)

Figure 92
GONADAL STROMAL TUMOR
Tumor cells are set off by basement membranes and in some places are oriented about a lumen. There is a definite resemblance to an adenoma arising from collecting tubules. X400. (Fig. 87 from Fascicles 31b and 32, First Series.)
Gonadal Stromal Tumors

Figure 93
GONADAL STROMAL TUMOR
The tumor appears to be intratubular. The cells are either cuboidal or low columnar with regular nuclei surrounded by considerable eosinophilic cytoplasm. X305.

Figure 94
GONADAL STROMAL TUMOR
The tumor appears to be intratubular, but the tubules are giant-sized. Note the large cells at the periphery and the smaller cells in the center of the tubules. X305.
Tumors of the Testis

Figure 95
GONADAL STROMAL TUMOR
The tumor consists mostly of interlacing bands of spindle cells. A similar picture may be seen in gonadoblastoma. X350.

Figure 96
GONADAL STROMAL TUMOR
The tumor consists of spindle-shaped cells. Note the cells with clear lipid-laden cytoplasm. X305.
MALIGNANT GONADAL STROMAL TUMOR

The tumor seems to form solid sheets of cells with a delicate fibrous stroma. Mitoses were present (arrow). X305.

MALIGNANT GONADAL STROMAL TUMOR
(Figures 98—101 from same case)

The tumor forms solid sheets. Note variation in staining of cells. X230.
Another area of the tumor in figure 98 shows spindle cells and one area suggestive of granulosa cell tumor. X230.

The granulosa follicle appearance is quite suggestive in this area of the tumor shown in figure 98. X230.
Gonadal Stromal Tumors

Figure 101
MALIGNANT GONADAL STROMAL TUMOR
(Figures 98—101 from same case)
Metastasis to the liver showed a picture similar to
that in the primary tumor. X230.

Figure 102
SERTOLI CELL NODULE IN UNDESCENDED TESTIS—MALDEVELOPMENT
This circumscribed nodule of small, closely packed tubules is a characteristic low power appearance. X48.
Differential Diagnosis. In many cryptorchid testes, groups of seminiferous tubules may be seen, lined by prominent infantile spermatocytic cells in young patients and Sertoli cells in adults (figs. 102, 103). Designation of such areas as adenoma or tumor is not justified unless there is a distinct tumor formation with compression of the surrounding tissue.

Malignant versus Benign Tumor. Malignancy is uncommon, but the majority of patients have not been followed for five or more years. Of 70 cases of gonadal stromal tumors reported in the literature, 10 were malignant (Teilum). In our own material, however, the incidence of metastases is only about 10 percent. Almost all metastases developed within five months. The criteria for determining malignancy have not been clearly defined. Cellular anaplasia, increased mitosis, capsular or adnexal extension, and vascular invasion (figs. 97, 98) are important criteria. In our experience, polymorphism and increased mitoses of the primary tumor are the two most reliable criteria, but the actual demonstration of metastases is the indispensable evidence of malignancy.

Gonadal Stromal Tumor versus Leydig Cell Tumor. It has been previously stated that the cells in gonadal stromal tumor may have a vacuolated or ground-glass eosinophilic cytoplasm; in fact, they may be indistinguishable from Leydig cells. In gonadal stromal tumor, cells are frequently intratubular; they are spindle-shaped with basal nuclei and usually fairly uniform in size. The spindle cells resemble theca interna cells. Careful examination may show transitional stages from Sertoli cells to lutein-like or Leydig-like cells (fig. 101).

Gonadal Stromal Tumor versus Mesothelioma. Since both gonadal stromal tumor and mesothelioma may be biphasic or may consist of spindle-shaped cells, differentia-
tion may be quite difficult. Mesothelioma is extremely rare. Invariably, it is extratesticular and usually papillary or tubuloacinar; rarely, it is a pure spindle-shaped tumor. Mesothelioma is commonly associated with considerable proliferative activity of the adjacent mesothelial cells. Special stains are also helpful; mesothelioma has no lipid but may contain PAS positive material and acid mucopolysaccharide. Involvement of the testis is usually secondary.

**Gonadal Stromal Tumor versus Adnexal Sarcoma.** Differentiation from an adnexal sarcoma is relatively easy. The spindle-shaped cells of gonadal stromal tumor are usually plumper and lighter staining; they rarely form the interlacing bands seen in sarcoma. The biphasic pattern is usually absent in sarcoma and involvement of the testicular parenchyma is secondary to adnexal involvement.

**Gonadal Stromal Tumor versus Secondary Carcinoma.** Differentiation from a metastatic carcinoma may be very difficult. The cells in epithelial gonadal stromal tumors are usually larger and contain some lipid but no mucin; glandular and acinar formation is absent. These tumors usually involve one area of the testis and rarely show single or small groups of cells in the uninvolved portion. It should be emphasized that once embryonal carcinoma is excluded, any epithelial tumor which involves the interstitium of the testis, shows glandular and acinar formation, and is obviously invading vascular spaces, should be regarded as metastatic carcinoma unless proved otherwise.

**METASTASIS.** Metastases are rare, but have been seen in 10 percent of cases. Histologically, metastatic tumor may be identical to the primary tumor (fig. 101) or may consist chiefly of one of its components. The sites of metastases are the retroperitoneal lymph nodes, liver, or lungs.

**TREATMENT.** Inguinal orchietomy is the initial treatment of choice. In a majority of cases, no further treatment is indicated unless there is histologic evidence of malignancy or clinical evidence of metastasis. Surgery for metastatic foci, if practical, seems to be the only feasible treatment, since it is doubtful that radiation therapy or chemotherapy will affect the course of the disease.

**NATURAL HISTORY.** Gonadal stromal tumor occurs in patients of all ages, but chiefly in children. It is generally slowly growing and benign with a malignancy rate of 10 to 15 percent.

**References**


Lippert, M. B., Sarfaty, G. A., Wilson, H., Bardin, C. W., and Fishman, L. M. Metabolism of testosterone and...


Melicow, M. Personal communication, 1973.


TUMORS WITH GERM CELL AND GONADAL STROMAL ELEMENTS

Two categories may be recognized; those in which the two elements are intermingled, and those in which two distinct tumors are seen. The latter are rare in man, but common in dogs. Our discussion is confined to the first group.

GONADOBLASTOMA

SYNONYMS AND RELATED TERMS: Gonadocytoma; tumors of dysgenetic gonads; dysgenetic gonadomas; mixed germ cell tumors.

DEFINITION. Gonadoblastoma is a tumor forming a distinct mass and containing an intimate mixture of abnormally proliferating germ cells and immature or mature granulosa and/or Sertoli cells, with or without Leydig, theca, or lutein-like cells.

CLINICAL SIGNS AND SYMPTOMS. Scully reported 74 patients with gonadoblastoma whose ages ranged from 1 to 73 years. The tumor is restricted almost exclusively to individuals with an underlying gonadal disorder. Clinical diagnosis depends not only upon the presence of a tumor and its occasional secretion of significant amounts of steroids, but also upon the abnormal nature of the gonads and secondary sex organs. Scully divided his patients into three groups: nonvirilizing phenotypic female (25); virilizing phenotypic female (35); and phenotypic male (13). However, in 22 of 30 patients in whom karyotype testing had been done, XY with 46 chromosomes were present. In about one third of the patients, the tumors were bilaterally located.

ENDOCRINE ACTIVITIES. A patient may manifest androgenic, estrogenic, or no endocrine symptoms. Elevation of gonadotropins was reported in a few patients. None of the 13 phenotypic male patients had elevated 17-ketosteroids, but five had gynecomastia.

ORIGIN. Twenty-two of the lesions in the cases assembled by Scully were in a distinct gonadal streak, 18 were in the testis, and 61 were in a gonad of unknown nature. In about half of the cases where a streak was established as the site of the tumor, the opposite gonad was also a streak which usually contained a second gonadoblastoma. In 9 of 16 cases in which the tumor arose in the testis, the opposite gonad was a streak, which was the site of a second gonadoblastoma in three
patients. In five cases, a testicular gonadoblastoma was associated with the presence of a testis on the opposite side with gonadoblastoma in one.

GROSS. Gonadoblastoma varies in size from barely detectable to 8 cm. in diameter. Teter reported a case in which the tumor measured 30 cm., due largely to overgrowth of a germinoma. Color and consistency vary with the amount of seminomatous elements present; thus it may vary from gray, indicating a predominance of seminoma cells, to yellow or brown, due to Sertoli-granulosa-Leydig-lutein cells. This tumor may be soft and fleshy, firm or resemble cartilage, flecked with granules of calcification, or almost totally calcified.

MICROSCOPIC. Characteristically, the tumor consists of distinct aggregates of actively proliferating germ cells, usually in intimate mixtures with Sertoli and granulosa cells. In a majority of cases, varying numbers of Leydig cells and/or luteinized cells of stromal origin are also present.

The germ cells of gonadoblastoma are similar to those of seminoma (dysgerminoma); mitotic activity was observed in 85 percent of cases, including even small tumors.

Gonadoblastoma may show a spectrum in the same slide from almost pure stromal tumor to almost pure seminoma-dysgerminoma, with lobulation and lymphoid infiltration (figs. 104—109). When the tumor consists of seminoma-dysgerminoma elements, the telltale appearance of gonadoblastoma persists in a few typical Sertoli-granulosa cell areas at the periphery. When the tumor consists almost entirely of Sertoli-granulosa cell elements, there is persistent scattering of seminoma cells. In other areas or tumors, seminoma cells are seen in intimate relationship with Sertoli-granulosa cells.

The Sertoli-granulosa elements show three basic patterns of growth: (1) surrounding individual germ cells, simulating an ovarian follicle (fig. 105); (2) surrounding circular spaces, resembling Call-Exner bodies (fig. 107); and (3) lining the periphery of nests or solid tubular structures that contain germ cells. Varying amounts of gonadal stroma resembling ovarian stroma may be seen. The large rounded or hexagonal Leydig cells or lutein-like cells have round nuclei surrounded by abundant hexagonal cytoplasm. No Reinke’s crystals are demonstrated. The cells usually occur in clumps. Hyalinization and calcification are not infrequently observed in the tumors. Pettigrew and associates demonstrated that Sertoli cells are capable of producing hyaline and basement membrane. Although variable, some calcification was observed in 81 percent of Scully’s cases. Calcification begins in Call-Exner-like spaces as psammoma bodies. With advancing degeneration, these structures fuse to form mulberry-like masses in which laminations are often still visible. Fibrosis with hyalinization leads to formation of fibrocalcific masses and sparse or absent tumor cells.

Varying numbers of Leydig-lutein-like cells are seen. Scully observed them in 44 percent of patients under 16 years of age, in contrast to 85 percent of those over 16 years of age.

In about 50 percent of cases, there were some foci of seminoma (dysgerminoma) which are indistinguishable from pure seminoma. In addition to seminoma, Scully reported another type of germ cell tumor, either in the gonad harboring gonadoblastoma or in the opposite gonad. In one patient with karyotype 45X/46XY with stigmata of Turner’s syndrome, a mucinous cystadenoma was present in the same gonad;
Tumors of the Testis

Figure 104
GONADOBLASTOMA
(Figures 104—106 from same case)
A distinct tumor in a normally descended testis of a 67 year old phenotypic male shows definite cords. Note that while the seminiferous tubules at the periphery are atrophic, others are dilated and lined by normal cell population. X28.

Figure 105
GONADOBLASTOMA
(Figures 104—106 from same case)
This is a higher magnification of figure 104 showing tubules filled with a mixture of Sertoli and germ cell elements. X145.
GONADOBLASTOMA
(Figures 104—106 from same case)
This higher magnification of figure 105 shows elongated Sertoli cells surrounding and enmeshing large germ cells with vacuolated cytoplasm. X350.

GONADOBLASTOMA
The intratubular tumor consists of Sertoli cells surrounding round hyaline Call-Exner-like bodies with interspersed germ cell components. Three corpora amylacia are seen. The seminiferous tubules in the adjacent testis are lined by a single layer of vacuolated Sertoli cells. X90.
in another patient, a few squamous elements were present; two patients had solid teratoma; four had embryonal carcinoma or entodermal sinus tumor. In four patients, the opposite gonad was replaced by a seminoma. In one patient, the presence of calcified foci led Scully to assume it was a burned-out gonadoblastoma; in another case, the opposite gonad had an infantile embryonal carcinoma (entodermal sinus tumor) which metastasized in the same form.

Gonadoblastomas should be thoroughly examined for the presence of other elements. Several patients in whom embryonal carcinoma was found, either in the tumor-bearing gonad or the opposite gonad, developed metastases.

DISCUSSION. Scully's designation of gonadoblastoma for this group of tumors seems an excellent choice, since it denotes a neoplastic change of both germ cell and stromal elements; it appears to recapitulate the embryonic development of the gonads.

Our experience with gonadoblastoma confirms that of Scully. The tumor may consist predominantly of one element or the other; the presence of Leydig or lutein-like cells depends to a great extent upon the stage of development of the gonad, the adequacy of representation, or their interpretation. No justification exists for separating these groups into individual or separate categories. The term gonadoblastoma is especially appropriate, as it is properly non-
committal as to the type of the gonad from which the tumor arises or the type toward which it is differentiating.

DIFFERENTIAL DIAGNOSIS. Gonadoblastoma versus Primitive Gonad. When gonads are removed from patients with dysgenesis, differentiation between a normal primitive gonad and a gonadoblastoma may present some difficulty. The size of the gonad may be helpful in diagnosis; if the gonad is unexplainably larger than normal, it probably denotes a tumor. In small gonads, the presence of a distinct mass is the most differentiating feature. The disproportion between mitotic activity of germ cells and stromal elements may also be a helpful diagnostic aid.

Gonadoblastoma versus Seminoma. Seminoma constitutes one element of gonadoblastoma; unless there is definite indication of proliferating stromal elements, the neoplasm should not be diagnosed as gonadoblastoma. The presence of calcified psammoma bodies, or mulberry-shaped calcification without other elements, would not justify the diagnosis of gonadoblastoma, but should lead to a more detailed study of the specimen.

Gonadoblastoma versus Gonadal Stromal Tumor. The presence of large, clear, spherical, or polyhedral seminoma cells distinguishes this group from ordinary gonadal stromal tumor. Difficulty may be experienced in separating true gonadoblastomas and those in which proliferating intratubular Sertoli cells may entrap preexisting germ cells. Usually, these germ cells show no mitotic activity.

Gonadoblastoma versus Gynandroblastoma. These tumors should not be confused as the latter consists of a gonadal tumor in which both Sertoli-Leydig cells and theca-granulosa cell elements are present without any germ cells. Such tumors are not usually associated with gonadal dysgenesis.

NATURAL HISTORY. Gonadoblastoma occurs almost invariably in a dysgenetic gonad or in an undescended testis, but rarely in a normal gonad. It is usually benign; to date, only the germ cell element in the gonadoblastoma, or the germ cell tumor in the contralateral testis has metastasized. Tumors that show increased mitotic activity or invasion of the nontumorous portions of the gonad should arouse suspicion of malignancy.

METASTASIS. No reports are available of metastasis of both elements. The germ cell elements, either seminoma or embryonal carcinoma, or tumors in the contralateral gonad may metastasize.

TREATMENT. Removal of the tumor-bearing gonad is the treatment of choice. The rudimentary sex organs and the contralateral gonad, if it is abnormal or undescended, should also be removed. In patients with aggressive and invasive seminoma (germinoma), radiation therapy may be considered. In patients with teratoma, embryonal carcinoma, or infantile embryonal carcinoma, lymphadenectomy or other therapy should be considered.

References


TUMORS OF THE TESTIS IN CHILDREN

GERM CELL TUMORS

Germ cell tumors in infants and children present only three basic histologic patterns. No acceptable case of choriocarcinoma has been reported. Infantile embryonal carcinoma and teratoma occur most often during the first three years of life; seminoma occurs but rarely, and only in children beyond the age of 10. Tumors derived from specialized gonadal stroma occur in children from birth to the age of puberty, but most often during the first five years. Tumors showing both germ cell and gonadal stromal elements occur in older patients. Tumors of fibrovascular tissue are similar to those observed in other organs. Secondary tumors consist principally of lymphomas, neuroblastomas, and nephroblastomas.

In contrast to the reported increasing incidence of testicular tumors in adults, no increase in the incidence of these neoplasms has been reported in children (Li and Fraumeni).

INFANTILE (JUVENILE) EMBRYONAL CARCINOMA

SYNONYMS AND RELATED TERMS: Yolk sac tumor; endodermal sinus tumor; clear cell adenocarcinoma; orchidoblastoma; adenosarcoma of rete testis; vitelline tumor; mesonephric tumor; mesonephroma.

DEFINITION. Infantile embryonal carcinoma is a germ cell tumor showing malignant epithelial cells that range from flat to low columnar and forming reticular, acinar, papillary, or solid areas; and malignant mesenchymal elements with angiogenic capabilities. Less frequently, deposits of hyaline eosinophilic basement membrane material may be seen.

INCIDENCE. Infantile embryonal carcinoma is the most common testicular tumor in infants and children and constitutes about 60 percent of such tumors.

CLINICAL COURSE. The tumor is almost always confined to children between the ages of four months to three and one-half years. Enlargement of the testis, with or without pain, is the chief symptom. No endocrine manifestations have been reported. Orchiectomy is advocated, with or without lymphadenectomy, chemotherapy, but no radiotherapy. Prognosis for this tumor is relatively favorable compared to adults, since only about 30 percent of the children die from metastases—almost all within the first two years.

GROSS. The testis is invariably enlarged and may increase from one or two times normal size up to 8 cm. in diameter. The cut surface is homogeneous, grayish white, lobulated, and usually a solid resilient tumor which is mucinous and appears somewhat fatty (pl. I-E). Small cystic and hemorrhagic areas may be seen. The tumor is nonencapsulated and replaces part or all of the testis. Rarely, there may be extension to the adnexa or a break through the tunica.

MICROSCOPIC. Infantile embryonal carcinoma has a characteristic pattern consisting of spaces of varying size lined by flat epithelial cells alternating with more cellular areas (fig. 110). The principal histologic pattern consists of anastomosing glandular (fig.
or ductal structures lined by low columnar, cuboidal, or flat epithelium. Sometimes papillary areas alternate with solid sheets of tumor cells. The large, irregularly shaped nuclei have variable chromatin distribution and one or more prominent nucleoli. Occasionally, the nuclei are closely packed and suggest syncytial masses. Sometimes they are elongated or spindle-shaped, resembling endothelial nuclei. The cytoplasm is usually vacuolated and the cell border is indistinct. The cytoplasm contains glycogen and considerable amounts of lipid, often doubly refractile.

The presence of fine to coarse vacuolization of the epithelial-type cells is a characteristic feature of this tumor (fig. 112). Some of the small vacuoles coalesce to form large vacuoles that seem to merge with the host vascular spaces (fig. 113). The stroma ranges from myxoid to fibrous cellular primitive mesenchyme that varies in amount (fig. 114). Frequently, it merges with epithelial elements making it difficult to differentiate between the two components. Both epithelial and mesenchymal elements seem to be angiogenic as manifested by areas that simulate angiosarcoma (fig. 113); it is difficult, if not impossible at times, to determine which are cytoplasmic vacuoles, reticular, myxomatous, or vascular spaces. Often, these merge with each other and are reminiscent of early trophoblastic angiogenic activity. Although vascular invasion may suggest a guarded prognosis, it does not necessarily indicate a fatal outcome.
INFANTILE EMBRYONAL CARCINOMA

Figure 112
The tumor forms a reticular pattern with many small and large vacuoles. X165.

Figure 113
Angiogenesis is apparent as manifested by the merging of the spaces with vascular channels. X265.

Figure 114
There is a considerable amount of newly formed mesenchymal tissue in between papillary and tubular structures. X165.
Preexisting seminiferous tubules and collecting ducts seem to communicate with distinct neoplastic foci in many tumors. This led Willis to believe they originated from seminiferous tubules. We consider this evidence, however, that the tumors originate from germ cells.

Careful examination will reveal some teratoid structure in almost every tumor, such as a duct lined by tall columnar epithelium, a nest of cartilage, or an epidermal cyst. We have seen two cases in which areas of distinct teratoma were intermingled with the tumor (fig. 115).

HISTOGENESIS. Mostofi believed the tumor originated from germ cells and preferred the term infantile embryonal carcinoma based on his finding of teratomatous areas in the tumors. He observed identical histologic features in tumors of adult patients, usually associated with teratoma. Teoh and associates believed the tumor originated from seminiferous tubules and designated it as orchidoblastoma. Abell and Holtz regarded this tumor as a germ cell tumor and referred to it as juvenile embryonal carcinoma. Teilum, impressed with its similarity to endodermal sinus of rodents, labeled it endodermal sinus tumor. Pierce and associates, who compared the tumor in mice with that in children, considered it a yolk sac or vitelline tumor. Although this tumor does resemble the yolk sac-endodermal sinus structures in many areas, and it falls within the category of extra-embryonic germ cell tumor, we prefer the term infantile embryonal carcinoma because it defines the several histologic characteristics of the tumor. A similar pattern is occasionally seen in adult testicular tumor, usually in association with adult embryonal carcinoma, teratoma, and/or seminoma.

METASTASIS. Metastatic tumor presents the same histologic features as the primary tumor. Metastasis in children is by way of both lymphatic and hematogenous routes to the same sites as embryonal carcinoma in adult patients who have primary germinal tumors.

TREATMENT. Inguinal orchiectomy is the treatment of choice. In many cases, retroperitoneal lymph node dissection, radiation therapy, and chemotherapy have been attempted (Abell and Holtz; Tefft et al.; Schweisguth and Gérard-Marchant). Radiation therapy is contraindicated because it may interfere with normal growth or immune response; it may lead to radiation-induced fatal aplastic anemia and possible radiation-induced nephritis or even osteogenic sarcoma in later life. Opinion differs on whether prophylactic chemotherapy should be given routinely or confined to cases which show retroperitoneal or other metastasis.
Postoperative follow-up is imperative and if a solitary metastasis develops, surgical treatment must be seriously considered. Follow-up examination of a 3 year old boy, two months after orchiectomy, revealed a solitary pulmonary metastasis which was removed. He was alive and well three and one-half years later.

NATURAL HISTORY. Death occurred within 18 months from metastases in about 30 percent of the infants and children in our study. In each fatal case, there was clinical evidence of metastasis within the first year.

TERATOMA AND TERATOMA WITH MALIGNANT AREAS

INCIDENCE. These tumors comprise about 40 percent of testicular tumors in children ranging from seven days to 13 years of age. Most patients are under four years of age.

GROSS. Teratoma varies from a simple tumor like an epidermal cyst to a more complex tumor composed of cystic and solid areas, cartilage, and bone.

MICROSCOPIC. Most teratomas are composed of mature elements. The types of tissue usually encountered are: central nervous system, enteric and respiratory structures, abortive eye, epidermal cyst, bone with marrow, and cartilage. In a few instances, immature teratomatous structures are seen that consist of elongated epithelial-like cells arranged around a cavity, reminiscent of primitive neurogenic elements. Occasionally, very cellular primitive mesenchymal elements are encountered and lead to a diagnosis of teratoma with malignant areas.

METASTASIS. We are not aware of any report of metastasis from teratoma of the testis in infants.

A 13 year old boy had a mass in the testis and the epigastrium which consisted mostly of mature teratoma with some undifferentiated areas. Presumably, death occurred from metastasis.

TREATMENT. Inguinal orchiectomy is the preferred treatment; however, in a few instances a small epidermal cyst or teratoma has been enucleated. Follow-up records of these patients are incomplete, but we do not recommend enucleation for teratoma. Retroperitoneal lymph node dissection has sometimes been performed.

NATURAL HISTORY. In contrast to testicular teratoma of adults, which metastasizes in about 30 percent of cases and causes death, testicular teratoma in infants and children has a much better prognosis, even though it may have distinctly undifferentiated neuroectodermal or mesodermal elements.

SEMINOMA

While seminoma is the most common adult testicular tumor, no acceptable seminoma has been reported in infants. Its occurrence in older children constitutes about 5 percent of childhood testicular tumors; the youngest patients in our material were 10 and 11 years of age.

Orchiectomy and retroperitoneal lymph node dissection revealed typical seminoma with granulomatous reaction with metastases in a 10 year old boy. He was treated with postoperative radiation and at last follow-up three years later, he was asymptomatic but then he was lost to follow-up. An 11 year old boy had a seminoma that was somewhat more anaplastic. He had a radical orchiectomy followed by postoperative radiation. He was asymptomatic for five years, but then was killed in an automobile accident.
TUMORS OF INFANTILE TESTIS DERIVED FROM SPECIALIZED GONADAL STROMA

Tumors of gonadal stroma are more frequent in infants and children. They comprise about 19 percent of testicular tumors in this group. Leydig cell tumor is usually found in an older age group. Patients with other gonadal stromal tumors range in age from a few hours to 11 years, but most are younger than six months of age. Macrogenitosomia has invariably been observed in children with Leydig cell tumor. Gynecomastia is sometimes present in patients with gonadal stromal tumor and in one patient 17-ketosteroids were reported elevated.

Gross and microscopic appearances are similar to those seen in adult patients. Although follow-up is incomplete, none of our juvenile patients with gonadal stromal tumors has developed metastasis; however, a malignant Sertoli cell tumor which metastasized to a retroperitoneal lymph node has been reported in an 8 year old boy. The boy was living and well two years following surgery (Rosvoll and Woodard).

References

RARE AND UNUSUAL TUMORS

MESENCHYMAL TUMOR

Hemangioma, fibroma, lipoma, and other such tumors are rarely encountered and present no diagnostic problem. Various types of sarcoma occur and usually involve the adnexal structures primarily and the testis secondarily. Rarely, they are primary in the testis (figs. 63—65). While such tumors raise the possibility of a one-sided development from some teratomatous element, we believe that they should not be classified as teratomatous in origin unless definite teratomatous, embryonal carcinomatous, choriocarcinomatous, or seminomatous elements are identified.

BRENNER TUMOR OF THE TESTIS

Brenner tumor of the testis is extremely rare; only three cases have been reported in the literature (Goldman). It is believed to arise from a müllerian vestige in the epididymal testicular groove.

References

UNCLASSIFIED TUMORS

An occasional testicular tumor is seen which is impossible to classify from the first sections of the primary growth. Such a tumor may be designated as unclassified until additional sections or histologic characteristics of metastatic tumor assist in providing a more specific diagnosis. Figure 62 shows a large tumor that consisted of undifferentiated spindle-shaped cells with areas of osteoid and chondroid matrix (figs. 63—65). Further sectioning, however, revealed a focus of spermatocytic seminoma (fig. 66). The metastatic tumor showed no seminomatous elements, but consisted of undifferentiated spindle cells.

TUMORS OF THE COLLECTING SYSTEM

Tubuli recti, the rete testis, and the efferent tubules are lined by epithelium which has the same origin as Sertoli cells, modified in the case of rete testis to epithelium which varies from cuboidal to flattened cells. Hyperplasia, adenoma, and adenocarcinoma of this ductal system are rare. They are difficult to distinguish from each other, except in early stages, because of their tendency to extend and involve the other portions of the collecting system (figs. 116—119).

The most common tumors of the collecting system originate in the rete testis during the fourth, fifth, and sixth decades. They are located in the hilar region and vary in color from grayish white to brown. The cells, reflecting the histologic character of the rete, are usually small cuboidal, with large, rather elongated nuclei and scanty cytoplasm. The nuclei tend to pile up and the cells are densely packed. They may form papillary processes and occasionally acinar structures. The stroma is abundant and hyalinized.
Tumors of the Testis

Figure 116
PAPILLARY ADENOCARCINOMA OF RETE
(Figures 116 and 117 from same case)
Rete passages are partially filled with papillary tumor growth. Almost all rete epithelium is involved and invasion of connective tissue stroma is evident. X75. (Courtesy of Dr. J. D. Feek, Kirkland, Wash., and Dr. W. C. Hunter, Portland, Ore.; also fig. 77 from Fascicles 31b and 32, First Series.)

Figure 117
PAPILLARY ADENOCARCINOMA OF RETE
(Figures 116 and 117 from same case)
The cell detail of carcinoma of rete is shown and the papillary glandular nature of the tumor is evident. X355. (Courtesy of Dr. J. D. Feek, Kirkland, Wash., and Dr. W. C. Hunter, Portland, Ore.; also fig. 78 from Fascicles 31b and 32, First Series.)
Figure 118
PAPILLARY ADENOCARCINOMA OF RETE
(Figures 118 and 119 from same case)
This is a low power view showing a papillary adenocarcinoma. Portions of the rete are seen in the upper right. X90.

Figure 119
PAPILLARY ADENOCARCINOMA OF RETE
(Figures 118 and 119 from same case)
This higher magnification of figure 118 shows pseudostratified columnar cells with vacuolated cytoplasm surrounding a vesicular nucleus with a single prominent nucleolus. X350.
Scully and Parham described a tumor with abundant eosinophilic cytoplasm and round to oval nuclei, containing single or double prominent central nucleoli, large irregular, hyperchromatic nuclei, and prominent mitoses. The cytoplasm of numerous cells enclosed various-sized, round or irregular, dark brown or eosinophilic globules surrounded by clear halos. There was no evidence in the sections of origin from the rete, but hypertrophy of some rete cells was seen.

Other tumors consist of tall columnar epithelial cells with vacuolated cytoplasm and round or oval vesicular nuclei. The cells form papillary and acinar structures.

DIFFERENTIAL DIAGNOSIS. In arriving at a pathologic diagnosis of such tumors, it is essential that origin from rete testis and collecting ducts be definitely established. In our experience, the extension of seminoma to the rete is frequently misdiagnosed as carcinoma of rete testis. In this condition, the epithelium of the rete shows little or no hyperplasia. The rete cells are displaced by large cells, each containing a hyperchromatic nucleus surrounded by vacuolated or eosinophilic cytoplasm.

Another source of confusion is interpretation of the picture seen in atrophic, collapsed, or cryptorchid testis when there is a relative increase, or even hyperplasia, in the number of visible tubuli recti or the rete. In such cases, the normal architecture is always maintained.

Other lesions that should be excluded are adenocarcinoma originating from müllerian or mesonephric remnants, and mesothelioma.

TREATMENT. Orchietomy is the initial treatment. In the absence of any follow-up data for a large series, further treatment would presumably be similar to that for primary germ cell tumors.

References

SECONDARY TUMORS INITIALLY MANIFEST AS TESTICULAR NEOPLASMS

Malignant lymphoma is the most frequent secondary tumor of the testis initially manifested as testicular neoplasm. Much less frequently, other metastatic neoplasms may also be seen.

MALIGNANT LYMPHOMA

SYNONYMS AND RELATED TERMS: Reticulum cell sarcoma; lymphosarcoma; Hodgkin's disease; plasma-cytoma; lymphoblastoma.

DEFINITION. Malignant lymphoma is a malignant testicular tumor in which there is massive infiltration of the interstitium by one or more neoplastic elements of the reticulo-endothelial system sometimes without prior evidence of a systemic disease.

INCIDENCE. Including all age groups, malignant lymphoma constitutes about 5 percent of tumors of the testis in our material. In patients over 50, however, it is the most frequent tumor of the testis. In contrast to the germinal tumor, which rarely involves the Black population, malignant lymphoma of the testis occurs in all races.

CLINICAL SIGNS AND SYMPTOMS. Malignant lymphoma may occur at any age ranging from two and one-half years to 87 years, although the majority of patients have reached the sixth and seventh decades (average 51 years). Enlargement of the testis, with or without pain, is the chief symptom; about 25 percent of patients present with more generalized symptoms such as weight loss, anorexia, and weakness. Except for unilateral enlargement of the testis, physical examination is usually negative, although occasionally there may be enlargement or nodularity of the opposite testis. The blood lymphocyte count is within normal limits in most patients, but it is elevated in about 8 percent of cases.

Hematologic studies are usually not made prior to orchiectomy. When malignant lymphoma has been diagnosed, studies should be made to determine the involvement of lymph nodes, bone marrow, and other organs. Curiously, in these cases the skin shows lymphomatous nodules more frequently than in those without testicular involvement.

GROSS. One or both testes are enlarged, and the enlargement is usually diffuse. The cut surface shows a bulging, firm, grayish white, usually solid tumor with a granular surface and areas of hemorrhage and necrosis. The tumor is nonencapsulated but it compresses the testicular parenchyma to the periphery (fig. 120).

MICROSCOPIC. Detailed histologic features of malignant lymphoma are beyond the scope of this fascicle. More than half of malignant lymphomas consist of pure reticulum cell sarcoma (fig. 122). In about one third of cases, the cells are lymphocytes; the remainder are either lymphoblastic or of mixed type with reticulum cells, lymphoblasts, and lymphocytes. Hodgkin's disease has not been noted in the testis proper.

Neoplastic cells of lymphoma densely infiltrate the interstitium of the testis (fig. 121), surround and compress the seminiferous tubules, but only later do they invade through the basement membrane (fig. 123).
Figure 120
MALIGNANT LYMPHOMA
The tumor is grayish white, soft, and has areas of necrosis and hemorrhage.

Figure 121
MALIGNANT LYMPHOMA
(Figures 121 and 123 from same case)
Note the massive infiltration of the interstitium. X100.
Invasion of the seminiferous tubules usually occurs from the outside in advanced stages, with eventual extension into the lumen of the tubules.

DIFFERENTIAL DIAGNOSIS. Malignant Lymphoma versus Germ Cell Tumor. Malignant lymphoma of the testis is frequently confused with seminoma (1 of 4) and occasionally with embryonal carcinoma (1 of 10). Seminoma cells are larger and have much more clear or granular cytoplasm; the nuclei are larger and more vesicular with one or two nucleoli. The cells have a distinct border and form a mosaic pattern. Embryonal carcinoma is lobulated; its cells have a distinct epithelial appearance that frequently form glandular, papillary, or tubular structures. In lymphoma, the infiltrating cells have scant cytoplasm. The nuclear chromatin distribution is different and the infiltrate is very cellular, dense, and mostly interstitial with diffuse interspersed tubules. In contrast to seminoma in which the cells form a mosaic, there are distinct clear spaces between lymphoma cells. The cells are usually identifiable as reticulum cells and lymphocytes.

Figure 122
MALIGNANT LYMPHOMA
The infiltrate consists of reticulum cells. X395.

Figure 123
MALIGNANT LYMPHOMA
(Figures 121 and 123 from same case)
Note the extension of the tumor into the seminiferous tubule. This is in contrast to granulomatous orchitis in which the infiltrate starts in the seminiferous tubules. X395.
Malignant Lymphoma versus Granulomatous Orchitis. It is often difficult to distinguish malignant lymphoma from granulomatous orchitis. In granulomatous orchitis, most of the infiltrate involves the seminiferous tubules, and the basement membrane is frequently destroyed. The cells of the tubules are replaced by macrophages and other benign cells, often unidentifiable. Interstitial infiltration is mild and localized in the early stages and usually pleomorphic, consisting of lymphocytes, plasma cells, and macrophages. In lymphoma, the seminiferous tubules show compression atrophy from the massive cellular infiltration of the interstitium. Invasion of the tubules is late and occurs from the outside progressing inwardly. The infiltrating cell is predominantly of a single cell type, and the cells are usually primitive and neoplastic and not the polymorphous type seen in granulomatous orchitis.

TREATMENT. Initial treatment for testicular lymphoma is inguinal orchectomy. After the correct diagnosis is established, recognition of the process as a manifestation of a systemic disease becomes obvious. After diagnosis of malignant lymphoma is confirmed, the urologist is then faced with a serious decision, particularly if the patient has no other manifestations. Thorough investigation should be made to determine the presence of lymphadenopathy or skin lesions, the condition of the opposite testis, the blood, and the bone marrow.

NATURAL HISTORY. About 25 percent of patients have involvement of the opposite testis, sometimes after an interval of several years. In about 17 percent of cases, cutaneous nodules appear. Central nervous system, gastrointestinal, nasopharyngeal, and visceral involvement almost invariably occur and 90 percent of the patients die of generalized lymphoma within two years. In a few, especially older patients, the course of the disease is prolonged for many years.

Levin and Mostofi reported seven cases of plasmacytoma. The ages of patients ranged from 26 to 66 years. In four patients, the initial symptom was testicular enlargement; in the other three, testicular enlargement followed extratesticular symptoms. The tumor cells varied in degree of differentiation; some were readily identified as plasmacytic (fig. 124), while others initially resembled reticulum cell sarcoma and only later were recognized as plasmacytoma. In all but one case, testicular plasmacytoma was eventually associated with extratesticular plasma cell myeloma.

Figure 124
PLASMACYTOMA
The infiltrating cells are obviously mature and primitive plasma cells. X395.
Secondary Tumors

METASTATIC CARCINOMA INVOLVING THE TESTIS

Despite its rarity, metastatic carcinoma of the testis may simulate a primary testicular neoplasm. Price and Mostofi have reported six cases simulating a primary tumor in a study of 38 proved metastatic carcinomas of the testis in 1,600 tumors of the testis. The primary sites in order of descending frequency were: lung, 14; prostate, 12; stomach, 3; kidney, 3; colon, 2; pancreas, 2; bladder, 1; and rectum, 1.

CLINICAL SIGNS. The ages of patients ranged from 20 to 80 years; 21 percent were between 20 and 39 years, 13 percent were between 50 and 60 years, and 66 percent were older. The left testis was more frequently involved than the right in autopsy cases (14 to 10), and there was bilateral involvement in 4 of 6 clinically manifest cases.

GROSS. The testis may be enlarged, normal, or small; the largest weighed 79 grams. The tumor may be nodular, localized, or cause diffuse enlargement of the testis.

MICROSCOPIC. Small nests and groups of tumor cells are most commonly seen in the interstitium with relative sparing of seminiferous tubules which may be compressed or show thickening of the basement membrane, atrophy, and hyalinization (figs. 125, 126). The histologic character of metastatic tumor in the testis is identical to that of the extratesticular primary tumor. However, at times the appearance is suggestive of Leydig cell tumor. Only rarely and in advanced
stages is there invasion of the tubules. In the majority of cases, tumor cells are found within vascular spaces of the parenchyma, tunic, or adnexa.

OTHER METASTATIC TUMORS

Melanoma (fig. 127), neuroblastoma, and nephroblastoma may manifest first as a testicular tumor, but such cases are extremely rare.

TUMORS OF THE TESTIS IN OLDER PATIENTS

More than 60 percent of testicular tumors encountered in patients over 50 years of age are categorized as secondary tumors initially manifested as testicular tumor. This is in contrast to the juvenile group of patients in whom infantile embryonal carcinoma and teratoma are the most frequent testicular tumors. It also contrasts with adult men in whom seminoma accounts for about 40 percent of testicular tumors.

Malignant lymphoma is the most common tumor in the older age group and constitutes about 40 percent of the cases. Seminoma comprises over 60 percent of germinal tumors alone, followed in order of frequency by embryonal carcinoma, Leydig cell tumor, teratoma and teratoma with embryonal carcinoma, gonadal stromal tumor, and sarcoma of the adnexa.

References


* * * * *
TUMOR-LIKE CONDITIONS OF THE TESTIS

Two important tumor-like conditions include granulomatous orchitis, briefly discussed on page 134 under differential diagnosis of lymphoma, and malakoplakia of the testis.

GRANULOMATOUS ORCHITIS

This chronic inflammation of known or unknown etiology that results in enlargement and hardness of the testis may clinically or pathologically simulate neoplasia. Two categories may be recognized: idiopathic and that of known etiology.

INCIDENCE. Among 6,000 testicular tumors, we found 120 cases of idiopathic granulomatous orchitis. Of interest is the frequent occurrence of this lesion among the Black population.

ETIOLOGY. A most attractive theory—that the disease is a manifestation of autoimmunity—was first proposed by Cruickshank and Stuart-Smith. They found sperm-agglutinating antibodies in the serum of 1 of 6 cases of granulomatous orchitis. Such antibodies have neither been tested nor observed in a majority of cases, nor attributed to secondary reaction to extravasated sperm. In most of our cases, only one testis was involved; we have seen cases in which only a portion of the testis is involved which does not support the autoimmune concept.

Urinary tract infection has been reported in about two thirds of cases, mostly with gram negative bacilli. In a few instances, cultures of the lesion have demonstrated gram negative bacilli or fungi (Candida). There may be a history of prostatectomy, herniorrhaphy, inguinal operation, hernia, or trauma. Vascular impairment is present in a substantial number of cases and may be the most important etiologic factor.

CLINICAL SIGNS OR SYMPTOMS. Idiopathic granulomatous orchitis usually occurs in older people. In our material, the youngest patient was in the fourth decade, the oldest, in the eighth. Onset of the disease may be sudden or insidious. Testicular enlargement is the most common symptom and may be accompanied by pain, tenderness, a dragging sensation, or heaviness.

GROSS. Usually, the testis is slightly enlarged, but it may be considerably enlarged. The cut surface is nodular, yellowish, hard or rubbery, and may involve part or all the testis. There may be areas of infarction or abscess formation. The epididymis and tunica are sometimes involved.

MICROSCOPIC. Two rather distinct histologic patterns have been designated as granulomatous orchitis; i.e., those in which initial and primary manifestation is in the seminiferous tubules, with secondary involvement of the interstitium, and those in which primary involvement is in the interstitium, with secondary involvement of seminiferous tubules. In more advanced or later stages, it may be impossible to distinguish between the two, but the appearance of seminiferous tubules may provide a clue to the initial lesion.

The first type is generally classified as idiopathic granulomatous orchitis, since an etiologic agent is rarely demonstrable. There is destruction of germ cell elements and replacement by an admixture of cells. In early stages, neutrophilic leukocytes may be present, but the major cell population in the florid phase consists of large round cells with eosinophilic or vacuolated cytoplasm and vesicular nuclei (figs. 128, 129). Some, if not most of these cells are derived from Sertoli cells and many show phagocytic properties. Multinucleated giant cells and epithelioid
cells are frequent (fig. 130). There is infiltration of the basement membrane in which fibers are separated one from another. In the earliest stages, there are varying degrees of interstitial infiltration, from scant to marked, but the infiltrating cells consist entirely of lymphocytes, plasma cells, monocytes, and cells resembling those in the tubules. Rare multinucleated giant cells, usually seen in later stages, are also present, probably as a result of escape of such cells from the destroyed seminiferous tubules. Distinct granuloma formation in the interstitium is rare. In later stages, with destruction of the basement membrane, sheets of eosinophilic cells with granular eosinophilic cytoplasm are seen diffusely infiltrating the stroma.

The second type is usually associated with a definite etiologic agent and may be divided into two distinct categories: Those in which the interstitial infiltration is predominantly granulomatous, and those in which it is lymphoid and plasmocytic without any definite granuloma. The latter picture is one of chronic nongranulomatous orchitis, but often erroneously designated as granulomatous. In both types, the seminiferous tubules show a variety of changes: they may be within normal limits; they may show infiltration of basement membrane with or without extension of the infiltrate into the lumen; the germ cell elements may show varying stages of degeneration; the seminiferous tubular cells may be completely replaced by Sertoli and phagocytic cell elements; or the tubules may be hyalinized.

DIFFERENTIAL DIAGNOSIS. In our experience granulomatous orchitis is most frequently confused with malignant lymphoma or Hodgkin’s disease. The differential diagnosis has been discussed on page 134.

True granulomatous orchitis may also be confused with infectious granuloma. Tuberculosis primarily affects the epididymis, but in later stages may extend to the testis;
however, the epididymis is always involved. Sperm granuloma is almost entirely confined to the epididymis and the cord. In sarcoidosis, fungal diseases, and secondary syphilis, involvement is primarily of the interstitium. While some seminiferous tubules may be affected, the infiltrate and the granulomatous reaction are almost entirely in the interstitium. In most of these lesions, there are areas of necrosis and suppuration.

In early stages, true granulomatous orchitis may simulate Sertoli cell tumor, since the affected seminiferous tubules may contain many large epithelioid cells with vacuolated cytoplasm. The histologic character of Sertoli cell tumors has been discussed in detail; suffice it to say that in granulomatous orchitis there is a polymorphic infiltrate involving not only the seminiferous tubules but also the interstitium. Such infiltrate is not seen in Sertoli cell-gonadal stromal tumor.

In all cases of granulomatous orchitis, search should be made not only for possible etiologic agents but also for Michaelis-Gutman bodies. These consist of intracellular and extracellular pale blue or grayish staining spherules. These round bodies are usually positive for calcium and for iron; however, there may be a small amount of calcium or a small amount of iron, or considerable amounts of both, or none. The bodies are usually located in large macrophages with eosinophilic or vacuolated cytoplasm and small round nuclei. Identification of such bodies would lead to the diagnosis of malakoplakia (pl. II-D).

DISCUSSION. Diagnosis of idiopathic granulomatous orchitis should be made only after thorough investigation for possible etiologic agents.

References
INTRATUBULAR SYNCYTIOTROPHOBLASTIC CELLS
A. A single seminiferous tubule contains two syncytiotrophoblastic cells and a clump of small cells with vacuolated cytoplasm. Elsewhere the testis had a seminoma. X265.

LEYDIG CELL TUMOR
B. Note the Reinke's crystals in this tumor. X1700.

MALAKOPLAKIA
C. Michaelis-Gutman bodies are shown as spherules. X450.
TUMORS AND TUMOR-LIKE CONDITIONS OF TESTICULAR ADNEXAL STRUCTURES
(EPIDIDYMIS, SPERMATIC CORD, CAPSULE, AND SUPPORTING STRUCTURES)

With the exception of cystadenomas of the epididymis, occasional dermoid cysts of the spermatid cord, and rare papillary tumors that may arise from the appendices of the testis or epididymis, the tumors and tumor-like lesions of the epididymis, spermatid cord, and testicular tunics are of mesenchymal origin. Although carcinomas of the epididymis are recorded in the literature (Fisher and Klieger; Salm), a careful review of our cases involving this organ has failed to disclose a single clearly documented case. Most of the cases in our material, sent in as primary carcinoma, proved to be metastatic carcinoma, mesothelioma, or extension or metastasis of a primary germ cell tumor of the testis.

Almost any tumor of soft tissue derivation may arise as a primary tumor in this region. With few exceptions, the clinical and pathologic features of these intrascrotal mesenchymal tumors are identical to those that occur in other regions, which have been fully discussed in Fascicle 1, Second Series, "Tumors of the Soft Tissues." However, the more important mesenchymal tumors of the epididymis, spermatid cord, and testicular tunics will also be included in this fascicle.

Although the anatomy and histologic characteristics of these regions are discussed in many textbooks, the presence of certain vestigial structures of these organs needs to be emphasized (Diagram 3; Arey). Remnants of the processus vaginalis may persist in the spermatid cord, and these may become cystic, forming the so-called hydroceles of the cord. The rare examples of mesothelioma of the cord are probably also derived from the processus vaginalis. Four other vestigial structures in these regions are well recognized: (1) The appendix testis (hydatid of Morgagni) is usually described as a fan-shaped, sometimes pedunculated structure arising from the tunic of the testis beneath the head of the epididymis. This usually consists of a core of loose connective tissue, which may contain tubular inclusions, with a covering epithelium of müllerian type. It is thought to be of müllerian origin corresponding to the fimbriated end of the fallopian tube (Presman et al.); (2) The appendix epididymis is usually a pedunculated cyst arising from the anterosuperior pole of the
Tumors of the Testis

epididymis. The cyst is covered by serosa and lined by tall columnar epithelial cells which often are ciliated; between the serosa and the epithelium is a layer of loose connective tissue. Most authorities consider the appendix epididymis to be a remnant of the Wolffian (mesonephric) duct; (3) The paradidymis (organ of Giraldès) consists of a group of coiled tubules, sometimes pedunculated, lying in the connective tissue of the spermatic cord at the level of or just superior to the head of the epididymis. The paradidymis is also considered to be of Wolffian origin; and (4) The vasa aberrantia (organ of Haller; cranial and caudal aberrant ductules) is represented by a group of Wolffian tubules usually associated with the floor of the groove between the testis and the body of the epididymis. In our experience, the histologic appearance and the presumed tissue of origin of these structures are not as clear-cut as the literature might indicate. In particular, the histologic features of the appendices of the testis and epididymis are often identical, and we have found it difficult to determine whether these vestigial structures are of mesonephric or Müllerian origin. While no clearly defined neoplasms have been described as arising from these structures, in our material an occasional papillary lesion of the tunic seems to be derived from one of these structures.

References


ADENOMATOID TUMORS

SYNONYMS AND RELATED TERMS: Adenomatoid mesothelioma; adenofibroma; adenofibromyoma; adenomyoma; angiomatoid tumor; fibroma; lymphadenoma; lymphangioma; mesothelioma, myoadenofibroma; adenomatoid leiomyoma; mixed leiomyoma; lymphangioma.

INCIDENCE AND SITE. Adenomatoid tumors are the most common tumors of the paratesticular tissues, representing 32 percent of all tumors involving these organs. They have a very restricted anatomic distribution limited to the epididymis, testicular tunics, and rarely the spermatic cord in the male, and to the uterus and fallopian tubes, and rarely the ovary and parovarium in the female, and in the retroperitoneum adjacent to or in the adrenal gland. In the male, most of these tumors arise either in, or adjacent to the lower or the upper pole of the epididymis,
with the lower pole predominating in a ratio of 3 to 2. Involvement of the body of the epididymis or the testicular tunics away from the vicinity of the epididymis occurs occasionally. Four of the tumors in our series occurred in the spermatic cord without any connection to the epididymis, and a rare tumor was found in the parietal tunic. Bilateral involvement has been reported (Morin), but is very rare.

CLINICAL FEATURES. The age distribution in our cases is from 18 to 79 years; the tumors occurred most often during the third, fourth, and fifth decades. The mean age at the time of surgery was about 36 years. The great preponderance of patients are Caucasian, but 14 percent are Black and 1 percent are Oriental. The left side is involved slightly more often than the right, but the difference is not significant. Clinically, adenomatoid tumors present as small, solid, intrascrotal tumors which do not transilluminate. They are nearly always asymptomatic, found on routine physical examination, or incidentally at autopsy or orchiectomy for some other condition. An occasional patient notes mild pain or discomfort in association with the nodule. The tumors have usually been present for several years without appreciable growth. In our experience, the tumors have proved uniformly benign. We have not encountered malignancy of the type reported by Soderstrom and Liedberg, and by Fisher and Kliger. The histologic appearance of the tumors as reported by these authors and as depicted in their photomicrographs makes us doubt their authenticity as adenomatoid tumors.

GROSS. Adenomatoid tumors are small, ranging from 0.4 to 5.0 cm. in diameter. The tumors are oval or flattened and disklike, firm to hard, and most are well demarcated. They are usually attached to the testicular tunics (fig. 132), often appearing to be embedded in the tunics, but those involving the head of the epididymis may be embedded deeply in that structure (fig. 133). The tumors generally cut with fibrous consistency, and the cut surface has a gray, tan, or white fibrous appearance.

MICROSCOPIC. Microscopically, there are two major elements: epithelial-like cells and fibrous stroma. In addition, many of the tumors contain bundles of smooth muscle and scattered collections of chronic inflammatory cells (fig. 134). All these elements exhibit considerable variation in appearance and distribution, so the histologic pattern of

Figure 132
ADENOMATOID TUMOR OF GLOBUS MINOR
The tumor is circumscribed, but is not encapsulated. There is a nodule of smooth muscle fibers at the upper left and a focus of abundant fibrous stroma just to the right of center. X7.
ADENOMATOID TUMOR

This adenomatoid tumor has an even admixture of epithelial-like elements and stroma. The latter contains two foci of lymphocytes. X70.

any given tumor may be quite variable. Variation of these elements, especially the epithelial-like cells and the stroma, are partly responsible for the bewildering list by which these tumors have been designated.

The epithelial cells may be arranged as solid strands or cords, often interlacing and producing a plexiform pattern (figs. 135, 136); as tubular and/or glandular structures, also interconnected and interlacing (glandular type); or as dilated spaces resembling those seen in lymphangiommas (fig. 137). The cells may be cuboidal or low columnar, or they may be flattened and endothelioid in appearance,
Figure 135
SOLID CELL CORD TYPE ADENOMATOID TUMOR
An occasional cord demonstrates lumen formation. The stroma is composed of reticular and fibrous tissue. X160.

Figure 136
ADENOMATOID TUMOR
Cells range from flattened and endothelioid to cuboidal. Many cells are distorted by large, intracellular vacuoles, and stretched out cytoplasmic remnants form bridges from one side of the cell cord to the other. Vacuolization may be the mechanism of lumen formation in these cords. X485.
although they do not exhibit the characteristic spindling out that is seen with endothelial cells. In general, cuboidal or columnar cells predominate in the solid and glandular types, whereas the endothelioid cells predominate in the angiomatoid type. This distribution is not absolute, however, and cuboidal cells may be found lining dilated angiomatoid spaces, whereas flattened cells may be arranged as solid strands or cords. While any one tumor may be classified by its predominant pattern (solid, glandular, or angiomatoid), all three patterns are usually found in any given tumor.

Another fairly common feature of adenomatoid tumors is the presence of vacuoles in the epithelial-like cells (fig. 136).

These range in size from minute to large, and replace most of the cytoplasm of the cell. Vacuole formation, in fact, may be the mechanism of lumen formation, and in some tubules or glandular spaces strands of attenuated cytoplasm may bridge across the lumen and produce a characteristic pattern.

The nuclei generally are round or oval, centrally placed, and either vesicular or rich in chromatin. A single nucleolus is usually present, and mitoses are not observed. In the nonvacuolated cells, the cytoplasm is acidophilic and finely granular. Although some authors have stated that the mucicarmine stain is sometimes positive for mucin both in the vacuoles and in the spaces (Glenn), the mucicarmine stain in our material has been negative.

The stroma ranges from loose connective tissue (fig. 138) to dense, collagenized tissue which is sometimes focally hyalinized. Variations in the amount and character of the stroma are frequent, some containing almost no stroma while others are composed predominantly of stromal elements. Many adenomatoid tumors exhibit a prominent knob or bundle of smooth muscle at one pole of the tumor replacing most of the stroma at that point (fig. 139). Some tumors have scattered bundles of smooth muscle dispersed throughout the tumor. In about 3 percent of the tumors, smooth muscle is abundant throughout the tumor and is the dominant element. Tumors of this type have been reported as mixed lymphangioma and leiomyoma (Halpert; Malisoff and Helpern) or as adenomatoid leiomyoma (fig. 140; Wilson). The literature debates the significance of muscle tissue in adenomatoid tumors. Some regard it as incorporated normally present muscle, while others regard it as proliferating muscle and an integral part of the tumor.
ADENOMATOID TUMOR

Adenomatoid tumor shows bundles of smooth muscle at one pole. Masson stain. X100.

Figure 138

ADENOMATOID TUMOR

The stroma is composed of reticular and fibrous tissue which outlines the epithelial-like tubules. Reticulin stain. X165.

Figure 139
Tumors of the Testis

Figure 140
MIXED ADENOMATOID TUMOR AND LEIOMYOMA
(SO-CALLED ADENOMATOID LEIOMYOMA)
The stroma between the smooth muscle bundles contains adenomatoid tubules. X125.

Lymphoid cells are present in most of the tumors, often occurring as inconspicuous, scattered collections. In about one half of the tumors, the lymphoid cells are grouped in the form of small nodules generally scattered about the periphery of the tumor. A small percentage of the tumors exhibit foci of ischemic necrosis, often associated with an acute inflammatory exudate.

Although generally well circumscribed, we have noted extension of the tumor elements into adjacent tissues in a small percentage of cases. This is most often seen in tumors arising in the region of the mediastinum testis. Extension of tumor elements—both epithelial and stromal—into the interstitium of the rete testis and rarely into the subjacent testis parenchyma (fig. 141) was seen in 40 percent of tumors involving the epididymal caput. Extension through the tunica into the immediate subjacent testis parenchyma occurs rarely in tumors involving the tunics of the testis. Such extension has no prognostic significance.

ORIGIN. The nature and origin of this strange tumor is unknown. The lesion is usually considered a neoplasm, but is considered by some pathologists to be a reaction to injury or inflammation. Its origin from epididymal epithelium, endothelium, mesothelium, wolffian (mesonephric) epithelium, and from müllerian mesenchyma have all been proposed (Jackson). Marcus and Lynn compared the ultrastructure of an adenomatoid tumor with that of a

Figure 141
ADENOMATOID TUMOR
Extension into the superficial subtunica portion of the testicular parenchyma occurs rarely. X210.
lymphangioma, a hemangioma, and a mesothelioma and concluded that adenomatoid tumor was structurally unrelated to hemangioma and lymphangioma. They found it impossible to distinguish morphologically between the cells of an adenomatoid tumor and those of a mesothelioma. In the female, transition from pelvic mesothelium into the lesion as downward growths is easily demonstrated. Although favoring mesothelial origin, we prefer the term adenomatoid to distinguish the lesion from the rare true mesothelioma of the scrotum.

References


FIBROUS PSEUDOTUMORS

SYNONYMS AND RELATED TERMS: Fibroma; pseudofibromatous periortitis; reactive periortitis; inflammatory pseudotumor.

Lesions that constitute reactive fibrous proliferations are the second most common tumor-forming lesions of the testicular adnexae. While they are not strictly neoplasms, they do form nodules and are often mistaken for neoplasms; thus, we feel discussion of these lesions is justifiable.

Diffuse fibrous thickening of the testicular tunics, with or without hyalinization and/or calcification, is found in many hematoceles and hydroceles, especially if these lesions have been traumatized or inflamed. All gradations from early organizing granulation tissue, through productive fibrosis, to scarring and hyalinization are seen.

Less well recognized is the fact that similar reactions can occur as a localized process. While the etiology of localized nodules is not as clear-cut as that of diffuse lesions, we have accumulated enough cases to trace the same pathways of development. Over two thirds of the cases occur in the testicular tunics, but about 10 percent of these nodules are found in the epididymis and the remainder occur in the spermatic cord. In the testicular tunics and epididymis, the lesions are predominantly fibrous in character, but about one half of those occurring in the cord present the histologic features of fibroxanthoma, sclerosing lipogranuloma, or sclerosing hemangioma.
In the testicular tunics, the nodules may be single or multiple, and either may be associated with diffuse fibrous thickening of the testicular tunics.

These nodules occur in all age groups, and they are fairly evenly distributed from the third through the sixth decades. They present clinically as asymptomatic, intrascrotal nodules, and about 45 percent are associated with a hydrocele which may be small or large. A history of prior trauma or of epididymo-orchitis is obtained in about 30 percent of the patients.

GROSS. Fibrous pseudotumors present the appearance of a typical “fibroma,” being well circumscribed, oval, and very firm. The cut surface has a white fibrous appearance, which may be tan or yellow if inflammation is still present. They measure from less than 0.5 to 7 or 8 cm. in diameter. When multiple nodules are present, they are generally of slightly smaller size than a single nodule (fig. 142).

MICROSCOPIC. The microscopic appearance ranges from that of organizing granulation tissue (fig. 143) to nodules composed entirely of hyalinized tissue (fig. 144) in which there may be foci of calcification and rarely bone formation (fig. 145). Between these extremes, the nodules are composed of proliferating fibroblasts in a stroma characterized by numerous small capillaries and extensive collagen production. Remnants of inflammation are evidenced by scattered foci, occasionally nodular, of inflammatory cells consisting predominantly of lymphocytes, plasma cells, and histiocytes, and sometimes admixed eosinophilic leukocytes. Persisting inflammatory cells may be absent entirely in nodules composed of scar tissue or hyaline tissue. In the cord, the nodules may have the appearance of fibroxanthoma or sclerosing lipogranuloma (see Fascicle I, Second Series, ‘Tumors of the Soft Tissues’).

In the literature, this lesion has generally
been regarded as a fibroma, but since this term implies that it is neoplastic, we have adopted the term fibrous pseudotumor which is more indicative of its true nature. Its clinical course is benign.

Figure 143
FIBROUS PSEUDOTUMOR
This shows the early organizing inflammatory stage of fibrous pseudotumor. The granulation tissue exhibits persisting inflammatory cells, and there is beginning deposition of collagen fibers. X350.

Figure 144
FIBROUS PSEUDOTUMOR
This is a hyalinizing fibrous pseudotumor with persisting focus of chronic inflammatory cells. X60.
RHABDOMYOSARCOMA

Rhabdomyosarcoma, particularly the juvenile form, is the most frequent tumor of the spermatic cord in our material. The few examples of pleomorphic type rhabdomyosarcoma have clinical and pathologic features identical to those of pleomorphic rhabdomyosarcoma occurring in other anatomic sites (Fascicle 1, Second Series, “Tumors of the Soft Tissues”).

Juvenile Rhabdomyosarcoma

SYNONYMS AND RELATED TERMS: Embryonal rhabdomyosarcoma; alveolar rhabdomyosarcoma; sarcoma botryoides.

This tumor is the most frequent para-testicular tumor in infants, children, and young adults. Patients ranged in age from 5 months to 28 years in our series. Rhabdomyosarcoma occurs more often in infants and young children. With the advent of puberty, the incidence rate again rises to peak at age 19, after which it declines rapidly. Juvenile rhabdomyosarcoma occurs more frequently in Caucasians, but 13 percent of the patients in our series were Black; the tumor also occurs in Orientals.

CLINICAL FEATURES. This tumor usually presents as a large intrascrotal solid mass. Mild pain or discomfort may be noted. Most juvenile rhabdomyosarcomas exhibit gradual progressive enlargement. Occasionally, there may be rapid growth. A majority of these tumors occur within the scrotum, although a few may be found between the apex of the scrotum and the external inguinal ring. The surgeon usually finds a large para-testicular tumor compressing the testis and epididymis to one side (fig. 146). Local extension to the testicular tunics is common and may involve the parietal layer; rarely, the parietal tunics are nearly replaced by tumor so that the testis is suspended in a sac with

References


Myosarcoma of the lower end of the spermatic cord has been sectioned and appears as a white ovoid mass, slightly larger than and immediately above the testis. Fixation of tumor to testis without actual infiltration of testis is common. (From Friedman, N. B., and Ash, J. E. Atlas of Genitourinary Pathology. Washington: American Registry of Pathology, 1946; also fig. 102 from Fascicles 31b and 32, First Series.)
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walls of rhabdomyosarcoma. The epididymis is sometimes invaded, and rarely the testicular parenchyma. The literature contains several reports of primary rhabdomyosarcoma of the testis (Alexander), of the epididymis (Walker and Cameron), and of the tunics (Areàn and Kreager). However, the precise site of origin of this tumor which is usually large and extensive, may be difficult to determine. While primary rhabdomyosarcoma of the testis, epididymis, or tunics may exist, we believe that most intrascrotal rhabdomyosarcomas are primary in the intrascrotal portion of the cord.

GROSS. The tumors range from 1.0 to 20.0 cm. in diameter. They are circumscribed but not encapsulated, and the cut surface is generally tan or gray-white with a fibrous consistency.

MICROSCOPIC. As Patton and Horn have indicated, the histologic features of rhabdomyosarcoma mimic those of developing embryonic skeletal muscle. The histologic pattern of this tumor varies from case to case, and even in different areas of the same tumor. Patterns range from those of undifferentiated malignant mesenchymal tumor (fig. 147), through a myxomatous stage mimicking myxoid liposarcoma (fig. 148), to a spindle cell pattern resembling fibrosarcoma (pl. III-A), or pleomorphic rhabdomyosarcoma. Any or all these basic patterns may be seen, and diagnosis is governed by cellular structures that are indicative of rhabdomyo-

Figure 147
EMBRYONAL Rhabdomyosarcoma of spermatic cord
This pattern resembles that of an undifferentiated malignant mesenchymal tumor. X700.

Figure 148
EMBRYONAL Rhabdomyosarcoma
The pattern in this myxomatous area in an embryonal rhabdomyosarcoma resembles that seen in myxoid liposarcoma, but no embryonal lipoblasts are present. X175.
blastic differentiation: (1) Cells with a budlike extension of intensely acidophilic cytoplasm from one pole of the nucleus (pl. III-B); (2) cells with elongated, straplike cytoplasm staining intensely with eosin and brilliant red with Masson (pl. IV-A); (3) pleomorphic and/or bizarre cells often shaped like tadpoles or racquets (pl. IV-B) (in tumors containing considerable collagen, the cells are spindle-shaped, but the presence of rhabdomyoblastic cells may be confirmed with Masson stain; pl. IV-A); and (4) cross-striations which are rarely found until straplike or pleomorphic cells appear, and prolonged search may be necessary for their identification (pl. V-A). Well fixed tissue, cut at 4 to 5 microns, carefully mounted, and not too heavily stained with hematoxylin and eosin or Masson stains aids materially in identification of cells with cross-striations (pl. V-B).

The alveolar type of juvenile rhabdomyosarcoma is now generally recognized as a variant of embryonal rhabdomyosarcoma; an alveolar pattern was present in some portion of the tumor in about 15 percent of our cases. A small percentage of tumors we studied had a predominantly alveolar pattern which was identical to that described in Fascicle I, Second Series, "Tumors of the Soft Tissues" (pl. VI-A). The clinical features and behavior of these tumors are identical to the embryonal type.

COURSE AND PROGNOSIS. There was local recurrence in the scrotum following local excision or orchietomy in about 10 percent of our cases; a few survivals have been noted after excision of recurrent tumors. Juvenile rhabdomyosarcoma metastasizes by way of the blood stream, and lymphatics, most often to retroperitoneal lymph nodes. But, when these nodes are excised in conjunction with orchietomy, they are usually negative. Metastasis may appear from two weeks to 27 months after primary therapy which is generally orchietomy. In fatal cases, death usually occurs within 24 months after excision of the tumor. Autopsy generally discloses that the tumor has widely disseminated with the bulk of metastasis in the retroperitoneal lymph nodes and is often associated with peritoneal sarcomatosis. In a few instances, the metastatic tumor literally encases the abdominal organs. Other frequent sites of metastasis include the lungs, the pelvic bones, the ribs, and vertebrae. We found no metastases to the central nervous system.

TREATMENT. The number of reported cases is rather small, but, in our experience, patients who had radical orchietomy and retroperitoneal lymphadenectomy survived longer than those with other forms of therapy. In children, orchietomy and inguinal node dissection resulted in better survival rates than orchietomy and retroperitoneal node dissection.

Undifferentiated Malignant Mesenchymal Tumor

A few of our cases had clinical and pathologic features identical to those of juvenile rhabdomyosarcoma, but we were unable to demonstrate clear-cut evidence of rhabdomyoblastic differentiation. The histologic features of these tumors consist of foci of undifferentiated round cells of mesenchymal type, associated with stellate mesenchymal cells arranged loosely in a myxomatous matrix. Such areas are identical to two basic patterns described for juvenile rhabdomyosarcoma (pl. VI-B). Inasmuch as we did not observe spindling out of the cells, collagen production, or evidence of rhabdomyoblastic differentiation, we classified these as undifferentiated malignant mesenchymal tumors, although we believe they are a variant of juvenile rhabdomyosarcoma. This concept is supported by their clinical behavior and prognosis which are identical to those of juvenile rhabdomyosarcoma.
PLATE III
(Plates III and IV from same case)

Rhabdomyosarcoma

A. This tumor composed of interlacing bundles of spindle-shaped cells resembles fibrosarcoma. Differentiating rhabdomyoblasts can be seen as large cells with dark nuclei. X130.

Embryonal rhabdomyosarcoma

B. Budlike accumulations of intensely eosinophilic cytoplasm are indicative of early rhabdomyoblastic differentiation. X1260.
PLATE IV
(Plates III and IV from same case)

A. This low power view demonstrates formation of long, straplike cells that are also indicative of rhabdomyoblastic differentiation. Such cells may or may not exhibit cross-striations. Masson stain. X130.

B. This bizarre, tadpole-shaped cell with multiple nuclei and eosinophilic cytoplasm is indicative of rhabdomyoblastic differentiation. Masson stain. X750.
RHABDOMYOSARCOMA

A. Several straplike cells with cross-striations are present. Masson stain. X100.

RHABDOMYOSARCOMA

B. This is an area of cartilaginous differentiation in an otherwise typical rhabdomyosarcoma. X100.
ALVEOLAR RHABDOMYSARCOMA
A. This pattern may be found in areas of an otherwise typical embryonal rhabdomyosarcoma, or the entire tumor may be composed of tissue with this pattern. X175.

UNDIFFERENTIATED MALIGNANT MESENCHYMAL TUMOR
B. The pattern resembles that of the undifferentiated and myxomatous stages of embryonal rhabdomyosarcoma, but in these tumors there is no evidence of rhabdomyoblastic differentiation. X195.
Cystadenoma of the Epididymis

SYNONYMS AND RELATED TERMS: Papillary cystadenoma; papillary clear cell cystadenoma; papillary hyperplastic nodule; papillary adenoma; hamartoma.

This benign, possibly hamartomatous, lesion is situated within, or in close apposition to the head of the epididymis. It is characterized by ectasia of the efferent ducts and by papillary formations, which are usually covered by vacuolated cells with clear cytoplasm. The tumor may be unilateral or bilateral, and represents the epididymal component of Lindau’s disease.

The first well documented example of cystadenoma of the epididymis was reported in 1956 by Sherrick, although cysts and adenomas of the epididymis had been reported in cases of Lindau’s disease many years previously (Melmon and Rosen). The English language literature contains seven cases that occurred in patients with Lindau’s disease and 10 cases of the tumor not associated with Lindau’s disease, four of which are included in our series.

There was unilateral involvement in 11 of our cases and bilateral involvement in five. Four patients had Lindau-von Hippel disease. Those patients with unilateral involvement experienced no difficulty following excision of the lesion. Thus, unilateral papillary cystadenoma of the epididymis may be regarded as a forme fruste of Lindau’s disease. All five patients with bilateral involvement, however, developed lesions in other organs: two had brain tumors of uncertain histogenesis (atypical ependymoma, atypical hemangioblastoma), one had visual problems of undetermined nature, one had multiple cysts of the kidneys, and the other patient had cystadenoma with the identical histologic features of the epididymal lesion removed from his spermatic cord. The nature and distribution of this lesion indicates that bilateral epididymal cystadenoma constitutes an incomplete type of Lindau’s disease.

The patients were from 16 to 68 years of age in the cases we reviewed; the tumor occurred slightly more often during the second and third decades. Seven patients were Caucasian, two were Black, two were Oriental, and the race of the other patient was not recorded. The presence of a small nodule in the region of the head of the epididymis was the only noteworthy clinical finding. The right epididymis was involved slightly more often than the left when the lesion was unilateral. Generally, the tumor had been present for a number of years, was asymptomatic, and did not enlarge appreciably. It was embedded in the substance of the head of the epididymis or attached to that structure by fibrous bands.

References

GROSS. Cystadenoma of the epididymis ranges from 1.6 to 5.0 cm. in diameter and is a cystic or solid, tan or brown nodule. On cut section, it may be multicystic, well encapsulated, or circumscribed (fig. 149) and have a mottled, light gray or tannish brown surface with yellow foci. The fluid within the cystic spaces is clear, yellow, or hemorrhagic.

MICROSCOPIC. Two findings are common to all lesions: Ectasia of the efferent ducts, and papillary formations (fig. 150). The tumor seems to arise from the efferent ducts that show all degrees of ectasia from slight dilatation to microcystic formation. Such ducts are lined with cuboidal cells, the cytoplasm of which is usually clear and vacuolated. Papillary processes, simple or complex, arise from the walls of some or nearly all the ducts, and sometimes become so extensive they fill up the cystic spaces giving the tumor a solid appearance. In such areas, the pattern is similar to that of some renal cell carcinomas, and distinction from metastatic renal cell carcinoma may be difficult. The covering cells of the papillae are identical to those lining the ectatic spaces, but may be tall columnar rather than cuboidal (fig. 151). Vacuolation may be marked, and secretory droplets sometimes protrude from the apices of the cells. The stroma is composed of dense fibrous tissue, which may be focally hyalinized. Inflammatory cells are present.
usually not numerous, although small foci of lipogranulomatous inflammation are occasionally seen in the stroma. The histologic structure of bilateral lesions and tumors associated with Lindau’s disease are identical except for the additional finding of foci with a histologic pattern seen in cerebellar hemangioblastoma (fig. 152). Such a focus has also been seen in one unilateral tumor.

The authors believe this lesion arises from the efferent ducts of the head of the epididymis, which are of mesonephric derivation. Association of some cystadenomas of the epididymis with Lindau’s disease suggests that this tumor may be a hamartoma.

Figure 151
CYSTADENOMA OF EPIDIDYMIS
(Figures 150 and 151 from same case)
The papillary processes are covered and the glandlike spaces are lined by cuboidal to columnar epithelial cells with clear or vacuolated cytoplasm. The spaces between papillae and the lumens of the glandlike structures are filled with a deeply eosinophilic homogeneous material resembling colloid. X300.

Figure 152
CYSTADENOMA OF EPIDIDYMIS
Cystadenoma in a patient with Lindau’s disease contains an area histologically resembling that of the cerebellar hemangioblastoma of Lindau’s disease. X130.
Mural Papilloma in Spermatocele

Figures 153 and 154 illustrate two cases of spermatocele in which small, 3 to 8 mm., mural nodules proved microscopically to be papillomatous.

Figure 153
MURAL PAPILLOMA IN SPERMATOCELE
(Figures 153 and 154 from same case)
Portions of the wall of a spermatocele contain a small mural papilloma. X35.

Figure 154
MURAL PAPILLOMA IN SPERMATOCELE
(Figures 153 and 154 from same case)
The lesion is attached to the wall of the cyst by a small pedicle of fibrovascular tissue. The papillae are covered by tall columnar cells, some of which are ciliated. Some of the cells contain clear vacuoles in the cytoplasm. X130.

References

TUMORS OF FATTY TISSUE

LIPOMA

Most lipomas of the spermatic cord are probably not true neoplasms, but simply localized collections of mature adipose tissue. Although lipoma is the second most common tumor of the spermatic cord in our material, it was in most cases an incidental finding at autopsy, or at the time of surgery for another condition, usually inguinal herniorrhaphy.

LIPOSARCOMA

Although this rare tumor is usually well differentiated, it may recur locally after excision. It occurs predominantly in the 39 to 88-year age group and presents as a large, firm tumor either within the scrotum or in the inguinal canal. Slow, progressive enlargement is the rule. The tumor usually resembles a lipoma, but is often multilobular or multinodular. The cut surface generally appears firmer than that of ordinary lipoma, and may exhibit foci of mucinous appearance. Microscopically, the tumor may contain foci of mature adipose tissue. However, a combination of areas of sclerosis and the presence of bizarre, pleomorphic giant cells should arouse suspicion of liposarcoma (fig. 155). The presence of mucinous foci with a characteristic, plexiform type of vascular pattern (fig. 156) is a diagnostic aid and the finding of embryonal lipoblasts (fig. 157) confirms the diagnosis.

Figure 155
SPERMATIC CORD: LIPOSARCOMA
(Figures 155—157 from same case)
The adipose tissue is undergoing fibrosis and contains several pleomorphic giant cells. X350.

Figure 156
SPERMATIC CORD: LIPOSARCOMA
(Figures 155—157 from same case)
The tumor contains foci in which the stroma is myxomatous and has a typical plexiform vascular pattern. X130.
TUMORS OF SMOOTH MUSCLE

LEIOMYOMA

In the epididymis, leiomyoma occurs on an average of one leiomyoma for every nine adenomatoid tumors, and their possible relationship has already been discussed. Leiomyoma presents the same clinical and pathologic features in the epididymis as it does when it occurs in other organs. We have not encountered a malignant smooth muscle tumor of the epididymis.

LEIOMYOSARCOMA

Tumors of smooth muscle in the spermatic cord are rare, but may be malignant. It is as difficult to distinguish between leiomyoma and leiomyosarcoma in this area as it is in other organs. Our series contained seven benign tumors and 13 malignant tumors.

Of the 13 patients with malignant tumors, three had local recurrence; two of these later died of metastases. Three other patients died of metastatic tumor without developing local recurrence. Pleomorphism of the cells and the presence of more than one or two mitotic figures per high power field are indicative of a possible malignant course.

References

MESOTHELIAL PROLIFERATIONS AND MESOTHELIOMA OF THE TUNICA VAGINALIS

Other than adenomatoid tumors which have been discussed earlier, lesions of the testicular tunics that appear likely to be of mesothelial origin always present two difficult problems for the pathologist. First, he must decide whether the lesion is of mesothelial origin, whether it is a metastatic carcinoma mimicking mesothelioma, or a tumor originating from the appendices of the testis or epididymis, the rete testis, or the epididymis. Secondly, if the lesion is judged mesothelial, he must determine whether the lesion is a benign reactive mesothelial proliferation or a true neoplasm of mesothelial tissue. While there are no easy answers to these two problems, certain guidelines may be useful.

REACTIVE MESOTHELIAL PROLIFERATIONS

In our experience, this may take one of several forms. The simplest is the presence of entrapped mesothelial cells in the walls of a hydrocele, a hematocele, or a diffuse fibrous pseudotumor. These may appear as individual dark-staining cells, small nests, or clumps of cells within a fibrinous matrix or the proliferating fibrous stroma (fig. 158). Glandlike spaces may be formed by these cells (fig. 159). Another consists of a downgrowth of mesothelial cells that usually form small tubular or glandlike extensions (fig. 160). The proliferating mesothelial cells may form simple papillary projections surfaced by cuboidal or rarely low, columnar, mesothelial cells (fig. 161). These proliferations may occur in hydroceles of the cord and in hernia sacs as well as in the tunica vaginalis.

Figure 158
MESOTHELIAL PROLIFERATION
Nests of entrapped mesothelial cells are present within the wall of an organizing vaginalitis. X300.
Figure 159
MESOTHELIAL PROLIFERATION
Entrapped mesothelial cells are evident in the wall of a hydrocele sac. The cells are arranged in the form of individual strands, small nests, or around tubular or glandlike spaces. X165.

Figure 160
MESOTHELIAL PROLIFERATION
Downgrowth of mesothelial cells forms tubular or glandlike spaces. This section is from the wall of a hydrocele sac. X185.
MALIGNANT NEOPLASMS OF THE TESTIS.

Tumors of the Testis

Figure 161
MESOTHELIAL PROLIFERATION
Focal proliferation of mesothelial cells is in a somewhat papillary formation. The lesion appeared as a small gray nodule on the inner surface of a hydrocele sac. X195.

MESOTHELIOMA

Exclusive of adenomatoid tumor, true neoplasm of mesothelial origin is rare. Although more common in older age groups, this tumor may be seen in younger adults and, rarely, in children. It usually presents as a hydrocele associated with a firm mass, or with a testis that feels harder than normal. Gradual enlargement of the hydrocele, and sometimes of the associated mass, is seen in about half the cases. The usual treatment is excision of the hydrocele sac, combined with orchietomy.

GROSS. Hydrocele fluid is usually clear. The major portion of the sac lining may be smooth and glistening, but some portion of the lining, and sometimes all the lining, will ordinarily present a shaggy or papillary appearance representing the tumor. This is often combined with a solid or partly cystic tumor, ranging from 0.6 to 6.0 cm. in maximum diameter. The tumor may be tan, white, yellow, or brown and is frequently quite friable.

MICROSCOPIC. The tumor usually has a complex structure with papillary processes combined with tubulo-alveolar structures and often solid sheets of cells (fig. 162). The cell structure is variable; the cells covering the papillary processes are usually rounded and cuboidal, but may be flattened and endothelioid, or rarely low columnar (fig. 163). Similar cells line the tubulo-alveolar spaces. When the cells are arranged as solid sheets, variation in size and shape is the rule, but marked cellular pleomorphism and bizarre cells are rare. In these areas, the cells often have a marked epithelioid appearance with acidophilic, ground-glass cytoplasm and large, centrally placed, moderately vesicular, round nuclei (fig. 164). Psammoma bodies are sometimes found in the papillary areas (fig. 165).
MESOTHELIOMA (Figures 162, 163, and 166 from same case)

This basically papillary but complex mesothelioma of the tunica vaginalis arose in a hydrocele sac. The wall was thickened and had a papillary appearance. X70.

Figure 162

Figure 163

MESOTHELIOMA (Figures 162, 163, and 166 from same case)
The cells are cuboidal and appear orderly in this higher power view. The nuclei are oval, vesicular, and have a moderate-sized nucleolus. X395.
Figure 164
MESOTHELIOMA
Epithelioid cells with ground-glass cytoplasm appear in a mesothelioma of the tunica. In areas, tubular and glandlike spaces are apparent. X130.

Figure 165
MESOTHELIOMA
Pure papillary mesothelioma with psammoma bodies arose in a persistent processus vaginalis from a 15 year old boy. X130.
Despite such variations in histologic features, the tumors arise from the mesothelial lining of the tunic, and it is often possible to trace continuity between cells of the mesothelial lining of the hydrocele sac and those of the tumor. This is helpful in differentiating this tumor from metastatic carcinoma (fig. 166). Although mesothelial cells may produce hyaluronic acid, they do not produce epithelial mucin so that stains for mucin may be helpful in distinguishing mesothelioma from metastatic mucinous carcinoma. Differentiation between papillary reactive mesothelial proliferation and papillary mesothelioma may at times be impossible. In general, lesions in which the papillary processes are simple are regarded as mesothelial proliferation, whereas those in which complex papillary formations are present are mesothelioma.

Based on the available evidence, pure papillary tumors have nearly always proved benign. Those of a more complex structure may recur, and over a prolonged period develop multiple recurrences.

There are a small group of tumors, usually in older men, which have a histologic pattern generally indistinguishable from that of mesothelioma, that have produced multiple recurrences. Occasionally, these tumors metastasize to the inguinal lymph nodes and rarely to the lungs. A number of cases have been reported in the literature under a variety of terms depending upon the apparent histogenesis of the individual case (Kasdon; Salm; Söderström and Liedberg). All these tumors have the same histologic characteristics, and although their histogenesis is unknown, mesothelial derivation seems probable.

References

SECONDARY TUMORS

SECONDARY CARCINOMA

Most carcinomas involving the spermatic cord, epididymis, or testicular tunics are secondary and incidental findings at autopsy or at orchiectomy for primary germ cell tumor of the testis. Rarely, involvement of these regions by a metastatic tumor is the initial clinical manifestation of a tumor which is primary in another organ, usually the stomach, kidney, and prostate.

LYMPHOMA

Lymphomatous involvement of the epididymis, spermatic cord, and testicular tunics is rare and nearly always secondary to malignant lymphoma manifesting primarily as a testicular tumor.

References


MISCELLANEOUS TUMORS OF EPIDIDYMIS, SPERMATIC CORD, AND TESTICULAR TUNICS

DERMOID CYSTS AND TERATOMA

Our material contains two examples of dermoid cysts of the spermatic cord, both presenting in the inguinal canal just external to the external inguinal ring. These were clearly within the spermatic cord and were not attached to the skin. In each case, the testis was negative to palpation. There were no primary teratomas of the epididymis, the spermatic cord, or the testicular tunics.

MELANOTIC HAMARTOMA

SYNONYMS AND RELATED TERMS: Retinal anlage tumor; melanotic progonoma; neuroectodermal tumor of infancy; retinoblastic teratoma.

Our files contain records of three examples of these strange pigmented tumors of unknown histogenesis occurring in the epididymis. We are aware of three further reports in the literature (Frank and Koten;
Eaton and Ferguson; Zone). Our records show that one infant was four months old and two were five months of age; two were Caucasian and one was Black. These pigmented tumors, 2.0 and 2.5 cm. in diameter, microscopically displayed nests of epithelial-like cells. Two types of cells were encountered: the small dark-staining cells with a vesicular nucleus and a large nucleolus, often clumped together forming a glomeruloid structure; and surrounding second cells which were larger, with eosinophilic cytoplasm containing melanin and surrounding a larger, sometimes vacuolated nucleus (fig. 167). The stroma was fibrous and hyalinized. The tumors have remained benign during a 3-year follow-up.

BRENNER TUMOR

Ross has reported a Brenner tumor beneath the tunica albuginea close to the head of the epididymis but distinct from it and the testis. Histologically, the lesion was entirely similar to Brenner tumor seen in the region of the ovary.

References

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 (fig. 168); 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, which lie on either side of the urethra and the ducts of which empty into the sides of the verumontanum; and the anterior lobe, a vestigial structure represented by

![Diagram of the prostate]

Figure 168

PROSTATE

This anatomic sketch of the prostate shows the transverse section at the level of the colliculus seminalis (upper) and the sagittal section (lower): (A) Posterior lobe; (B) middle lobe; (C) anterior lobe; and (D) lateral lobes. Note the position of the posterior lobe, inferior and posterior to the ejaculatory ducts. (Fig. 1 from Fascicles 31b and 32, First Series; also from Moore, R. A. The evolution and involution of the prostate gland. Am. J. Pathol. 12:599-624, 1936.)
from 8 to 10 acini, anterior to the urethra (fig. 169). 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 embedded in connective tissue stroma make up the male prostate. The glandular epithelium consists of two layers: tall, columnar, luminal cells and flattened, cuboidal, basal cells (fig. 170). The epithelium rests on a thin 0.07 to 0.10 micron, homogeneous, eosinophilic basement membrane, which has been proved by electron microscopy. The stroma consists of approximately equal amounts of smooth muscle and fibrous tissue.

Fisher and Jeffrey described two main cell types ultrastructurally (fig. 171). The predominant columnar or glandular cell extends from the lumen of the prostatic acinus to the basement membrane, which consists of definite bands of moderately electron-dense amorphous material. The nuclei are generally uniform in size and configuration and contain moderately dense nuclear granules surrounded by a double nuclear membrane. Nucleoli are infrequent. The cytoplasm contains a moderate number of round or ovoid mitochondria. The Golgi apparatus consists principally of aggregates of small vesicles, and, to a lesser extent, of more elongated lacunae. Larger vacuoles, bounded by a solitary limiting membrane, extend from the
Golgi region to the apical portion of the cell and are often densely packed. Not infrequently, they contain electron-dense granules as well as other smaller vacuoles. Many bodies exhibiting the reaction product for acid phosphatase are evident. Variable villiform extensions of apical cytoplasm extend into acinar lumina from the glandular cells. In some, small pinocytic vesicles, as well as dense bodies, seem to arise from evaginations of apical cytoplasmic membranes. The endoplasmic reticulum is not conspicuous and consists only of small, short membranes and rounded lacunae with ribosomes in their limiting membrane. Other ribosomes and occasional lipid droplets are scattered. In some glandular cells, parts of cytoplasm are replaced by aggregates of filaments which exhibit a parallel arrangement of two fibers 60 to 80 angstroms apart. At high magnification in good preparations, the filaments seem to be comprised of subunits of granules with a periodicity of 20 to 40 angstroms. Such cytoplasmic aggregates often appear in cells with a large number of secretory vacuoles, especially near the Golgi apparatus. Identical filamentous material arranged in a lamellated pattern is seen in acinar lumina and corresponds to corpora amylacea. Apposition of gland cells is linear, with occasional desmosomes in the cell membrane.

The basal cell is more polygonal, with a relatively large nucleus possessing a serrated border. Its cytoplasm appears more electron-dense than that of the glandular cell because it lacks secretory vacuoles. Mitochondria, endoplasmic reticulum, free ribosomes, and relatively inconspicuous Golgi apparatus are present. This cell type does not appear to extend to the lumen. Although basal cells have a linear attachment to columnar cells, they are often separated by lacunae of various size containing evaginations of their cytoplasm. Such formations appear
Portions of normal prostatic acinus reveal secretory, columnar cells, some of which rest directly on the basement membrane. The nuclei of others, which terminate on basal cells, appear serrated. The columnar cells are replete with secretory vacuoles. An occasional secretory vacuole is noted beneath the nucleus. Mitochondria and occasional lipid droplets are also present. The apical cytoplasm of two of the secretory cells is relatively free of organelles, and its villous surface is no longer extant. This appearance is indicative of apocrine secretory activity. Some secretory vacuoles in peripheral cells appear to be emptying into the lumen, the so-called merocrine secretion. X5400. (Fig. 1 from Fisher, E. R., and Sieracki, J. C. Ultrastructure of Human Normal and Neoplastic Prostate. In: (Ed.) Sommers, S. C. Pathology Annual. New York: Appleton-Century-Crofts, 1970.)

*Electron micrographs were prepared from tissue fixed in osmium tetroxide in veronal buffer, pH 7.5, and embedded in Maraglas except those demonstrating acid phosphatase. These were initially fixed in cold 4 percent formalin in phosphate buffer, pH 7 for 3 hours; sectioned; treated with b-glycerophosphate, lead nitrate, and ammonium sulfide; postfixed in 1 percent osmium tetroxide and embedded after dehydration as above. The following symbols apply to all photographs:

**Be:** basal cell  
**Bm:** basement membrane  
**C:** centriole  
**Ca:** corpus amylaceum  
**Cl:** capillary lumen  
**Co:** collagen  
**D:** desmosome  
**Er:** coarse endoplasmic reticulum  
**F:** filaments  
**Gl:** glycogen  
**Go:** Golgi apparatus  
**Ls:** lacuna  
**Lr:** lipofuscin body  
**Ly:** dense body, lysosome  
**M:** mitochondria  
**Mt:** microtubules  
**Mv:** microvilli  
**N:** nucleus  
**Nu:** nucleolus  
**R:** free RNA  
**Rb:** residual body  
**Sc:** secretory cell  
**Sm:** smooth muscle cell  
**Sv:** secretory vacuoles
more prominently in 25 percent of benign prostatic hyperplasia than in normal glands.

Although Liavag reports an increase in mitotic activity in hyperplastic prostates, the absence of mitotic figures in such prostates is noteworthy and suggests that the change is hypertrophy rather than hyperplasia, that the cellular division is amitotic, or that mitosis has been completed during fixation (Mostofi).

Division of the prostate into inner female and outer male zones is based not only on embryologic observation but also on arterial injection studies, and more recently on ultrastructural findings. The outer zone appears to form a horseshoe-shaped collar around the inner zone.

Normal development and maintenance of the prostate and other male secondary sex organs are dependent upon endocrine stimulation. Prepubertal castration or destruction of the pituitary gland prevents normal growth and development of the prostate, and substitution androgen therapy restores normal maturation of the gland. However, such substitution of pituitary gonadotropic therapy is effective only in the presence of functional testicular tissue or with administration of testosterone. Postpubertal castration or hypophysectomy result in atrophy of the prostate, which may be reversed with replacement therapy; administration of estrogens results in atrophy of the prostate.

With advancing age, the prostate undergoes certain involutional changes. The earliest change is "senile" atrophy which begins near the end of the fifth decade, simultaneously with a decreased androgen level, and occurs primarily in the outer zone. This is followed by nodular hyperplasia and secondary hyperplasia, most often located in the inner zone. Examination of the prostate of older patients often shows areas of carcinoma that are located in the peripheral or outer zone. Many of these remain quiescent, but some may progress and develop clinical manifestations.

Nonneoplastic or neoplastic enlargement of the prostate affects almost every man who reaches the age of 50. Nonneoplastic nodular hyperplasia is the most common symptomatic tumor-like condition in man and carcinoma of the prostate is the second most frequent cause of death from cancer in the male population in the United States. Yet, despite a tremendous amount of literature, little is known about the etiology, pathogenesis, early diagnosis, prevention, or proper treatment of this condition.

The interrelationship of hyperplasia and atrophy with carcinoma, and the frequency of these diseases in man necessitate a comprehensive review of the full spectrum of their reaction potential. The prostate gland must be regarded as a labile, restless organ with a tremendous potentiality ranging from seemingly quiescent atrophy to a wide spectrum of growth phenomena—from locally confined benign but progressive growths, to locally confined and slowly growing but invasive neoplasms, to most aggressive metastasizing tumors. Curiously, all these manifestations occur at a time when testosterone, the chief stimulus to the maintenance and growth of the prostatic epithelium, is on a progressive decline.

References


HYPERPLASIA OF THE PROSTATE

SYNONYMS AND RELATED TERMS: Benign prostatic hypertrophy; prostatic adenoma; adenomatous hypertrophy; benign enlargement; glandular and stromal hyperplasia; hyperglandular and stromal hyperplasia; fibroglandular hyperplasia; prostatism; nodular hyperplasia.

DEFINITION. Hyperplasia of the prostate is a benign enlargement of the prostate gland that results from varying degrees of hyperplasia of glandular and/or fibromuscular elements.

GEOGRAPHIC DISTRIBUTION. In the United States, the disease appears a decade earlier in Black men than in White men (Kahle and Beacham). The frequency is reported to be high among Protestants, very low among Jews, and intermediate among Catholics; higher among married men, especially the widowed and divorced, and among fathers; higher in urban and metropolitan areas than in rural and nonmetropolitan districts; and high among members of the same family (King et al.).

Prostatic hyperplasia is rarely seen in Koreans, Japanese, Asiatic Indians (Chang and Char), and Bantus (Van Der Reiss). Recent studies indicate that the disease is more prevalent than previously believed in Japan (Oomura et al.), Indonesia (Tan), and North India (Ahluwalia and Tandon). Perhaps the clinical rarity of the disease in these geographic areas is due to the fact that hyperplasia in these groups is more fibromuscular than glandular, and reveals itself on rectal examination as a small, moderately firm gland rather than a large, soft, boggy gland.

These reports, although quite interesting, must be accepted with reservation since few comprehensive and controlled incidence studies have been made. Mortality rates based on death certificates and reports are unreliable, and comparisons and conclusions are almost meaningless.

PROSTATIC HYPERPLASIA IN OTHER ANIMALS. Although prostatic hyperplasia is common in man, the dog and the mastomy are the only animals manifesting spontaneous prostatic hyperplasia. Enlargement of the prostate gland occurs in both, but its histologic features and histogenesis differ from those in man. Diffuse parenchymatous glandular hyperplasia, cystic degeneration, and squamous metaplasia with secondary infection are the chief histologic features. There is a tremendous qualitative predominance of columnar secretory epithelium with papillation into dilated alveoli; nodular hyperplasia and the stromal component seen in human patients are rarely evident. Interestingly, canine hyperplasia is not confined to old age, and impairment of defecation is a more frequent symptom than urinary disturbance; possibly this is due to the fact that periurethral hyperplasia is less frequent.

ETIOLOGY. Many proposed theories concerning the cause of prostatic hyperplasia have been discussed in detail elsewhere (Mostofi). Infection, arteriosclerosis, and neoplasia have no demonstrable basis as etiologic agents. Racial, social, environmental, constitutional, metabolic, and endocrine factors may be involved. As yet, there is no conclusive evidence that any of these factors produce hyperplasia of the prostate.

PATHOLOGIC ANATOMY. Prostatic hyperplasia rarely occurs before the age of 50. Usually, the chief symptom is obstruction to the flow of urine. The prostate may be enlarged. The enlargement may be diffuse or focal; it may be firm (fibromuscular) or unduly soft and boggy (glandular). The prostate must be carefully examined for areas of induration or hardness.

SITE OF ORIGIN. It is generally accepted that prostatic hyperplasia occurs initially in the periurethral portion of the middle and lateral lobes (the inner "female" zone of the
prostate in contrast to the outer subcapsular "male" zone) and consists of fibromuscular hyperplasia with subsequent involvement of the stroma by proliferating glands (figs. 172, 173).

GROSS. The hyperplastic gland may be small and hard or large and soft, depending upon the proportion of fibromuscular or glandular tissue. In contrast to the lobular architecture of the normal prostate, the rather spongy hyperplastic nodules form a mass that appears to compress the surrounding tissue into a fake capsule. Cut surfaces of the nodules are pale, compact or cystic (figs. 173, 174), and finely trabeculated (fig. 175). If the hyperplasia is fibromuscular, the process may be diffuse without nodularity. The growth is invariably expansile and follows anatomic pathways peculiar to the periurethral situation of the prostate, resulting in a variety of topographic localizations of the enlargement. Randall recognized eight types and described them as follows: a lateral lobe that produces intravesical and intravesical enlargement but does not protrude into the bladder or distort the vesical neck; a posterior commissural or median lobe which forms a new middle lobe that protrudes into the bladder by elevating the floor of the trigone; lateral and median lobes that involve both intravesical and intravesical enlargements; a subcervical lobe that is usually intravesicular and pedunculated; lateral and subcervical lobes that protrude into the bladder and urethra; lateral, median, and subcervical lobes; an anterior commissural lobe; and a subtrigonal lobe.

Figure 172
HYPERPLASIA
In this photomicrograph, hyperplasia is confined to the periurethral zone while the subcapsular zone shows atrophy. Note the horseshoe-shaped arrangement. X3.
HYPERPLASIA

This illustrates nodular hyperplasia of the prostate, glandular type. In the right lateral lobe is a large, circumscribed, hyperplastic, glandular nodule with a honeycombed cystic structure. (Fig. 29 from Fascicles 31b and 32, First Series.)

HYPERPLASIA

This illustrates nodular hyperplasia of the prostate, stromal type. In the middle lobe just posterior to the urethra are two white, ovoid, hyperplastic stromal nodules that characteristically arise near the urethra. Glandular nodules are also present in the lateral lobes. (Fig. 30 from Fascicles 31b and 32, First Series.)
MICROSCOPIC. Moore, Swyer, Franks, Akimoto, and Kato have thoroughly described the histologic features of the nodules. In contrast to the uniformity seen in normal glands, hyperplastic glands show considerable variation in structural appearance. Varying degrees of glandular or stromal hyperplasia are seen (figs. 175—178) such as fibrous or fibrovascular hyperplasia found in early nodules; fibromuscular; muscular; fibro-adenomatous; fibromyoadenomatous; and purely adenomatous. Usually, the acini are enlarged and papillary processes of the epithelium project into the lumen (figs. 175, 176). Both ductal and acinar epithelium participate. Moore designated the acinar epithelium as active or inactive. The former, which predominates in normal mature glands, is in the process of reacting to hormonal stimulation by secretion. These tall, columnar cells

Figure 175
PRIMARY HYPERPLASIA OF Prostate
(Figures 175, 197, and 215 from same case)
Papillation of acini is seen in this primary hyperplasia of the prostate. X80.

Figure 176
HYPERPLASIA
(Figures 176 and 177 from same case)
A double layer of nuclei may be seen in the "active" glands. X300.
Benign Lesions

have poorly defined boundaries, abundant, finely granular or homogeneous cytoplasm, and basal nuclei that often form a double layer. The papillae are numerous and elongated, and the intralobular trabeculae are thin and delicate. Inactive cells resemble those seen in prepubertal prostate glands; they are cuboidal or low columnar with well defined cell walls, scanty vesiculated cytoplasm, and single-layered basal nuclei. Papillae are few and relatively small, and intralobular septa are thick and coarse. Characteristic, loose, fibromuscular stroma intervenes between acini and lobules and, in some areas, forms aglandular nodules (figs. 177, 178). However, the elastic tissue hyperplasia observed in the breast is not found in prostatic enlargement.

![Figure 177](image)

**Figure 177**
**STROMAL HYPERPLASIA**
(Figures 176 and 177 from same case)
A relatively large, aglandular, periurethral nodule is shown. X10.

![Figure 178](image)

**Figure 178**
**STROMAL HYPERPLASIA**
The hyperplasia is of fibromuscular tissue simulating a leiomyoma. X115.

No ultrastructural differences have been noted between normal (fig. 171) and hyperplastic epithelial cells, with the possible exception of intercellular lacunae (figs. 179, 180; Fisher and Jeffrey; Tannenbaum et al.).

There are conflicting reports relative to the DNA and RNA content of the hyperplastic prostate, but it appears to be increased. Comparison of phosphatase activity of normal and hyperplastic prostate glands shows a similar intracellular site of enzyme. Considerable phosphatase activity is seen in the lumina of dilated hyperplastic acini. The secretion is more concentrated and the free acid phosphatase is so active and present in such great amounts that a dense precipitate is found even at high pH where there is usually slight activity compared to optimal acid pH range.
Figure 179
PROSTATIC GLANDULAR HYPERPLASIA
Note the laminated luminal aggregate of filaments (A) in benign prostatic hypertrophy. Microvilli (MV) of cell surface, secretory vacuoles (SV), and Golgi structures (G) are conspicuous. A few mitochondria (M) and lipid droplets (L) are also present. The calibration mark represents a micron. X15,000. Inset represents the light microscopic appearance of a thick section of the area studied by electron microscopy. Identity of the filamentous aggregates with corpora amylacea (CA) is apparent. X100. (Fig. 14 from Fisher, E. R., and Jeffrey, W. Ultrastructure of human normal and neoplastic prostate. Am. J. Clin. Pathol. 44:119-134, 1965.)

Figure 180
PROSTATIC GLANDULAR HYPERPLASIA
This basilar portion of acinus from benign prostatic hypertrophy demonstrates marked lacunar separation of cells with villiform cytoplasmic extensions (L). Mitochondria (M), dense bodies (db), rough endoplasmic reticulum (Er), and cytoplasmic vesicles (v) are also evident. The basement membrane (BM) is subtended by collagen fibers (Co). The calibration mark represents a micron. X7000. (Fig. 15 from Fisher, E. R., and Jeffrey, W. Ultrastructure of human normal and neoplastic prostate. Am. J. Clin. Pathol. 44:119-134, 1965.)
Benign Lesions

Figure 179

Figure 180
Qualitative differences between hyperplastic and normal areas have been suggested by the demonstration of a distinctive carbohydrate metabolism, low respiration, aerobic and anaerobic glycolysis, and terminal electron transport systems resembling those of carcinoma (Tolins and Moore; Barron and Huggins; Fujita).

In addition to hyperplastic glandular and stromal elements observed in these nodules, other changes include secondary hyperplasia, atrophy, and epithelial metaplasia.

In secondary hyperplasia, the histologic picture is somewhat different and its pathogenesis is obscure. There is diffuse but irregular hyperplasia of the epithelium in a prostatic acinus that otherwise shows involution (fig. 181). According to Moore, increase of collagenous tissue and decrease of smooth muscle, typical of older age, are seen in the intralobular stroma. The acini are round or oval and they are dilated and lined by a double layer of epithelium which may be thin. The hyperplastic epithelium is tall and the cytoplasm is reticulated; there is evidence of secretion. The nuclei are large and vesiculated. There is focal hyperplasia with inward buckling of the epithelium without forming true papillae. Thus, secondary hyperplasia is characteristic of the "old" prostate and is rarely seen in a prostate that does not also show nodular hyperplasia. Its incidence is relatively low, however, since it is observed in only 5 percent of all senile glands.

Physiologic atrophy in the prostate, which may involve the epithelium, the acini, or the stroma, has been described in detail by Moore. In atrophy of the prostate, epithelial cells are cuboidal; the cytoplasm is granular and reticulated, cell boundaries are distinct, and there is no scalloping toward the lumen. The somewhat hyperchromatic nucleus fills at least half the cell. Later the cell becomes flatter and the cytoplasm more homogeneous and acidophilic. There is associated atrophy of the acini and the stroma (fig. 182). Acinar atrophy usually involves an entire lobule within which the acini are smaller, collapsed, and closely packed; some contain a granular acidophilic material. In its early stages, stromal atrophy consists of proliferation of fibroblasts around the acini, followed by hyalinization of the collagen. Moore referred to these changes as sclerotic atrophy.

The histologic changes of epithelial metaplasia in the prostate have been adequately described by Mostofi and Morse. Metaplasia of prostatic acinar epithelium may be seen in association with infarction of the prostate in about 25 percent of prostatic
nodular hyperplasia. Metaplasia may occasionally be spontaneous, secondary to previous estrogen administration, to transurethral resection, or to infection. Squamous metaplasia is the usual response of the prostatic ducts to estrogen. Grossly, infarction of the prostate presents a well circumscribed hemorrhagic or yellowish brown area (fig. 183).

Figure 182
"ATROPHY" OF PROSTATE
The glands are collapsed and the epithelial lining is low cuboidal and pyknotic. X130.

Figure 183
RECENT INFARCT OF PROSTATIC HYPERPLASTIC NODULE
The well circumscribed, slightly discolored infarcted nodule bulges on cut surface. Small foci of hemorrhage are visible. (Fig. 14 from Fascicles 31b and 32, First Series.)
In metaplasia due to infarction, the acinar and ductal epithelium is replaced by flattened squamous or transitional epithelium (figs. 184, 185). The epithelium may be from 3 to 5 layers thick. It may line the acini or fill the acini or the duct, with the formation of solid nests with a whorled appearance. Intercellular bridges are rare. The cells are well differentiated and show neither anaplasia nor increased or abnormal mitotic activity.

Early in infarction, metaplastic cells are at the periphery of a zone of coagulation necrosis; as healing takes place, they are seen in an area of scarred stroma.

Metaplasia of the ductal or terminal alveolar epithelium, unassociated with apparent infarction, alteration in the stroma, or infection, may occur spontaneously in the presenile prostate. A mass of spindle-shaped epithelial cells oriented with their long axis at right angles to the acinar or ductal wall replaces the normal acinar or ductal epithelium. The cuboidal luminal cells are oriented toward the lumen. There is no basal layer. The cells are well differentiated, and there is no evidence of anaplasia or invasion. Nests of transitional epithelium are occasionally found in the prostate and usually involve the major ducts. In a few instances, transitional epithelium may extend to smaller branches, but it is always limited to the ducts, is indistinguishable from transitional epithelium of the prostatic urethra, and shows no evidence of neoplasia.
PATHOPHYSIOLOGY. Enlargement of the prostate per se causes no obvious disturbance. The resultant disturbance is secondary to effects on the urethra, bladder, kidney, and prostate gland itself.

Obstruction results from elongation, tortuosity, and compression of the posterior urethra. Elevation of the urinary outlet above the level of the floor of the bladder and the ball-valve action of the enlarged middle lobe contribute to incomplete emptying of the bladder, which in turn, results in residual urine and infection, with or without calculus formation. Stretching of the vesical sphincter musculature by the enlarged middle lobe produces incompetence of the sphincter which results in constant dribbling. Pressure on, or interference with the nerves supplying the sphincter may also contribute to incontinence. In an effort to overcome the obstruction, the vesical musculature undergoes hypertrophy. Hypertrophy of the criss-crossing vesical musculature results in the characteristically ribbed appearance of the muscle bands. Efforts to increase the intravesical hydrostatic pressure to overcome obstruction at the bladder neck result in outpocketings of the mucosa through the thinner portions of the wall which form false diverticula (fig. 186). If untreated, the process progresses to decompensation with dilation of the bladder and thinning of the wall. The latter results in loss of sphincter action of the vesical musculature normally exerted on the intramural portion of the ureter. Dilatation of the ureter and the renal pelvis and secondary infection may cause renal insufficiency and eventually hypertension in some cases.

An enlarging nodule causes compression of the surrounding normal prostatic tissue. Since all the blood supply is from the periphery, such compression interferes with the blood supply and results in infarction of the nodule in about 25 percent of prostates with hyperplasia. Other than sudden total anuria due to the larger size of the infarcted prostate and/or hematuria, such infarction may be associated with elevated total serum and prostatic acid phosphatase and lead to an erroneous diagnosis of carcinoma.

In addition to these serious and symptomatic manifestations, certain biochemical changes have also been reported and discussed in detail by Mostofi.

TREATMENT. Either medical or surgical treatment may relieve urinary obstruction and prevent vesical distention. Obviously, the choice of therapy must be tailored to the patient and the experience of the urologist. Specific details of treatment are beyond the scope of this fascicle.

Figure 186
DECOMPENSATION OF BLADDER
Typical lateral and medial lobe hyperplasia of the prostate has resulted in considerable dilatation and trabeculation of the bladder.
PROGNOSIS. For most patients, considerable relief may be obtained by conservative methods. A majority of those requiring surgery obtain excellent results. The careful selection of treatment for each individual patient will aid in reducing mortality rates and provide the best results.

References


Van Der Reis, L. Benign prostatic hypertrophy and coronary heart disease; correlation or coincidence? J. Am. Geriatr. Soc. 7:866-869, 1959.

BENIGN TUMORS OF THE PROSTATE

Adenoma, myoma, and fibroma are rare and difficult to identify. Most such lesions are, in fact, manifestations of benign prostatic hyperplasia. Two rare benign lesions, however, merit brief consideration.

ADENOMA AND PAPILLARY ADENOMA OF THE UTRICLE

These tumors usually occur in relatively young men; they may be manifested by obstruction or bleeding. Cystoscopically, they present as cherry red papillary projections in the prostatic urethra. Histologically, they resemble adenomatous hyperplasia. Butterick and associates have described aberrant prostatic tissue in the urethra which presents an identical appearance.

BLUE NEVUS OF THE PROSTATE

This lesion is a histologic curiosity, but may be confused with melanoma. Usually, it is an incidental finding with a clinically diagnosed hyperplastic prostate. Its characteristic feature is infiltration of the fibromuscular stroma by stellate and spindle-shaped cells, containing finely granular, brown pigment in the cytoplasm. The cells are distributed diffusely, either in clumps or single cells, with elongated branching cytoplasmic processes (fig. 187). The brown pigment may obscure the nuclei. Identification of the pigment is essential before it is regarded as melanin, since iron pigment may be seen in a number of hyperplastic prostates secondary to hemorrhage and infarction. Also, some prostates contain lipofuscin pigment. The pigment must be iron negative; it should be positive with Masson Fontana stain and bleachable. Further identification can be established by electron microscopy.

Figure 187
BLUE NEVUS

This blue nevus of the prostate shows brown pigment. (Courtesy of Dr. Wellington Jao, Chicago, Ill.) X350.

References


MALIGNANT TUMORS OF THE PROSTATE

Nearly all malignant tumors of the prostate gland are carcinomas arising from acini and ducts. When the term carcinoma is used without qualification, it refers to such glandular lesions. Other types of malignant neoplasms, e.g., transitional and squamous cell carcinoma and a variety of sarcomas, are occasionally encountered as well as the extremely rare carcinosarcomas.

CARCINOMA

SYNONYMS AND RELATED TERMS: Differentiated adenocarcinoma; anaplastic adenocarcinoma; cribriform carcinoma; adenocarcinoma; acinar carcinoma; alveolar carcinoma; alveolar adenocarcinoma; carcinoma simplex; cylindrical (duct) cell carcinoma; glandular carcinoma; small cell carcinoma; mucinous carcinoma; papillary carcinoma; carcinoma xanthomatodes.

DEFINITION. Carcinoma is a malignant tumor arising from the acinar and/or ductal epithelium of the prostate that may vary considerably in its glandular differentiation, anaplasia, and behavior.

INCIDENCE AND PREVALENCE. Clinically, carcinoma of the prostate constitutes the second most frequent cause of death from carcinoma in the male population of the United States and the fifth most frequent cause in Great Britain (Kennaway). The classic autopsy studies of Muir, Rich, and Moore have been followed by the studies of Baron and Angrist, Edwards and associates, Franks, and Halpert and associates. These later studies recorded figures of 46, 18, 11, and 37 percent, respectively, for incidental cancer of the prostate in routine autopsies. Hirst and Bergman reported that by the ninth decade the incidence rate increases to 80 percent. Gyorkey reported an overall autopsy incidence of 9.3 percent and an incidence of 12.2 percent after the age of 50.

Such prevalence rates are not entirely academic. Given time, with an increasing age of the population, these slowly growing tumors may assume more aggressive characteristics.

VARIATION IN RACIAL AND GEOGRAPHIC DISTRIBUTION. Segi showed that the age-adjusted death rates from cancer of the prostate in 24 countries were highest among the Black population in the United States (23.3 percent), followed by males of Norway, Switzerland, Australia, Union of South Africa, Sweden, and the White population of the United States (14.3 percent). Israel and Japan were listed as the twenty-third and twenty-fourth countries (7.3 and 1.1 percent, respectively). Akazaki and co-workers noted that the prevalence of incidental carcinoma found at autopsy varied only slightly with the rates reported from the United States, Japan, and Columbia.

ETIOLOGY. Some endocrine disturbance either alone or with other factors seems suspect, but as yet there is no convincing evidence for possible causes of carcinoma of the prostate. Kipling and Waterhouse observed that male workers exposed to cadmium compounds developed a statistically significant increase of carcinoma of the prostate.

PROSTATIC CARCINOMA IN ANIMALS. The incidence of adenocarcinoma of the prostate in dogs is about 10 percent (Grant; Sticker); this tumor also occurs in horses and cows. Engle and Stout reported carcinoma of the prostate in an old monkey.

Moore and Melchionna induced squamous cell carcinoma and leiomyosarcoma of the prostate by injection of a 5 percent solution of 1:2 benzpyrene into the prostate of rats. Seventy-five percent of the rats devel-
opened tumors which were unaffected by castration. Dunning and associates produced squamous cell carcinoma of the prostate by implantation of methylcholanthrene into the prostatic lobes of rats.

Horning produced transplantable adenocarcinoma by impregnating fragments of prostatic epithelium with 20 methylcholanthrene crystals and grafting subcutaneously into a host mouse of the same strain, age, and sex. Scott expressed doubts that this was true adenocarcinoma. However, Smith obtained similar tumors and squamous cell carcinoma by transplanting bits of mouse prostate and methylcholanthrene subcutaneously. Bredler continued the growth of Smith's tumors through several generations. While the sex of the host had no effect on the tumor growth, transplantation into younger animals resulted in rapid growth. Neither castration nor estrogen administration affected growth of the tumor.

The most interesting and important attempt at carcinogenesis has been that of Paulson and his associates. They observed that cultures of hamster prostatic tissue infected with Simian virus 40 underwent transformation 5 to 8 days after injection. When injected into homologous hosts, these transformed cells produced malignant tumor. Prostatic acid phosphatase (tartrate inhibited phosphatase) was demonstrated in the culture of transformed cells, in the tumors, and in the serum of tumor-bearing animals. Viral antigens could be demonstrated in the infected cells. If a relationship between viruses and carcinoma of the prostate could be found in man, it would be important for diagnosis, treatment, and control. In three spontaneous adenocarcinomas of the prostate, Györkey showed viral particles displaying morphologic features that resembled oncornoviruses.

Mirand produced squamous cell carcinoma, adenocarcinoma, and leiomyosarcoma by injection of 20 methylcholanthrene into rat prostates. The first two tumors metastasized by both vascular and lymphatic channels. Some of the squamous cell carcinomas were androgen dependent, others, independent.

PATHOLOGIC ANATOMY. In its early and possibly curable stage, the disease is asymptomatic. For early detection of this disease, competent rectal examination should be made of every man over 40 years of age. Regrettably, however, this most important clinical test is often omitted. A discrete firm or stony-hard area must be regarded as indicative of cancer unless proved otherwise. Jewett (1956) and Hudson and Stout have shown that half of such nodules are malignant. However, since a substantial number of such nodules are benign, biopsy of the prostate should be examined before a definitive diagnosis of carcinoma is given, even though the acid phosphatase level may be elevated. The presence of a nodule imposes a responsibility on the pathologist as well as the urologist to rule out a carcinoma.

As the disease progresses, most of the prostate becomes a hard, irregular mass with sharp ridges. Extension outside the gland initially involves the base of the seminal vesicle, the membranous urethra, and the bladder. With invasion of the seminal vesicle, a plateau develops which terminates abruptly at the cephalic end of the growth and forms the rectal shelf.

Fixation of the prostate gland to adjacent structures is accepted as evidence of extension beyond the prostate unless proved otherwise. In more advanced carcinoma, the entire bony pelvis is filled, producing a so-called frozen pelvis. Invasion of the rectum with mucosal ulceration is rare; however, invasion of lymph nodes near the tip of the semi-
nal vesicle may easily be detected. "Blind" biopsy for carcinoma, especially in its early stages, has resulted in many false negative and false positive diagnoses. Carcinoma is apt to be missed if it is small, surrounded by hyperplasia or otherwise buried within the prostate, or if it is located more anteriorly. One fact needs special emphasis—induration and hardness result from stromal reaction. In a medullary carcinoma, there is little stromal proliferation and consistency of the tumor is soft.

**Differential Diagnosis.** Granulomatous prostatitis, calcific nodules in the prostate, prostatic infarct, and prostatic atrophy may clinically simulate carcinoma of the prostate. Generally, any of the following rectal findings should alert one to a diagnosis of carcinoma: (1) a rough and irregular capsule, induration with adhesions and fixation of the prostate (especially involving the seminal vesicle irrespective of its hardness); (2) an indurated area or nodules in the prostate; (3) elevated or nonelevated smooth or irregular edges; and (4) adhesion and fixation of the prostate to the adjacent tissue, especially the seminal vesicle.

**Laboratory Diagnosis.** Radiologic, biochemical, cytologic, pathologic, and other laboratory procedures are utilized to diagnose carcinoma of the prostate.

**Radiologic Findings.** In every patient suspected of carcinoma of the prostate, not only intravenous pyelography is indicated but complete radiologic survey including pelvis, vertebrae, ribs, shoulders, femur, and skull. Most frequent sites are the pelvis, lumbosacral spine, and the upper parts of the femur. The most common type of bone metastasis is osteoblastic, but some patients may also have osteolytic lesions. In a few patients, only osteolytic metastases are found.

Radioisotopes of strontium (St_{185}) and zinc (Zn_{69}) are also valuable. St_{185} may detect metastases not visible in routine radiographs (Faber) and Zn_{69} is used for prostatic scanning (Johnson et al.), but at the present both are of limited value in diagnosis.

Seminal vesiculography may help to differentiate prostatic carcinoma from hyperplasia—narrowing, elongation rigidity, and amputation of ducts are the characteristic findings in carcinomatous involvement (Fetter et al.), but these are late manifestations. Immunologic diagnosis of carcinoma of the prostate is in experimental status (Ablin et al.).

**Biochemical Findings.** In about 60 percent of patients with carcinoma and 80 percent of those with metastases to bone, total serum acid phosphatase (TSAP) is elevated, but declines after orchiectomy, estrogen therapy, and adrenalectomy.

The prostate gland is not the only source of TSAP; it is also derived from erythrocytes, liver, kidney, and bone. Elevated TSAP is not necessarily diagnostic of carcinoma inasmuch as all instances of elevation are not due to this disease. Hyperparathyroidism, multiple myeloma, Gaucher's disease, Paget's disease, and other diseases of bone may also manifest elevated total serum acid phosphatase. It is essential to determine the prostatic fraction of serum acid phosphatase (PAP); the L-tartrate inhibition of Fishman and Lerner and the alpha naphthyl phosphate substrate of Babson and associates are two of the most reliable methods.

Cook and associates utilized the Fishman and Lerner method for 2,408 patients and reported elevated PAP in 100 percent of patients with distant metastases, 87 percent of those with bony metastases, and 47 percent of those with local soft tissue metastases; no elevation was reported for those patients with carcinoma localized to the prostate.

Not all elevations of PAP indicate carci-
Carcinoma of the prostate inasmuch as digital and operative manipulation, catheterization, and recent and old infarction commonly observed in hyperplasia may result in significant elevation of both TSAP and PAP. Kendall found the enzyme elevated after manipulation in about 6 percent of patients with hyperplasia compared to 32 percent of those with untreated carcinoma and premanipulation normal PAP. Elevation may continue for 24 hours or longer (Still).

Doe and Mellinger reported that both TSAP and PAP manifest a circadian variation with the highest point reached at about 2:00 P.M. and the lowest at 11:00 P.M.

Neither urinary acid phosphatase, mainly renal in origin, (Fernandez et al.) nor parotid gland acid phosphatase (Delroy and Penner) is of any diagnostic value.

Serum **alkaline phosphatase** is helpful in following the course of osseous metastases of prostatic origin, but it is of no diagnostic value because fractures, Paget's disease, hyperparathyroidism, and hepatic disease also give high levels.

A number of other chemical changes have been described, but none compare to the usefulness of acid and alkaline phosphatase.

Twelve percent of patients with carcinoma of the prostate show **fibrinolytic activity** in the serum, and carcinoma of the prostate is the only neoplastic disease in which fibrinolysis occurs in the absence of anoxemia. Preoperative determination of this activity may alert the urologist to the possibility of excessive bleeding during and after prostatectomy (Tagnon et al.).

**Cytologic Findings.** Cytologic examination may be of some use for diagnosis in prostatic carcinoma. In positive smears, whether urinary or from needle aspiration, cells occur as well spaced clumps and distinct cells, not as single malignant cells (fig. 188). The cells are generally larger than those of the normal prostate. Cell borders are indistinct; in single cells, the borders are peripherally frayed. The cytoplasm is relatively scanty and somewhat reticulated, staining light blue. The nuclei are relatively large and of various size and shape; they are usually hyperchromatic, and occasionally have nucleoli. In anaplastic carcinoma, the cells appear singly or occasionally in small, irregular clumps. The cells are often small with moderate or scanty bluish-staining cytoplasm and round or oval nuclei with much variation in size, shape, and staining. Less frequently, they are much larger and more bizarre with a wide variety in size, shape, and staining of cells and nuclei.

![Figure 188](image_url)

**Carcinoma**

Note the variation in size, shape, and staining of nuclei in this nest of neoplastic epithelial cells. X350.
Positive urine smears are rarely found in early and incidental silent carcinoma. False positive diagnoses are sometimes made because of the presence of bizarre hyperchromatic nuclei of seminal vesicular origin. Some false negative smears are obtained from patients with well differentiated carcinoma. Such instances prevent total dependence on cytdagnosis and demand histologic confirmation. Nevertheless, between 60 and 70 percent of patients with prostatic carcinoma have a positive cytologic finding (Mason; Ekman et al.; Williams et al.).

Prostatic massage improves the results. In 10,410 smears made from 2,445 patients, Frank and Scott found 296 with class 3, 4, or 5 smears. Of these, 117 had histologically proved carcinoma. This represented an accuracy of 46.7 percent in class 3 (suspicious) smears and 87.7 percent in class 4 or 5. Many urologists, however, are reluctant to massage a suspected malignant prostate. Regrettably, cytologic examination of the urine is not yet applicable to large scale screening and is of such limited value that most laboratories do not use it.

Smears of material removed by needle aspiration offer the greatest diagnostic accuracy (Franzen et al.).

Flocks and Cheng reported that 10 percent of their patients with stage 1 and 2 carcinoma had bone marrow smears that were positive for metastatic carcinoma; that figure rose to 60 percent for patients with clinically detected extraprostatic extension. Mehan and associates found several patients with stage 2 and 3 carcinoma who had positive bone marrow smears, even though their serum acid phosphatase levels were not elevated.

BIOPSY PROCEDURES. We have emphasized the need for pathologic confirmation of diagnosis of carcinoma of the prostate. Four methods of biopsy that may be used include: transurethral resection, perineal open or needle biopsy, transrectal open or needle biopsy, and open retropubic biopsy. Needle biopsy refers to any aspiration, whether trocar, punch, or needle. Transurethral resection is used primarily to relieve obstruction. It may lead to a diagnosis of carcinoma of the prostate in advanced cases, but must be regarded as unreliable. Obviously, an open biopsy, whether transrectal or perineal, would seem preferable to a blind needle biopsy, and it has its advocates. Perineal or transrectal needle or punch biopsy is used extensively and various instruments are available for this procedure. The most popular is the Vim-Silverman needle that permits multiple punctures. Perineal biopsy yields adequate tissue in 85 percent of patients (Fergusson, 1965a); it provides reliable diagnosis of early carcinoma of the prostate in about 70 percent of patients.

It should be emphasized that negative results from any biopsy, especially with a needle, do not rule out carcinoma. The tissue must not be squeezed because it then becomes impossible to interpret pathologic findings. Carcinoma implantation along the route of a needle biopsy has been reported by Burkholder and Kaufman, and by Labardini and Nesbit, but such a complication is surprisingly rare; only seven cases have been reported up to 1973.

CLINICAL CLASSIFICATION. There is general agreement regarding the basis of clinical classification, but disagreement exists over terminology and definitions. Two categories of cancer have been recognized:

(A) Incidental carcinoma not clinically manifest. Histologically, malignant areas may be found in 6 to 21 percent of tissue from a clinically benign prostate removed from a patient whose serum acid phosphatase is normal and who has no evidence of skeletal metastasis. Such a tumor has been variously
designated as latent or occult, but we prefer the term incidental since the tumor is neither suspected nor diagnosed clinically.

The term occult has also been applied to cases in which the patient presents with generalized metastases, but in which there is no clinical suspicion of a primary tumor in the prostate. The term occult has been used synonymously with latent; therefore, it is confusing. We prefer the term locally silent metastasizing carcinoma.

(B) Clinically manifest carcinoma. Efforts to stage this disease have produced various clinical classifications, all of which have been proposed. All classifications are based on the extent of prostatic involvement, local extension beyond the capsule, and spread to regional lymph nodes or distant sites. However, no agreement exists on nomenclature. For uniformity of criteria, classification must be based on clinical, biochemical, and radiologic determination, and biopsy confirmation of carcinoma (clinical staging), not on the examination of specimens removed at surgery or autopsy (pathological staging). The following clinical classification has been proposed.

(1) A single nodule occupying less than one lobe of the prostate with smooth and regular capsule, normal acid phosphatase, and x-rays.

(2) Tumor occupying one lobe or more of the prostate with smooth and regular capsule, normal acid phosphatase, and x-rays.

These two categories comprise about 10 percent of prostatic carcinoma and represent the early operable and potentially curable stage of the disease. It should be noted that local extension is usually underestimated, however, and there is often more tumor than suspected clinically (Jewett, 1956; Arduino and Glucksman; Flocks and Cheng; Byar and Mostofi).

(3) Extension of the tumor beyond the prostate with or without involvement of the seminal vesicle and/or bladder neck, normal acid phosphatase, and x-rays.

(4) Local extension beyond the capsule to the adjacent organs, but with normal acid phosphatase and no skeletal or other metastasis. Chute and Fox pointed out that the apparent local extension of the tumor may be nonneoplastic.

While these may be considered clinically definable stages, confusion results when there is elevation of acid phosphatase suggesting metastasis, but no supporting radiologic confirmation. In such cases, a careful bone survey, confirmation of the positive acid phosphatase, especially the prostatic fraction, determination of alkaline phosphatase, and investigation of all possible causes of elevated TSAP or PAP are essential. If the acid phosphatase level remains elevated, carcinoma should be regarded at least locally invasive, if not metastatic, and this tumor should be classified separately.

(5) Distant metastasis, as demonstrated by roentgenogram or by physical examination, constitutes the near end stage of the disease. Carcinoma usually involves the prostate extensively and there is elevation of the acid phosphatase level. The prostate may have been removed surgically or it may be normal or have only a nodule. The acid phosphatase level may be normal. Histologic evidence must, therefore, be established for diagnosis of carcinoma of the prostate.

SITE. Since Motz and Perearnau observed that benign prostatic hyperplasia arose from mucosal and submucosal glands, and Young reported that the most common site of carcinoma was the posterior subcapsular stratum, there have been a number of reports confirming these observations. Considerable confusion still exists, however, because the area of predilection has been variously defined. Rich designated the area
as the outer margin. Moore used the term posterior lobe, which he defined as the part posterior and posterolateral to the fan-shaped ducts that enter the sides of the urethra. Franks, and Brandes and associates used the terms inner and outer zones, corresponding to those of Motz and Perearnau, but Brandes used the term posterior lobe interchangeably with the outer zone. Weyrauch defined the posterior lobe as a truncated triangular area that extended from the base of the urethra to the posterior capsule. Strahan, on the other hand, designated the entire area posterior to the urethra and ejaculatory ducts as the posterior lobe. We prefer to divide the prostate into two portions: (1) the outer subcapsular zone which forms a horseshoe-shaped collar around (2) the inner perirectal portion (fig. 172). The two zones are often quite distinct, but admittedly they are not always sharply demarcated.

In a detailed study of step sections of surgically removed prostates, we found that the tumor was confined to the outer zone in 94 of 208 patients; in 109, it involved both the peripheral outer zone and the inner zone. The tumor was located centrally without any apparent tumor peripherally in only one case; in four, location could not be ascertained because of prior surgery.

GROSS. Identification of carcinoma of the prostate in its early stage is difficult, if not impossible, because most prostate glands are removed by transurethral resection. Carcinomatous curettings, however, can be distinguished by their usually firm, relatively solid, and frequently distinctive yellow or yellow-orange appearance. The consistency of this tumor is similar to that of scirrhou.s carcinoma of the breast. In total prostatectomy specimens, the tumor must be at least 5 mm. in diameter to be grossly discernible, but its firm or hard consistency is the pathognomonic feature. The tumor may consist of single or multiple nodules, irregular in outline, usually in contact with the capsule, and not sharply demarcated from the surrounding tissue. Many urologists can state with considerable accuracy whether the nodule is surrounded by normal tissue on two or three sides. About one-half the carcinomas have a distinct yellow flecking, are firm, and may be granular. Others are gray to white, homogeneous, or slightly fibrillar and hard (fig. 189).

As the tumor grows, the prostate becomes increasingly infiltrated and replaced by carcinoma; eventually it invades the urethra and the trigone anteriorly and the periprostatic tissue posteriorly. The tumor is usually poorly demarcated and merges with adjacent tissue (fig. 190). It usually remains firm, but occasionally may be soft with an increasing ratio of epithelial to stromal elements.

In 35 percent of the carcinomas in our series, invasion of the prostatic capsule occurred rather early. However, penetration of the capsule is late, especially posteriorly; it occurred in 15.9 percent of our cases. Denonvilliers' fascia is especially resistant to tumor extension, and this accounts for the extremely low incidence rate of 1.5 percent of rectal invasion by carcinoma of the prostate (Young).

Calculi, focal atrophy, and granulomatous prostatitis may grossly simulate carcinoma. Calcareous deposits in the prostate are stony-hard, but easily detected when sectioned. The atrophic area is usually quite small, while the granulomatous area is large. The atrophic area is irregular and ill-defined, but identifiable by its bluish white color and firmness. It usually has a moderately sharp scalloped border and a soft necrotic center (fig. 191).

MICROSCOPIC. Microscopic diagnosis of carcinoma of the prostate is often quite
Tumor can be seen as poorly defined subcapsular white area in the right lateral portion of the posterior lobe. (Fig. 3 from Fascicles 31b and 32, First Series.)

White tumor tissue occupies most of the posterior and left lateral lobes. There is capsular invasion in the left lateral posterior sector, and irregular extension into the middle and right lateral lobes. Note the intact posterior capsule, which is rarely invaded by tumor. The urethra is uninvolved as is usual until late in the course of the disease. (Fig. 4 from Fascicles 31b and 32, First Series; also from Moore, R. A. A Textbook of Pathology. Philadelphia: W. B. Saunders Co., 1951.)
Tumors of the Prostate

Figure 191
TUBERCULOUS LESION

Tuberculosis of the prostate in this illustration involves primarily the right lateral lobe. The tuberculous lesion has the white color of carcinoma, but may be distinguished from the latter by its sharp scalloped border and soft texture. (Fig. 5 from Fascicles 31b and 32, First Series; also from Moore R. A. Tuberculosis of the prostate gland. J. Urol. 37: 372-384, 1937.)

difficult. The most important and unequivocal criterion for diagnosis of malignant tumor is the occurrence of metastasis. However, rarely does the pathologist have tissue from metastatic foci, and, in a majority of cases, diagnosis must be based on needle biopsy or transurethrally resected tissue from the prostate.

Pathologic diagnosis of carcinoma of the prostate is based on one or more of the following: cellular anaplasia, histochemical and ultrastructural change, invasion, and architectural disturbance.

Cellular Anaplasia. Anaplastic carcinoma is readily identifiable. Cells vary in size, shape, and staining qualities and may be cuboidal or columnar. The nuclei may be large or small, but the nuclear membrane is irregularly thickened. The chromatin is course and unevenly distributed with one or two large, irregular nucleoli and one large intranuclear vacuole. Mitotic figures and giant cells are not uncommon. The cytoplasm is granular or vacuolated (figs. 192, 193). Carcinoma in which the cells are anaplastic may form acini of varying size, but more often the cells occur as solid sheets and clumps. Careful examination will reveal a residue of small acinar spaces.

In many prostatic carcinomas, however, only moderate or slight anaplasia is seen (figs. 194, 195). In the latter, the nuclei are small and fairly uniform with a delicate nuclear membrane and a fine network of
Carcinoma

Figure 192
CARCINOMA
The nuclei show severe anaplasia in this carcinoma, Grade III. Note the three mitotic figures. X350.

Figure 193
CARCINOMA
There is marked anaplasia of cells in this carcinoma, Grade III. Note the large vacuoles and nucleoli. X450.
chromatin evenly distributed. Mitosis and giant cells are rare. There is usually some variation in staining and size and shape of the nuclei; the nuclear cytoplasmic ratio may be higher than normal. The cytoplasm is clear or acidophilic, and the acini are usually smaller than normal. Instead of a double layer of cells lining the acini, there is a single row of nuclei.

The absence of mitotic figures in these well differentiated, probably early carcinomas is puzzling. Since there is obvious growth of the epithelium, manifested by the large number of acini, either the growth is amitotic or the mitotic activity is very slow or very fast. We have observed mitosis only in immediately fixed needle biopsy tissue and believe that the absence of mitotic figures in most carcinoma of the prostate may indicate rapid metaphase.

**Cytoplasmic Histochemical Reactions.** Histochemical studies of the cytoplasm may be helpful in the diagnosis of carcinoma of the prostate. Brandes and Bourne reported a reduction in the naphthol soluble esterase and in PAS reaction, an increase in fat, and a decrease and redistribution of acid phosphatase in carcinoma. Franks and associates found that normal prostatic secretions gave the histochemical reaction for neutral mucin, and that latent and clinical prostatic carcinoma secretes a sialic acid containing mucin in which the sialic acid residuals are sulfated. Such reaction is rarely seen in nonneoplastic glands; it is most frequently seen in well differentiated carcinoma and in small acinar and cribriform tumors (figs. 196, 197). Mucopolysaccharide is produced in considerable amounts in colloid carcinoma. A nonsulfated acid mucin is found in colloid carcinoma and in clinical carcinoma with extensive mucin secretion, but not in latent carcinoma. Myxoid areas found in colloid cancer also contain sulfated acid mucin, probably of stromal origin. Hukill and Vidone found that 39 of 50 carcinomas produced some type of mucoid
The cells show slight anaplasia in this carcinoma, Grade I. X435. (Fig. 9 from Fascicles 31b and 32, First Series.)

An area of mucus production is seen in this carcinoma of the prostate. X145
Tumors of the Prostate

Figure 197
CARCINOMA
(Figures 175, 197, and 215 from same case)
In the lower margin, the glands appear hyperplastic. In the second zone, there is evidence of anaplasia. In the central zone, the glands are large with vacuolated cells. In the upper zone, the glands form mucin. X115.

substance. At least three distinct substances, produced alone or together, were identified: neutral, nonsulfated, and sulfated mucopolysaccharide.

While foci of mucin production may frequently be seen in carcinoma of the prostate, only about 20 mucinous adenocarcinomas of the prostate have been reported. This tumor is less aggressive than nonmucinous carcinoma and is not responsive to estrogen therapy (Sika and Buckley; Joshi et al.). Before a mucinous adenocarcinoma is considered of prostatic origin, however, it is necessary to rule out a secondary mucinous adenocarcinoma or a carcinoma of periurethral or Cowper’s glands.

We concur with Braunstein that various lipid stains such as oil red O, Sudan black, and others prove most helpful in differential diagnosis. Many carcinomas of the prostate show increased lipid content and, occasionally, cytoplasm contains abundant lipid (carcinoma xanthomatoids). They are grossly soft and indistinguishable from hyperplasia. Fresh tissue is preferable, but formalin-fixed tissue may also give satisfactory results.

The most important and pathognomonic histochemical reaction is that for acid phosphatase (fig. 198). Fresh frozen tissue is preferable, but cold acetone or brief, 6-hour fixation in formalin may give satisfactory results. Cauterization should be avoided, but the technic is applicable for needle biopsy and for whole transverse cryostat sections. Both hyperplastic and neoplastic tissue may contain large amounts of acid phosphatase which decrease with an increasing amount of anaplasia. Parkin and associates have quantitated the phosphatase level. Activity was directly proportional to the number of acini, and inversely proportioned to the degree of cellular anaplasia.

Ultrastructure. The ultrastructure of carcinoma of the prostate has been described
Carcinoma

In comparison with normal and hyperplastic prostates, carcinoma shows extensive structural polymorphism with nuclear and nucleolar hypertrophy, increased numbers and pleomorphism of mitochondria, greater amounts of free ribosomes, variability in position of Golgi apparatus, decreased endoplasmic reticulum, and increased amounts of lipid droplets of variable morphologic structure.

Such changes are obviously those of poorly differentiated carcinoma. In well differentiated carcinoma, Fisher and Jeffrey observed atypical secretory activity, quantitative variability of cellular organelles, prominent nucleoli, and focal loss of basement membrane; these changes resemble those in testosterone-treated rabbit prostate. Mao and associates reported rod or rectangular, intranuclear inclusions, approximately 1000 angstroms in width and of variable length. Tannenbaum and associates reported intranuclear, viral-like inclusions (figs. 199—203). To date, electron microscopy has not been applied to borderline or difficult cases; such application appears somewhat impractical under present conditions.

Invasion. The diagnosis of carcinoma may be based on invasion when cellular anaplasia is equivocal or absent, and it is impossible to do histochemical and electron microscopic studies. Invasion may penetrate into adjacent organs, the seminal vesicle, the prostatic capsule, perineural spaces, vascular spaces, or the stroma.

Examination of the total prostate is advisable to determine any invasion of adjacent organs or the capsule. In biopsy material, the presence of acini in contiguity with skeletal muscle has been recognized as excellent evidence for extraprostatic extension. However, Kost and Evans, and Manley demonstrated that skeletal muscle cells and bundles occur normally in the prostate proper (fig. 204). Therefore, prostatic glands intermingled with skeletal muscle fibers should not be regarded as invasive, unless there is further supporting evidence for diagnosis of carcinoma.
This carcinoma of the prostate shows variation in size and density of the mitochondria. Note the pseudopodal extension (arrow) about the capillary. X7200. (Fig. 16 from Fisher, E. R., and Sieracki, J. C. Ultrastructure of Human Normal and Neoplastic Prostate. In: (Ed.) Sommers, S. C. Pathology Annual. New York: Appleton-Century-Crofts, 1970.)
ANAPLASTIC CARCINOMA CELL

In this portion of anaplastic carcinoma cell, the nucleus (N) is large, with prominent nuclear granules and large, conspicuous nucleolus (n). Golgi structures (G) are abundant and hypertrophied. The mitochondria (M) are large and vacuolated with needle-like cristae. Dense bodies (db) are relatively numerous. X9300. (Fig. 18 from Fisher, E. R., and Jeffrey, W. Ultrastructure of human normal and neoplastic prostate. Am. J. Clin. Pathol. 44:119-134, 1965.)

ANAPLASTIC CARCINOMA CELL

This is a portion of anaplastic carcinoma cell in the stroma. The cell cytoplasm contains many vacuoles (SV) not unlike the secretory vacuoles observed in normal and in benign prostatic hypertrophy. X6000. (Fig. 19 from Fisher, E. R., and Jeffrey, W. Ultrastructure of human normal and neoplastic prostate. Am. J. Clin. Pathol. 44:119-134, 1965.)
Figure 202
WELL DIFFERENTIATED CARCINOMA CELL
The basement membrane area (BMA) is disrupted by cytoplasmic extension (P) of well differentiated carcinoma cells. Mitochondria (M) are numerous and larger than normal. The cell cytoplasm is replete with free RNA (R). X12,000. (Fig. 16 from Fisher, E. R., and Jeffrey, W. Ultrastructure of human normal and neoplastic prostate. Am. J. Clin. Pathol. 44:119-134, 1965.)

Figure 203
WELL DIFFERENTIATED CARCINOMA CELL
Portions of adjacent well differentiated carcinoma cells demonstrate vacuolization and conspicuous and prominent Golgi structures (G). Mitochondria (M) are only slightly enlarged. X16,500. (Fig. 17 from Fisher, E. R., and Jeffrey, W. Ultrastructure of human normal and neoplastic prostate. Am. J. Clin. Pathol. 44:119-134, 1965.)
Invasion of the intraprostatic perineural spaces is the most reliable pathologic evidence for diagnosis of carcinoma of the prostate (fig. 205). This finding, however, has led to three misconceptions: (1) That the spaces represent lymphatic spaces; (2) that such invasion occurs in advanced carcinoma; and (3) that it indicates an unfavorable prognosis. Careful microdissection reveals that these are not lymphatic spaces, but represent perineural tissue spaces (Rodin et al.). We have noted perineural invasion in 85 percent of incidental and early carcinomas; although it is useful in diagnosis, it has no prognostic significance (Byar and Mostofi).

The mechanism of perineural invasion may be explained by our observation of an intimate relationship between nerve bundles and prostatic acini where the two structures are separated only by the acinar basement membrane (fig. 206). In such situations, the earliest evidence of invasion could well be that of perineural spaces. The foregoing refers, of course, to intraprostatic perineural spaces, not the nerves and ganglia in the prostatic capsule. Direct invasion of the nerve fiber may also be seen.

In addition to perineural spaces, lymphatic and blood vessels may be invaded. In our experience, vascular invasion occurs later and suggests a poor prognosis.

Search for invasion of the seminal vesicle should be carefully made because its presence not only confirms the diagnosis of carcinoma, but it also has important prognostic significance. Arduino and Glucksman reported 82.0 percent of tumors that invaded the seminal vesicle had pelvic node involvement. Only 7.3 percent of tumors without seminal vesicle invasion showed lymph node metastases.
Carcinoma cells infiltrate perineural spaces. X130.

The nerve bundle (arrow) is seen in close proximity to an acinus. Note that there is only a thin fiber separating the two. X380.
Invasion of the stroma (fig. 207) is an important adjunct in pathologic diagnosis of carcinoma of the prostate (Mostofi, 1952). However, whether a basement membrane actually exists around the prostatic acini and how a break may be recognized remain controversial. PAS, trichrome, and silver stains have suggested the existence of a basement membrane, but only recently has its presence been confirmed by ultrastructural studies. The membrane consists of thin, collagenous, connective tissue of variable thickness which invests and follows the outlines of acini in normal, hyperplastic, and atrophic glands. Muscle bundles are concentrically arranged around the acinar basement membrane. In early carcinoma of the prostate, focal loss of basement membrane may be seen with distinctly neoplastic epithelial cells invading the surrounding stroma. More unequivocal evidence of invasion is the juxtaposition of acini to smooth muscle fibers with loss of the regular whorled concentric arrangement of the latter (fig. 208). In either case, the break through the basement membrane in early carcinoma is not a generalized phenomenon, but is focal and present only in a few acini. In advanced carcinoma, invasion of the stroma is manifested by a back-to-back arrangement of acini and loss of intervening stroma.

Invasion of the prostatic capsule, periprostatic soft tissues, and the bladder wall is obviously indicative of an aggressive, malignant tumor.
Architectural Disturbance. Since cellular anaplasia and invasion are often difficult to recognize, absent or equivocal, and histochemical and electron microscopic features unavailable, disturbances of architecture constitute the most important criteria for recognition of carcinoma. Normally, the glands have a linear distribution radiating from the urethra and a characteristic convoluted outline. In hyperplasia, there is a distinct nodular appearance, but convoluted outlines are preserved while the linear pattern may be lost. In carcinoma, the linear pattern is lost, convolutions are lost, and acini seem to be growing irregularly in all directions from the central mass. Other features include the presence of many small acini, microacini, closely packed acini, variably sized acini, large acini without the usual convolutions, and acini having a cribriform pattern (figs. 209—219).

Incidental Carcinoma of the Prostate
This tumor may reveal any pattern seen in carcinoma of the prostate, but the most common is the small acinar pattern in which the acini are lined by a single layer of epithelial cells (fig. 209). The cytoplasm is amphophilic, basophilic, or vacuolated. The nuclei usually manifest some irregularity of size and shape. There may be a single vacuole and a prominent nucleolus, or homogeneously pale-staining nuclei without any distinct chromatin substance. In still other patterns, the nucleus is densely staining. Although neoplastic areas may be extensive, they usually involve a single lobule.

Figure 209
CARCINOMA ORIGINATING IN NODULE OF HYPERPLASIA
This hyperplastic nodule is for the most part circumscribed by characteristic encircling glands. Carcinoma is an ovoid nodule of small, closely packed glands among which a few large hyperplastic glands are still visible. X100. (Fig. 6 from Fascicles 31b and 32, First Series.)
Carcinoma in Situ of the Prostate

This term has been used to denote incidental carcinoma or clinically detected carcinoma in which neoplasia is intraacinar-cribiform, or the epithelium lining the acini is piled up or obviously neoplastic, but in which invasion of the stroma is not apparent. While there may be some justification for usage of the term for the latter type, it is undesirable because no proof exists that such carcinoma is entirely confined to acini, and because perineural invasion is present in over 90 percent of these early carcinomas. These changes are often seen at the margin of invasive carcinoma, and justify further investigation when observed alone. The interval between appearance of such changes and development of invasive carcinoma is unknown.

PATTERNS OF GROWTH. An amazing number of growth patterns reflect the degree of glandular and cellular differentiation and possible hormonal response in carcinoma of the prostate—not only from case to case, but on the same microscopic slide. Most frequently, the tumor has a glandular pattern, especially in early carcinoma. However, the glands may vary from minute (microacinar) (figs. 209, 210), to small, to normal, or they may be large or of mixed size. The glands may be regular or irregular; they may form a distinct nodule, or diffusely infiltrate the stroma (fig. 211). The glands are usually lined by a single layer of cells. Large glands are usually devoid of convolutions commonly encountered in hyperplasia, but, not infrequently, they may show papillary projections or occasionally an adenocystic pattern (fig. 212). Piling-up of the epithelium may lead to the cribriform pattern (figs. 213, 214) which is so pathognomonic of carcinoma of the prostate. Such glands are usually lined by fairly uniform cells with clear or amphophilic cytoplasm, but there may be moderate or marked cellular pleomorphism. Progression of intra-acinar growth may result in the partial or complete loss of glandular appearance with solid sheets forming a medullary pattern (figs. 216—218). Careful examination will often reveal residual microacini simulating pseudorosettes of neuroblastoma.

The basement membrane of the neoplastic acini may be retained, and the fibromuscular stroma may be normal, decreased, or completely lost, with glands closely packed back-to-back (fig. 215). A marked overgrowth of fibrous stroma, and carcinoma cells occurring singly or in rows or individual glands are evidence of scirrhous carcinoma (fig. 219). Such patterns are usually encountered in more advanced carcinoma. At times, not only the acinar but also the ductal elements may show neoplastic change. In still other instances, there may be marked desmoplastic reaction of the stroma, sometimes assuming a neoplastic appearance.

GRADING. There has been a recent surge of interest in grading (Pool and Thompson; Vickery and Kerr; Jewett et al.), but difficulties remain because most carcinomas present more than one histologic pattern. Gleason proposed a solution by recognizing a primary and a secondary pattern with one or more of five, seven, or nine patterns in each, ranging from the most to the least differentiated. Although he found this to be a valuable method of grading, his observations have not been confirmed.

A major difficulty in any grading system is that criteria for cellular anaplasia and glandular differentiation have not been clearly defined, and much of the categorization has been subjective and not reproducible.

In an effort to bring some objectivity into a grading system, Mostofi (1969) proposed a method based on the status of three elements: the epithelial cells, the glands, and the
stroma. To prevent confusion, the term cellular anaplasia was limited to nuclear atypia; i.e., the nuclei may show slight anaplasia, grade I, (fig. 195), moderate anaplasia, grade II, (fig. 194), or marked anaplasia, grade III, (figs. 192, 193).

It is proposed that the term differentiation be used to indicate gland formation; this would permit classification of the tumors into those that form glands (differentiated) and those that do not (undifferentiated).

Gland-forming tumors could be subdivided into those in which the glands are essentially of normal size (fig. 211), large (fig. 215), small or miniature (figs. 209, 210), or cribriform (figs. 213, 214). In nongland-forming tumors, the cells occur as sheets, cords, rows, or individual cells (figs. 216—218).

The amount and composition of stroma may be normal (fig. 211); stroma may be decreased (fig. 215), but still present with back-to-back glands, or it may be absent (fig. 213), overabundant, or scirrhous (fig. 219). These parameters are readily definable and preliminary studies in our laboratory suggest that they may correlate with prognosis.

Figure 210
CARCINOMA
This carcinoma of the prostate shows minute glands haphazardly scattered. X100.

Figure 211
DIFFUSE INFILTRATION BY WELL DIFFERENTIATED ADENOCARCINOMA
(Figures 195 and 211 from same case)
Carcinomatous acini show characteristic complete lack of orientation. A few large nonmalignant glands and ducts and a single corpus amylaceum can be seen. X45. (Fig. 7 from Fascicles 31b and 32, First Series.)
Tumors of the Prostate

Figure 212
CARCINOMA
A papillary cystic glandular configuration is seen in this carcinoma of the prostate. X28

Figure 213
CARCINOMA
Carcinoma is forming intraglandular papillation. In contrast to the secondary hyperplasia in figure 181, no stroma is seen between the papillae. X165
In this well differentiated carcinoma of the prostate forming glands, note the back-to-back arrangement of the acini. X115.
Figure 216
UNDIFFERENTIATED CARCINOMA
(Figures 205 and 216 from same case)
This undifferentiated carcinoma of the prostate shows rows of cells without any distinct glandular formation. X130

Figure 217
UNDIFFERENTIATED CARCINOMA
The cells grow in sheets and there is little, if any, glandular formation. X230.
This undifferentiated carcinoma of the prostate shows carcinoma cells that are small with dense nuclei and show no glandular formation. Note that the infiltrate is essentially monocellular. X180.

This carcinoma of the prostate shows increased stroma. X115.
PATHOGENESIS. For more than a generation, it has been accepted that carcinoma of the prostate originates from atrophic acini. This concept was based almost solely upon the observation that the two conditions occur in the peripheral subcapsular regions of the prostate and that carcinoma follows atrophy. The exact mechanism of the changes in the so-called atrophic epithelium and acini which results in carcinoma has not been demonstrated. Certain changes that can be observed in the epithelial cells of the subcapsular zone would seem to clarify this relationship.

The term atrophic, although descriptive of the light microscopic appearance of the cells, does not adequately categorize them. They are dormant or resting. Characteristically, the nuclei are dark-staining and arranged in a single row, and the cells are low cuboidal (fig. 182). Swelling and vacuolization are initial indications of activity in these dark-staining nuclei. The nuclei become larger and the cytoplasm more prominent and eosinophilic. Increased activity is apparent from an increased number of cells (fig. 220). The basement membrane seems to be broken, and the cells appear to stream out into the peripheral tissue. The cells retain their cuboidal shape; in its earlier stage, such carcinoma of the prostate consists of small glands lined by cuboidal epithelial cells that are somewhat darker-staining. These small glands may be found within the perineural spaces (fig. 221). However, not all such carcinomas are small and glandular in type.

It is generally believed that carcinoma and hyperplasia do not usually occur in the same nodule and that hyperplasia is not precancerous. Occasionally, particularly in incidental carcinomas, the two are associated, and in the study of serial sections of total prostate, we have seen areas that strongly suggest precancerous change in hyperplasia consisting of focal cellular anaplasia (figs. 222, 223). The nuclei are larger, the chromatin distribution is coarse, there is vacuolization, and the nucleoli are large. The cells appear to arise from the basal layer of acinar cells. One of the earliest indications of neoplasia is focal invasion of underlying tissue.

DIFFERENTIAL DIAGNOSIS. Typical and atypical hyperplasia, secondary hyperplasia, atrophy, metaplasia, granulomatous prostatitis, and involutional changes in the seminal vesicle are sometimes confused with carcinoma (Mostofi, 1952).
Note that while the acini still retain their atrophic pattern, the cells are obviously anaplastic and there is perineural invasion. X300.

Hyperplasia of the prostate is easily distinguished from carcinoma, in most instances, but focal areas of atypical epithelium in hyperplastic glands may be mistaken for carcinoma (figs. 224, 225). In hyperplasia, the acini are larger and always surrounded by a distinct band of avascular, collagenous, connective tissue which invests the acini and follows their outlines. The epithelium is double-layered, the cells are taller, and their nuclei smaller and more basal in position than epithelial cells of carcinoma, which are low. The nucleus occupies fully one half of the cell and has a prominent nucleolus. In hyperplasia, the glands are arranged in an orderly manner and form fairly well defined nodules.
Tumors of the Prostate

Figure 223
CARCINOMA ARISING FROM HYPERPLASIA
The hyperplastic epithelial cells are being crowded out by neoplastic cells originating from basal cells. X395.

Figure 224
ATYPICAL HYPERPLASIA
Some of the regular acini shown in this atypical hyperplasia are lined by piled up epithelial cells. X80.
Six of the acini show intraglandular proliferation of the epithelium resulting in a pseudo gland-in-gland pattern. X90.

**Secondary hyperplasia** can readily be distinguished from carcinoma on the basis of its architecture. Large acini are lined partly by a single layer of cuboidal epithelium and partly by papillary projections covered by similar epithelium (fig. 181). There is no evidence of nuclear anaplasia or invasion.

In **atrophy of the prostate**, small, sometimes closely packed, collapsed, acini lined by cuboidal epithelium with large nuclei may simulate carcinoma. It should be noted, however, that changes of atrophy involve the whole lobule. Many acini are collapsed, and they are always surrounded by a band of collagenous, connective tissue (fig. 182). There is no evidence of invasion of the stroma, and the stroma itself shows changes of sclerotic atrophy. The entire structure has an organoid pattern. On the other hand, there is no definite pattern in carcinoma; the stroma is invaded by neoplastic cells, the acini are smaller and more closely packed, and the cells have more cytoplasm.

**Squamous or transitional metaplasia of the prostate** which occurs in healed infarction of the prostate may simulate carcinoma (figs. 184, 185). This lesion is suspected if there has been a previous transurethral resection, or if bleeding and interference with urination suddenly appear after previous urinary difficulty. Histologic evidence of anaplasia, increased mitotic activity, or invasion is lacking; rather, the squamous or transitional cells are well differentiated. The most distinctive feature of metaplastic lesions, which is absent in carcinoma, is their association with ischemic necrosis or fibrous connective tissue stroma devoid of smooth muscle.

**Granulomatous prostatitis** is often misdiagnosed as carcinoma. Clinically, such a prostate is hard. Pathologically, several
reaction patterns may be seen. Sheets of large clear or pale pink-staining cells with small vesicular nuclei (fig. 226) may simulate clear cell carcinoma. Careful examination identifies them as macrophages. Another pattern presents a pleomorphic cell population in which small cells with pyknotic nuclei and vacuolated cytoplasm are arranged in rows or small groups simulating carcinoma (fig. 227). Some acini may occasionally be seen, but the epithelium is cuboidal or flattened and the lumen is filled with exudate. Other cells are recognizable as lymphocytes, plasma cells, and macrophages. In some cases of granulomatous prostatitis, there is a definite granulomatous reaction with multinucleated giant cells (fig. 228), epithelioid, and inflammatory cells.

Several helpful diagnostic features include: an admixture of cells; rarely, if ever, any true acinar formation; and invariable relationship of the lesion to a duct, with partial or complete loss of epithelium (fig. 229). Not infrequently, fragments of degenerating corpora amylacea may be seen in association with multinucleated giant cells.

In glandular carcinoma, the epithelium of the acini is usually well preserved, even when inflammation is also present. Necrosis is rare and the cells are usually uniform, unless there has been treatment with estrogens or other therapy.

Figure 226
GRANULOMATOUS PROSTATITIS
Many large cells with granular cytoplasm and small nuclei are shown. Note the absence of any glandular formation. The picture suggests malakoplakia of the prostate, but no Michaelis-Gutman bodies were found. X270.
Figure 227
GRANULOMATOUS PROSTATITIS
This granulomatous prostatitis shows cells with small round vesicular nuclei and clear cytoplasm. X80.

Figure 228
GRANULOMATOUS PROSTATITIS
Note the pleomorphism of cells, absence of acini, and the presence of multinucleated giant cells, epithelioid cells, and fragments of corpora amylacea. X210.
Involutional changes in the seminal vesicle are sometimes confused with carcinoma of the prostate. Not infrequently, in older patients, transurethral resection yields tissue that has several ductal structures, but in which superficial cells and those adjacent to the lumen are quite bizarre (figs. 230, 231). The nuclei are large, sometimes giant cell-sized. The hyperchromatic nuclei suggest malignancy when viewed by themselves; however, several features negate such a diagnosis: absence of nuclear vacuoles and nucleoli; normal nucleocytoplasmic ratio; superficial or intraluminal location of the cells and organoid pattern of the ducts.

BIOLOGIC BEHAVIOR. In discussing the biologic behavior of carcinoma of the prostate, we must realize the heterogeneity of cell population and the variable aggressiveness of the tumor cells. These factors are especially relevant in considering whether the well differentiated incidental and focal carcinomas are in fact true carcinomas. Carcinoma of the prostate does not always behave as aggressive carcinoma, and many patients harboring this tumor die of other causes or show no residual carcinoma on subsequent prostatectomy or at autopsy examination. We believe such findings do not negate a diagnosis of carcinoma; in fact, in 82 patients without clinically recognized carcinoma in whom biopsy showed carcinoma, Greene and Simon reported a 5-year survival of over 70 percent and a 10-year survival of 39 percent. Brendler reported 20 percent of the patients developed clinical carcinoma. It is quite possible that carcinoma was confined to the area that was surgically removed, and the biologic behavior was affected. Some patients with clinically manifest anaplastic carcinoma have lived for many years before the tumor metastasized.
Tumor-like Lesions

Figure 230
SEMINAL VESICLE SHOWING INVOLUTION
(Figures 230 and 231 from same case)
The back-to-back arrangement of the ducts and the hyperchromatism of nuclei simulate carcinoma. X75.

Figure 231
SEMINAL VESICLE SHOWING INVOLUTION
(Figures 230 and 231 from same case)
This higher magnification of one area shows the large size of nuclei, but the cells are surrounded by considerable cytoplasm. X1110.
It would seem that many patients have foci of clinically undetected carcinoma which remain dormant for many years; some of these tumors become clinically evident but are still contained, while others progress to local extension and eventually metastasize. While progression from focal to multifocal or diffuse carcinoma may often occur, such progression may be unrelated to the metastatic tumor which may develop any time during the life cycle of the neoplasm. Admittedly, there has not been adequate study of the natural history of carcinoma of the prostate, especially focal carcinoma.

LOCAL EXTENSION. Intraprostatic extension through the fibromuscular stroma, along the ducts, and in perineural spaces is the earliest evidence of extension of carcinoma of the prostate. The subcapsular location of most carcinomas of the prostate suggests that capsular involvement frequently appears early. Our studies demonstrate that about 70 percent of early carcinomas involved the capsule. Even excluding those tumors that were clinically suspected of capsular extension, about 50 percent of the remaining cases also showed capsular involvement.

There are three stages of capsular involvement: (1) tumor may extend to the capsule (20 percent); (2) it may invade but not penetrate the capsule (35 percent); or (3) it may penetrate the capsule (16 percent). Penetration of the capsule is a late phenomenon and indicative of poor prognosis (Byar and Mostofi, 1972). Proximity of the capsule to the tumor permits easy access to the capsule. The capsule, nevertheless, provides a strong fibrous barrier to extraprostatic extension of the tumor.

Confined by the fibrous capsule, carcinoma of the prostate tends to extend centrally. It has been previously stated that about 97 percent of tumors involve both the peripheral and the central portions. Ultimately, there is involvement of the bladder neck and the prostatic urethra. We have observed it in 50 percent of our early cases, and Kahler (1939) found extension to the bladder in 44 percent of his cases at autopsy. While involvement of the bladder, the urethra, and the ureterovesicle junction is not unusual, the mucosa of the posterior urethra and the bladder are amazingly resistant to spread of carcinoma. It has been observed in only a few of our cases, and Barringer found urethral mucosal involvement in only 1 of 145 cases at autopsy. Neoplastic ulceration is rare (Young).

Invasion of the seminal vesicle is rare in early carcinoma. Microscopically, we found only 30 instances in 175 cases. The findings indicated that seminal vesicle involvement occurs by spread through the muscularis and not by way of the ejaculatory duct. Mucosal involvement is usually delayed but most clinically detected carcinoma eventually invades the seminal vesicle.

Perivesical and perirectal involvement has been seen in 11 and 14 percent of cases, respectively (Arnheim), presumably by direct extension, lymphatic invasion, or a combination of both (Young). This is reflected in the high incidence of local recurrence and in the poor prognosis.

Further growth leads to invasion of the tissue around the seminal vesicle, the base of the bladder, and the membranous urethra. Denonvillier's fascia forms an excellent barrier, accounting for an extremely low incidence of rectal involvement—in 12 of 1,800 cases (Young, 1926). Invasion of the penis may manifest itself in priapism. Similarly, as with other pelvic malignant tumors, the eventual result of wide local spread is a frozen pelvis.

METASTASIS. Metastasis from prostatic carcinoma varies widely and is rare in a
Tumor-like Lesions

Clinically silent, incidental carcinoma. Many clinically manifest tumors are relatively slowly growing and late metastasizing, while, in some patients, progression is rapid. The incidence rate of metastatic tumor varies from 25 to 66 percent, depending upon the stage of the disease at the time of diagnosis (Bumpus, 1926; Vest).

At autopsy in manifest carcinoma, metastases to the lymph nodes (100 percent) most frequently involve the iliac, periaortic, hypogastric, and sacral nodes. The tracheobronchial nodes are usually affected later, but left supraclavicular involvement may be early.

Osseous metastases occur in 70 percent of cases. The pelvis and the sacrum are involved in 85 percent of cases, the lumbar spine in 59 percent, the femurs in 35 percent, the dorsal spine in 23 percent, and the ribs in 22 percent (Graves and Militzer). Osseous metastases are usually osteoblastic, 79 percent; mixed osteoblastic and lytic, 12 percent; osteolytic, 4 percent; and osteolytic, then osteoblastic, 3 percent; and subperiosteal osteoblastic, 1 percent (figs. 232—234; Jorgens).

Figure 232
METASTATIC CARCINOMA
Typical pelvic roentgenogram in metastatic carcinoma of the prostate reveals densities mottling almost all bones, which indicate osteoblastic metastases. A few radon seeds are visible over the left midsacrum. (Fig. 20 from Fascicles 31b and 32, First Series; courtesy of Dr. W. Seaman, St. Louis, Mo.)
Figure 233
OSTEOBLASTIC METASTASIS OF PROSTATIC CARCINOMA
A semicircular area of increased bone formation and marrow fibrosis is visible. Such lesions are responsible for the areas of radiopacity on the roentgenogram. X12. (Fig. 21 from Fascicles 31b and 32, First Series; also from Friedman, N. B., and Ash, J. E. Atlas of Genitourinary Pathology. Washington: American Registry of Pathology, 1946.)

Figure 234
OSTEOBLASTIC METASTASIS OF PROSTATIC CARCINOMA
This high power view shows that osteoblasts are numerous, while osteoclasts are almost nonexistent. Tumor fills all the interosseous spaces. X137. (Fig. 22 from Fascicles 31b and 32, First Series.)
Tumor-like Lesions

Figure 233

Figure 234
There is considerable disagreement concerning the mode of spread and the distribution of osseous metastases. The bones of the pelvis and lumbar spine nearest the prostate are generally regarded as the most frequent sites of involvement. Three theories have been advanced to explain the mode of spread. Warren and associates proposed that perineural lymphatic spread was an important auxiliary route for such dissemination of metastases. Batson advocated that the vertebral venous plexus was the usual route. On the basis of four carefully detailed autopsies, Willis proposed that such metastases follow the usual route of lymphatic and venous channels to the lungs, thence, by way of systemic circulation, to the bone.

The most common sites of visceral and soft tissue metastases are the lungs, liver, pleura, adrenals, and kidneys, but almost every organ or structure may show involvement.

TREATMENT. In any tumor, prevention is the best control, but because at present the cause of carcinoma of the prostate is unknown, total removal or destruction of the growth and control of metastases without increasing morbidity or mortality of the host is the goal. The critical position of the prostate in the urinary tract imposes concern to establish and maintain the patency of the urinary tract. The hormone sensitivity of the prostate challenges the urologist to control or eradicate the disease, and the inconsistency of response to therapy compels him to explore other methods.

Once diagnosis has been established, the urologist may select treatment from the following alternatives: no treatment; total prostatectomy; antiandrogen therapy (orchiectomy, estrogen therapy, hypophysectomy); radiotherapy (radioisotope, radium, or external radiation); cryosurgery; chemotherapy or immunotherapy; or any combination of these treatments. Details of the various forms of therapy are beyond the scope of this fascicle, but it should be emphasized that any treatment for carcinoma of the prostate must be individually selected for each patient.

For incidental and for focal carcinoma, any of the following seem to give the same results: no treatment, hormonal control (orchiectomy and estrogen therapy) alone, or total prostatectomy with or without hormone control. Most patients die of other causes than carcinoma of the prostate; only about 20 percent eventually develop aggressive carcinoma.

When a clinically diagnosed tumor is thought to be confined to the prostate and the patient is in good health with a life expectancy of 5 to 15 years, total excision of the malignant tumor is, at present, the therapy of choice. Admittedly, however, local chemotherapy and radiation which seem to have so many advantages over surgery have not been adequately evaluated.

In over 90 percent of patients in whom diagnosis of carcinoma of the prostate is made clinically, extension beyond the confines of the prostate can be demonstrated clinically, surgically, or pathologically. Obviously, some additional procedure beyond prostatectomy is indicated, especially since 25 percent of these patients show local recurrence and about 50 percent have lymph node or bone metastases (Flocks, 1965). However, a course of hormone therapy may permit surgical removal of the prostate.

For patients with established local extension, the therapeutic alternatives are total prostatectomy with cystectomy and even pelvic exenteration, endocrine control, chemotherapy, radiation therapy, cryosurgery, or other procedures.

Unless the patient dies of other causes
and irrespective of the type of therapy used, there is continued growth and spread of the tumor with eventual relapse of the patient. Further therapeutic measures include: administration of estrogens or other hormones; orchiectomy, if not previously done; bilateral adrenalectomy or hypophysectomy; radiation therapy, including radioisotopes, radium, and external radiation; chemotherapy; and immunotherapy.

EFFECTS OF ANTIANDROGEN THERAPY ON THE PROSTATE AND THE NEOPLASM. Following orchiectomy or administration of estrogens, certain changes appear in the urethra, the prostate, and some tumors. Both procedures result in atrophy of glandular epithelium and fibrosis, but estrogen therapy causes squamous metaplasia of the urethra and the prostatic ducts (fig. 235). The utricle shows epithelial hyperplasia and metaplasia. Effects on neoplastic cells are variable; estrogen therapy by itself is more effective than with orchiectomy, and massive (500-1000 mg. intravenous or 500 mg. orally) doses of estrogens are more effective than ordinary doses. Responsive neoplastic cells show the following changes: a decrease or loss of secretions and of acid phosphatase and other enzyme activity; reduction of 50 percent in size of the nuclei; condensation of chromatin and pyknosis; loss of nucleoli; and cessation of mitoses. Vacuolization of cytoplasm begins in the basal layer and enlargement results in coalescence of

![Figure 235](image)

ESTROGEN-INDUCED SQUAMOUS METAPLASIA OF PROSTATIC EPITHELIUM

The characteristic keratinized, ballooned cells are frequently found in cases of estrogen administration, or in hepatic cirrhosis, with retention of the estrogens normally present in the male. (Fig. 17 from Fascicles 31b and 32, First Series; courtesy of Dr. L. V. Ackerman, Stony Brook, Long Island, N. Y.)
Tumors of the Prostate

vacuoles and rupture of the cell membrane (figs. 236, 237). Fragmentation of pyknotic nuclei and free-floating nuclei are often seen.

Although these changes are quite distinct, proper fixation and comparison with pretreatment tissue are essential. The changes indicate cytotoxic effects of massive doses of estrogens, but, regrettably, all tumors do not respond favorably or they cease to respond after a period of time. A tumor that has failed to respond to smaller doses of estrogen may respond to more massive doses.

COMPLICATIONS OF ANTIANDROGEN THERAPY. While minor feminization may be encountered after orchiectomy, such changes are more pronounced after administration of estrogens and notable effects may be seen in the breasts.

Gynecomastia is the most serious and discomforting symptom. Tenderness of the nipples and enlargement and tenderness of the breasts are reliable proof that the patient is taking estrogens. Occasionally, because of discomfort and pain or for cosmetic reasons, mastectomy is necessary. Histologically,
there is proliferation and edema of the connective tissue, elongation and budding of the ducts, hyperplasia of the ductal epithelium, and, rarely, of the acini.

**Carcinoma of the breast** (fig. 238) has been reported by McClure and Higgins, and by Ackerman and del Regato. We have studied 13 patients with carcinoma of the prostate who had carcinoma in the breast. Breast carcinoma was diagnosed in 5 of the 13 patients prior to diagnosis of carcinoma of the prostate or before estrogen therapy. We believe the breast tumor was metastatic from the prostate in at least 3 of the 5 cases and in all the 8 remaining cases. Although the possibility that a primary carcinoma of the breast may arise after prolonged estrogen administration in men, it is more probable that estrogens create a favorable soil in the breast for development of metastases from prostatic carcinoma.

**Other Complications.** In an evaluation of various forms of therapy for carcinoma of the prostate, the Veterans Administration Cooperative Urological Research Group found that diethylstilbestrol in doses of 5 mg. daily to patients with early carcinoma of the prostate increased mortality during the first 6 to 9 months from nonneoplastic causes. The predominant finding was that of cardiac failure. Although no variables such as age, hypertension, diabetes, or status of the kidney were reported, and no postmortem findings such as the status of cardiovascular organs or residual carcinoma of the prostate were given, nevertheless, death rates were statistically higher. Such high mortality rates may be related to the salt-retaining properties of the estrogens.

**Complications of surgical and radiotherapeutic procedures** used in the treatment of carcinoma of the prostate include one or more of the following: incontinence, impotence, rectourethral fistula, perineal urinary fistula, stricture of the urethra, injury to the rectum or bladder, pyelitis, and pyelonephritis.

**PROGNOSIS.** The course of a prostatic carcinoma may be affected by clinical aspects, type of therapy, and the biologic characteristics of the neoplasm.

Rosenberg claimed that older patients do better than those who manifest carcinoma of the prostate before 61 years of age. Franks and associates (1958) reported that relatively few patients with carcinoma of the prostate who are over the age of 78 develop metastases. Tjaden and associates observed that many young patients under the age of 50
are first seen in an advanced stage of carcinoma of the prostate, although, occasionally, such a patient may live many years with little or no treatment. Byar and Mostofi (1969) reported better survival rates for patients less than 50 years of age; however, these were Army patients in whom carcinoma was often found on mandatory rectal examination before clinical symptoms had appeared. Recent figures reveal an influence of age upon mean survival even when corrected for normal mortality expectation (see bar graph). McKenzie reported that patients with symptoms of less than a year's duration had a more favorable prognosis. Patients with hypertension or urinary tract infection or a longer symptomatic period did less favorably. Patients with blood groups AB and those with metastases to lungs and soft tissue, in contrast to those with osseous metastases, have a more favorable prognosis (Veterans Administration Cooperative Urological Research Group, 1963; Cook and Watson). Beyond these elementary facts, however, we do not know why some patients do better than others.

Incidental carcinoma and focal carcinoma confined to the prostate generally have a more favorable prognosis. Conversely, a poorer prognosis may be expected for multifocal or diffuse carcinoma; carcinoma that has extended beyond the prostate as determined by surgical, clinical, and pathologic examination; tumor that metastasizes to lymph nodes or osteolytic metastases (Table VI); or tumors with persistent or recurrent high acid phosphatase (TSAP and PAP). The size of the tumor and whether it is completely surrounded by adequate normal tissue at the time of prostatectomy are also important factors. Tavares and associates have shown that prognosis seemed better for diploid and tetraploid tumors than for triploid and hexaploid tumors.

Perineural invasion has no prognostic significance. Several studies have claimed that the pattern and the grade of the tumor correlate with the length of survival (Pool and Thompson; Vickery and Kerr; Jewett et al.; Rous and Mallouh).

The multiplicity of possible treatment regimens and a serious lack of well controlled, statistically significant reports comparing patients not treated with those subjected to various types of therapy would seem to impose a serious responsibility on the urologist. Cook and Watson, however, claim that 10-year survivals are not significantly affected by the type of treatment.

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**CARCINOMA OF PROSTATE**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Median Survival Time</th>
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<tbody>
<tr>
<td>ALL AGES</td>
<td>3.0</td>
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<tr>
<td>UNDER 45</td>
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<tr>
<td>45-54</td>
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<td>55-64</td>
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<tr>
<td>65-74</td>
<td>3.6</td>
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<tr>
<td>75 &amp; OVER</td>
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Table VI
CARCINOMA OF PROSTATE
RELATIVE SURVIVAL RATES FOR PATIENTS DIAGNOSED 1940-69

| No. Cases | ALL STAGES | | | | LOCALIZED | | | | REGIONAL | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| No. Cases | 6008 | 11647 | 7321 | 7384 | 2925 | 6047 | 4414 | 4639 | 620 | 1626 | 1007 | 835 |
| 3-year | 49% | 59% | 64% | 66% | 64% | 73% | 76% | 77% | 43% | 59% | 67% | 71% |
| 5-year | 37 | 47 | 52 | | 51 | 61 | 65 | | 30 | 46 | 53 | |
| 10-year | 20 | 32 | | | 31 | 45 | | | 14 | 29 | | |
| 15-year | 14 | 24 | | | 23 | 35 | | | 8 | 19 | | |


ENDOMETRIOID CARCINOMA

SYNONYMS AND RELATED TERMS: Papillary adenocarcinoma of the utricle.

DEFINITION. Endometrioid carcinoma is an adenocarcinoma arising from utriculus masculinus; it is usually papillary, but may be infiltrating.

INCIDENCE AND PREVALENCE. The disease was first reported by Melicow and Pachter in 1967. Belter and Dodson reported a case in 1970, and Melicow and Tannenbaum added five more cases in 1971. While the number of reported cases suggests this tumor rarely occurs, it is probably quite prevalent. In all these cases, the patients were older men; four had hematuria, two reported frequency of urination, and one experienced acute urinary retention. The prostate glands of all patients were enlarged; three were smooth and soft while four were hard or indurated.

GROSS. Endometrioid carcinoma may be papillary and extend into the utricle resembling a papillary cystic tumor, or it may be papillary and infiltrating.

MICROSCOPIC. Two histologic patterns have been described (figs. 239—241). In one, the glands are lined by tall columnar epithelium with vacuolated cytoplasm and single or double layers of nuclei. In the other, the cells are cuboidal, often piled up, and the cytoplasm is granular.

DISCUSSION. The two patterns have been compared to endometrial and endocervical tumors (Melicow and Tannenbaum). The tumor may be entirely exophytic, or it may extend into the prostatic tissue for varying depths. We have seen several cases in which a definite prostatic carcinoma was observed elsewhere in the prostate—a coincidence that has not been reported.
Figure 239
ENDOMETRIOID CARCINOMA OF UTRICLE
(Figures 239 and 240 from same case)
This carcinoma of the utricle shows a papillary glandular configuration. X70.

Figure 240
ENDOMETRIOID CARCINOMA OF UTRICLE
(Figures 239 and 240 from same case)
This higher magnification of the lesion in figure 239 reveals tall columnar cells in a single or double layer. X350.
TREATMENT. Surgical removal of the tumor is preferable treatment; estrogen therapy and orchiectomy are considered inadvisable (Melicow and Tannenbaum).

PROGNOSIS. While the prognosis for endometrioid carcinoma appears fairly good, the number of cases thus far reported are too few and the period of observation too short for any reliable comment.

ADENOID CYSTIC CARCINOMA

This tumor of the prostate is composed of small, deeply staining, uniform cells that resemble basal cells. They are commonly arranged in anastomosing cords or ductal structures which contain a mucoid material. The whole tissue has a typical honeycomb or swiss cheese pattern (fig. 242). Adenoid cystic carcinoma is extremely rare. It has not been determined whether it represents a carcinoma of the rare aberrant salivary gland seen in the prostate, or is a manifestation of the neoplastic potential of the prostatic epithelium. It has no characteristic clinical pattern. Little is known of its clinical behavior other than the fact it probably is not amenable to antiandrogen therapy.
TRANSPORTINAL CELL CARCINOMA

Rarely, biopsy examination of the prostate of a patient with symptoms and signs of prostatism or prostatic carcinoma, reveals transitional cell carcinoma. In most patients, an antecedent or coexistent carcinoma of the bladder or urethra was found (fig. 243). About a third of the patients, however, had a primary transitional cell carcinoma of the prostate; in a number of instances, a definite adenocarcinoma of the prostate was also present. A majority of transitional cell carcinomas of the prostate originate from prostatic ducts (see Tumors and Tumor-like Conditions of the Male Urethra on page 269).

SQUAMOUS CELL CARCINOMA

Comments made relative to transitional cell carcinoma apply equally well here. Squamous cell carcinoma of the prostate is extremely rare (fig. 244). It may arise de novo in the ducts or urethra or it may appear following a period of estrogen therapy. As mentioned earlier, postinfarction squamous metaplasia often simulates squamous cell carcinoma and should be ruled out. Squamous cell carcinomas are usually primary carcinomas of the urethra secondarily involving the prostate (see page 267).
This low grade squamous cell carcinoma involves the prostate and appears to arise in epithelium of prostatic urethra. Invasion, while definite, is limited. X90. (Fig. 23 from Fascicles 31b and 32, First Series.)

References


Gyorkey, F. The Cancer of Prostate Gland. (Monograph, 1972—to be published)


______, and Cummings, R. H. Prostatic carcinoma treated by orchietomy: a secondary report based on 75 cases observed for at least 21 months following operation. J. A. M. A. 124:80-81, 1944.


Tumors of the Prostate


Segi, M. Cancer mortality for selected sites in 24 countries 1950-1957. Department of Public Health, Tohoku University School of Medicine, Sendai, Japan, 1960.


SARCOMA

INCIDENCE. Sarcoma of the prostate constitutes less than 0.1 percent of all prostatic malignant tumors. It may occur at any age, but 30 percent develop during the first decade of life and 75 percent occur before the age of 40. Sarcoma also occurs in elderly patients. Rhabdomyosarcoma is most commonly found in children, while leiomyosarcoma and fibrosarcoma occur in older patients.

SYMPTOMS AND SIGNS. The clinical findings are nonspecific and chiefly those of obstructive uropathy. In contrast to carcinoma of the prostate, sarcoma tends to grow much faster and may manifest itself as a perineal mass or a suprapubic mass. Pressure on the rectum may cause constipation, a sense of fullness, bloody stools, and an inability to evacuate. These symptoms, accompanied by urinary obstruction, are pathognomonic of sarcoma of the prostate. Deep pelvic pain is characteristic, and, in later stages of the disease, edema of the lower extremities, the perineum, and the scrotum is common.

Diagnoses of specific types of sarcoma of the prostate are based on a rectal examination to determine if the prostate is enlarged, symmetrical or asymmetrical, cystic, rubbery, hard, or soft.

NATURAL HISTORY. Sarcoma of the prostate has a potentiality for rapid growth. This is especially true for rhabdomyosarcoma. Fibromyosarcoma and leiomyosarcoma tend to grow more slowly. There is early compression of the prostatic urethra and invasion of the periprostatic and peri-vesical tissue. Extension anteriorly to the bladder and the abdominal wall and posteriorly to the rectum and perineum occurs in 75 percent of cases. Eventually, a large mass forms in the pelvis. Lymphatic and vascular invasion precedes involvement of the regional lymph nodes, the liver, and the lungs. Osseous metastases are more osteolytic.

The most common histologic types of sarcoma are rhabdomyosarcoma (figs. 245, 246), leiomyosarcoma (fig. 247), and lymphoma. Angiosarcoma, fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, osteogenic sarcoma, neurogenic sarcoma, and neuroblastoma have also been reported. It is sometimes difficult to further categorize an undifferentiated sarcoma.

DIFFERENTIAL DIAGNOSIS. On biopsy, malignant lymphoma may be difficult to differentiate from chronic prostatitis, undifferentiated carcinoma, or sarcoma. Similarly, leiomyosarcoma may be difficult to distinguish from stromal hyperplasia.

In chronic prostatitis, inflammatory reaction is usually related to the ducts; it is polymorphous with a mixture of lymphocytes, plasma cells, monocytes, and macrophages, and it infiltrates the acini and ducts. In malignant lymphoma, the cells are uniform; they infiltrate between individual muscle bundles with apparent compression and atrophy of the muscle (fig. 248) and may involve the acini.

Differentiation between a low grade leiomyosarcoma and stromal hyperplasia is sometimes extremely difficult, but a trichrome stain that reveals the fibromuscular nature of the latter may be helpful. Leiomyosarcoma cells are usually thinner and more interlacing.

TREATMENT. A biopsy is essential to determine the proper treatment in spite of the reluctance among some urologists to use this procedure for fear of seeding along the biopsy tract. The treatment of choice for malignant lymphoma is radiation therapy; 2 to 6-year results are favorable (Waller and Schullenberger). For other sarcomas, when
the tumor is confined to the prostate, total vesiculoprostatectomy is generally recommended (Vest). The outlook need not be hopeless if the patient receives early and vigorous treatment. If the tumor is inoperable, symptoms may be relieved by diversion of the urinary and fecal stream and radiation chemotherapy.

Figure 245
RHABDOMYOSARCOMA
This photomicrograph reveals none of the large ballooned giant cells so frequently associated with rhabdomyosarcoma, but the elongated straplike cells in several foci elsewhere showed cross striations. X515. (Fig. 27 from Fascicles 31b and 32, First Series.)
Figure 246
Rhabdomyosarcoma
This high power view shows the cross striations in the tumor cells. X1360. (Fig. 26 from Fascicles 31b and 32, First Series; also from Friedman, N. B., and Ash, J. E. Atlas of Genitourinary Pathology. Washington: American Registry of Pathology, 1946.)

Figure 247
Leiomyosarcoma
This tumor is very cellular, but shows the characteristic interlacing cell bundles, giving a whorled or herringbone appearance. The few remaining ducts and acini are widely scattered in the tumor. X90. (Fig. 25 from Fascicles 31b and 32, First Series.)
References


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Figure 248

LYMPHOMA

A uniform infiltration of large lymphocytes replaces the stroma and also involves the acinus in the center of the photomicrograph. X355. (Fig. 28 from Fascicles 31b and 32, First Series; courtesy of Dr. N. P. Rathbun and Dr. J. A. de Veer, Mesa, Ariz.)
CARCINOSARCOMA

In this tumor of the prostate, there are definite carcinomatous and sarcomatous elements. Desmoplastic reaction of the stroma (fig. 249) is seen in some prostatic carcinomas, usually following estrogen therapy. Sometimes, it is severe enough to lead to a diagnosis of sarcoma (fig. 250). Chondroblastic or osteoblastic areas may be present (fig. 251). There is concern in such cases whether it is a carcinoma with spindle cell areas and chondro-osteoblastic metaplasia, or a true carcinosarcoma. Each tumor must be evaluated by the extent and type of its noncarcinomatous elements and their relationship. If progressive stages can be demonstrated from carcinoma to spindle cells, if there seems to be a stroma for both components, and if the cells are undifferentiated, it is probably a rare spindle cell carcinoma. We believe most tumors designated as carcinosarcomas represent spindle cell carcinoma or desmoplastic reaction of the stroma. We would designate only lesions that contain definite neoplastic cartilage or bone formation or sarcoma as carcinosarcoma.
Figure 251
CARCINOSARCOMA
(Figures 249 and 251 from same case)
Note the extensive chondroid matrix formation from another area of the same tumor shown in figure 249. X115.

References


OTHER TUMORS AND TUMOR-LIKE CONDITIONS

A number of melanomas of the prostate have been reported. A metastatic melanoma should always be ruled out before diagnosis of a primary melanoma is accepted. Clinically, this tumor presents symptoms referable to prostatic obstruction or bleeding; histologically, it presents the same picture as melanoma in other sites. The importance of pigment identification in blue nevus is equally applicable for this tumor, since a number of carcinomas of the prostate may also contain lipofuscin pigment.

Tumor-like conditions of the prostate include prostatic hyperplasia, infarction, granuloma, and calculi which have all been described previously. (See Index for appropriate pages.)
TUMORS OF THE SEMINAL VESICLE

The seminal vesicles are bilateral saclike outpouchings from the vas deferens at its termination in the ejaculatory duct. They have irregular, branching lumens with numerous outpocketings lined by pseudo-stratified epithelium, which often contains yellow pigment and secretory granules. The vesicular wall is composed of smooth muscle similar to, but thinner than that which forms the wall of the vas. The vesicles are dependent upon testicular hormones for full development; after castration, the seminal vesicles and prostate atrophy markedly. This phenomenon is reversible by the injection of androgens.

Tumors of the seminal vesicle are rare—fewer than 100 have been described. It is unusual that the frequency with which tumor occurs in the prostate and the seminal vesicle should be so different when both arise from the same embryonic anlage and respond to the same hormone.

Tumors of this organ may be benign or malignant, epithelial or mesenchymal. The most common types are papillary adenoma, fibroma, and leiomyoma. Most malignant tumors of the seminal vesicle are papillary carcinoma; sarcoma occurs less frequently.

CARCINOMA

SYNONYMS AND RELATED TERMS: Adenocarcinoma; papillary adenocarcinoma; undifferentiated carcinoma.

DEFINITION. Carcinoma of the seminal vesicle is a rare malignant tumor arising from the epithelial lining of the seminal vesicle.

CLINICAL COURSE. The tumor occurs most often in patients over 50 years of age. Symptoms are similar to those for carcinoma of the prostate—urinary retention, dysuria, or hematuria. In some patients, a high level of urinary fructose has been observed (Mantz). Few cases are diagnosed early enough for curative radical surgery; most patients die within a year.

GROSS. In confirmed cases, carcinoma replaces the seminal vesicle; it may invade locally and extend to the prostate and to the opposite seminal vesicle. Obstruction of the prostatic urethra, internal urethral meatus, or lower portion of one or both ureters is common; extension to the rectum is rare. The tumors attain great size, frequently forming a mass 10 to 15 cm. in diameter.

MICROSCOPIC. Most of these tumors are papillary adenocarcinoma (figs. 252—254), but a mixture of adenocarcinoma and undifferentiated carcinoma is evident in some. Rarely, it may be all undifferentiated. The tumor consists of clear columnar cells, frequently with brown lipofuscin pigment, and they form acinar and papillary structures.

METASTASIS. Metastasis occurs in two thirds of the cases; it is similar in structure to the primary tumor.

DIFFERENTIAL DIAGNOSIS. Adenocarcinoma of the seminal vesicle is frequently a mistake in diagnosis. Most of the tumors referred to the Armed Forces Institute of Pathology reveal instead involutional changes in the seminal vesicle or carcinoma of the prostate. Tumor involving both the prostate and the seminal vesicle is probably
Tumors of the Seminal Vesicle

Figure 252
CARCINOMA
(Figures 252—254 from same case)
This carcinoma of the seminal vesicle shows a papillary glandular configuration. Note the thickened seminal vesicle at the edge of the tumor. X7.

Figure 253
CARCINOMA
(Figures 252—254 from same case)
This higher magnification shows papillary glandular configuration. Some glands are cystically dilated. Scattered mucin is seen. X130.
prostatic unless proved otherwise. The seminal vesicle must be principally involved and the carcinoma in the prostate must extend in from the outside to permit a diagnosis of carcinoma of the seminal vesicle. Not infrequently, diagnosis is made solely on the basis of a focal papillary configuration in a carcinoma of the prostate. The presence of a cystic structure does not necessarily denote a seminal vesicle carcinoma. Pigmentation of the cells is sometimes regarded as evidence for such a diagnosis; however, we have seen such pigmentation in unmistakable carcinoma of the prostate. Thus, we believe that diagnosis of carcinoma of the seminal vesicle should be made only when it can be demonstrated, both grossly and microscopically, that the seminal vesicle is principally involved. When extraseminal vesicle extension is present, direct continuity with the seminal vesicle must be demonstrated.

References

Mantz, F. Personal communication, 1971.
TUMORS AND TUMOR-LIKE LESIONS OF THE MALE URETHRA

The prostatic portion of the male urethra may be regarded as an extension of the bladder, and tumors occurring in this region resemble those seen in that organ. This portion of the urethra is surrounded by the prostatic gland and may be involved by prostatic diseases. The periurethral glands and ducts are located in the wall of the urethra, and tumors may also arise in these structures with secondary extension to the urethra. The floor of the prostatic urethra is occupied by the verumontanum which contains the ejaculatory ducts and the prostatic utricle. The epithelium of the prostatic portion of the urethra is transitional, while that of the membranous and penile (cavernous) portions is pseudostratified or stratified columnar. The fossa navicularis is lined by squamous mucosa, and patches of squamous epithelium may be found throughout the penile portion. Numerous outpouchings of the urethral mucosa communicate with the periurethral (Littre’s) glands while the bulbourethral (Cowper’s) glands are situated dorsal to the membranous portion into which the bulbourethral gland ducts empty.

POLYPS AND PAPILLOMAS

Several types of polypoid or papillary lesions in the male urethra may be classified by the type of epithelium present: transitional, columnar (resembling prostatic epithelium), or squamous. Those composed of squamous epithelium are squamous papillomas of the condyloma type, and are discussed on page 278.

Polypoid lesions covered by transitional epithelium include: polypoid urethritis (a lesion often mistaken for a neoplasm), simple fibrous polyp, and transitional cell papilloma. The latter will be discussed with transitional cell carcinoma.

Polypoid Urethritis

SYNONYMS AND RELATED TERMS: Urethritis polyposa; inflammatory polyp.

This urethral counterpart of polypoid cystitis may be differentiated from transitional cell papilloma and carcinoma by its stroma which is much more abundant, is heavily infiltrated by inflammatory cells, and is markedly edematous; it contains numerous telangiectatic blood vessels that are usually congested (fig. 255). This contrasts sharply with the delicate fibrovascular core of papilloma and carcinoma. In addition, the epithelium in polypoid urethritis may display any or all changes characterizing proliferative cystitis—epithelial hyperplasia, the formation of Brunn’s cell nests, the formation of cystic or glandular spaces, or the presence of lymphoid follicles in the stroma. The rare urethritis cystica is usually not associated with as much inflammation as the others. Squamous or mucinous epithelial metaplasia may also occur, or the epithelium may be focally or totally ulcerated.
plasia. The stalk is composed of loose connective tissue in which there may be small bundles of smooth muscle, and usually a central vascular core. The stroma is much less abundant than that seen in polypoid urethritis and lacks the inflammatory changes seen in that entity. These polyps may be differentiated from transitional cell papilloma by their lack of multiple papillary processes of papilloma and by their more abundant stroma. The histogenesis of these benign lesions is unknown; in children, they may represent anomalies of development, while in adults they are probably a variant of polypoid urethritis.

Fibrous Polyps

SYNONYMS AND RELATED TERMS Fibroepithelial polyp, simple polyp, pedunculated polyp

Fibrous polyps are long, narrow, tadpole or finger-shaped structures with the base always attached to, or very close to the verumontanum (fig. 256). They occur predominantly in children, but we have also seen them in young adults. Fibrous polyps may be up to 3.0 cm. in length and usually range from 0.3 to 0.5 cm. in diameter. They are covered by normal transitional epithelium in which there may be focal areas of squamous meta-

Figure 256
FIBROUS POLYP OF PROSTATIC URETHRA
This lesion is composed of a central vascular core and an abundant fibromuscular stroma covered by essentially normal transitional epithelium X40

Figure 255
POLYPOID URETHRITIS
A polypoid mucosal projection is covered by attenuated epithelium with formation of cell nests of von Brunn and early cystitis cystica. The lamina propria is edematous and the blood vessels are congested X37
Adenomatous Polyps with Prostatic Type Epithelium

SYNONYMS AND RELATED TERMS: Glandular polyp; ectopic, prostatic tissue in urethra; benign polyp; benign villous polyp.

Rare examples of sessile, polypoid, or papillary lesions arise from, or are immediately adjacent to the verumontanum. The epithelium is composed of tall columnar cells resembling the epithelium of prostatic acini. Because of their rarity, these lesions probably have not been clearly defined. Randall, in 1913, reported five cases under headings of “benign villous polyp” and “benign glandular polyp”. The three cases in the latter category may represent prostatic adenomatous nodules protruding into the urethra, but Randall felt that four of the tumors arose from the glands of the urethral mucosa, while the fifth was probably an adenomatous nodule from the prostate. Little more concerning these lesions appeared in the literature until 1962, when Nesbit reported 12 cases. He considered them benign aberrant outgrowths of prostatic epithelium, since the epithelium in two additional cases demonstrated acid phosphatase activity.

Butterick and associates reported 68 cases of ectopic prostatic tissue in the prostatic urethra; all the patients were young men. The presenting symptom was hematuria, and the histologic features were indistinguishable from hyperplastic prostate.

Our experience is limited to six adenomatous polyps in patients whose ages ranged from 17 to 66 years. All the lesions presented a similar histologic pattern of villous fronds, usually of simple type with delicate fibrovascular cores, covered by cuboidal to low columnar cells resembling those of prostatic acini (fig. 257). The cells were regular, although crowding was seen in some foci. In the lamina propria, beneath the

![Figure 257](image-url)

ADENOMATOUS POLYP OF PROSTATIC URETHRA

This sessile nodule is composed of tubulo-alveolar spaces and delicate papillary processes lined by columnar cells of the prostatic type. X50.
base of the tumor, there were normal-sized prostatic acini which had marked infoldings of their epithelial lining cells. The tumors were sessile rather than truly pedunculated; five arose in or near the verumontanum, and one arose from the bulbous portion of the urethra. There were two recurrences; in addition to the simple villous pattern, both contained complex glandular structures lined by closely packed, tall columnar cells with hyperchromatic nuclei. None had evidences of metastases.

CARCINOMA

Carcinoma of the male urethra rarely occurs. Approximately 400 cases have been reported (Lee and Bonney), but many are not well documented. McCrea and Furlong, in 1952, found 239 acceptable cases in the literature while Kaplan and associates accepted 221 and added 11 more cases in 1967. The tumor occurs in all races. Patients range in age from 13 to 91; the vast majority are over 50.

ETIOLOGY. The etiology of this tumor is unknown, but there is some evidence that chronic irritation may be a factor. A history of previous episodes of venereal disease or of urethritis is often obtained, and some patients report repeated dilatations of a urethral stricture. The possible relationship between urethral stricture and carcinoma of the urethra is difficult to assess, since the stricture may actually result from the tumor. Most authorities emphasize that investigation for carcinoma of the urethra should be made in any man over the age of 50 who develops a clinically apparent urethral stricture.

SITE. Carcinoma may arise anywhere within the urethra, but is more often located in the posterior (prostatic and bulbo-membranous) portion than the anterior (penile and fossa) portion. Fifty-four percent of the tumors reviewed by McCrea and Furlong occurred in the posterior portion, 41 percent in the anterior portion, and 11 percent occupied both portions. The bulbo-membranous portion of the urethra was the most common site of urethral carcinoma.

CLINICAL FEATURES. Symptoms of carcinoma of the male urethra are usually associated with obstruction of the urinary tract and are often combined with a purulent urethral discharge or hematuria, or both. If the tumor is situated in the anterior urethra, the patient may palpate the mass. Physical examination may disclose a palpable mass, evidence of periurethral or perineal abscess, often combined with sinus tracts and multiple fistulae or an enlarged prostate. A combination of urinary tract obstruction and an enlarged prostate not infrequently leads to a clinical diagnosis of prostatic hypertrophy. There have been few reports in the literature regarding endoscopic findings in urethral carcinoma. Apparently, there may be roughening or reddening of the mucosa, an exophytic cauliflower-like or papillary tumor, or an area of ulceration. By the time the patient is examined, tumors of the anterior urethra are usually 2 to 3 cm. in diameter and have invaded the corpus cavernosum; those of the posterior urethra may invade into or even beyond the prostate, or invade the base of the bladder. Periurethral or perineal abscesses with sinus tracts and/or fistulae are usually associated with tumors of the membranous portion.

PATHOLOGIC FINDINGS. Despite the fact that membranous and penile portions of the urethra are normally lined with columnar cells, the majority of urethral carcinomas are of squamous cell type; figures range from 69 to over 90 percent. While transitional cell carcinoma may occur at any location within the urethra, it most often occurs in the pos-
terior portion. A patient with transitional cell carcinoma of the urethra may also have transitional cell carcinoma of the bladder; this is particularly true of carcinoma of the prostatic urethra. It is not always possible to distinguish clearly between squamous cell carcinoma and transitional cell carcinoma, because the histologic patterns of undifferentiated or poorly differentiated squamous cell carcinoma are identical with those of poorly differentiated or undifferentiated transitional cell carcinoma. In addition, areas of squamous cell change are not an infrequent finding in a tumor that is predominantly a transitional cell carcinoma.

Transitional Cell Carcinoma
This tumor of the urethra exhibits the same spectrum of tumor patterns and cell differentiation as it does when it occurs in the bladder. Thus, the tumors may be in situ, well differentiated and papillary (papilloma, papillary carcinoma, grade I), infiltrative, or papillary and infiltrative with moderate or marked cellular anaplasia (fig. 258).

Squamous Cell Carcinoma
This tumor of the urethra resembles that seen in other organs in all respects. It is usually moderately well differentiated or well differentiated (fig. 259). This tumor is not extensively keratinizing, but foci of keratinization can usually be identified. The cells are anaplastic, sometimes pleomorphic, and contain frequent abnormal mitotic figures. In its earlier stage, urethral squamous cell carcinoma is often exophytic, but later usually becomes fungating or ulcerated.

The cells of either transitional cell carcinoma or squamous cell carcinoma may become spindle-shaped and mimic the histologic pattern of a sarcoma (fig. 260). Only careful attention to the structure of the tumor along the surface may enable the pathologist to be certain that a spindle cell tumor of the urethra is in reality a carcinoma rather than a sarcoma. Adenocarcinoma of the urethra is rare, and probably arises from the periurethral glands (see page 274).
Figure 259
SQUAMOUS CELL CARCINOMA
This is an early infiltrating squamous cell carcinoma of the prostatic urethra. The patient was a 64-year-old man who had had a previous prostatectomy and orchietomy for carcinoma of the prostate. The present tumor recurred, and the patient later died of metastatic squamous carcinoma. X70.

Figure 260
SQUAMOUS CELL CARCINOMA
This poorly differentiated squamous cell carcinoma, spindle cell type (pseudosarcoma), was found in the prostatic urethra in a 74-year-old man. The tumor later recurred and extended to involve the bladder neck and trigone. X675.
METASTASIS. Extensive local invasion is the rule with both squamous cell and transitional cell carcinoma of the urethra, but in our experience this occurs more rapidly and extensively with squamous cell carcinoma. Squamous cell carcinoma of the anterior urethra rapidly invades the corpus cavernosum, but the tunic and skin may be invaded later. Tumor situated more posteriorly also invades adjacent tissues, and tumor of the posterior portion or of the proximal portion of the penile urethra sometimes produces a palpable nodule at the base of the penis as a result of local invasion. Invasion of the prostate and the base of the bladder occurs with tumor of the prostatic urethra, which may also extend along the mucosal surface to involve the trigonal mucosa.

Invasion of lymphatic vessels and metastasis to regional lymph nodes are also frequent. While tumor of the anterior urethra usually metastasizes to inguinal and external iliac lymph nodes and tumor of the posterior urethra tends to metastasize to the deeper internal iliacs and hypogastric nodes, there are many exceptions; inguinal node metastasis is not uncommon from tumor of the posterior urethra. Despite early invasion of the corpus cavernosum, distant bloodborne metastases are rare in either anterior or posterior tumors, and distant visceral metastases usually are seen only in patients who have survived for appreciable periods of time.

COURSE AND PROGNOSIS. The prognosis for tumors of the anterior urethra is much better than for those of the posterior urethra. Five-year survival figures average 16 to 19 percent for tumors of the posterior urethra compared to an approximate 50 percent survival rate for patients with anterior urethral carcinoma. The difference is due to the greater accessibility of the anterior urethral tumors permitting earlier diagnosis and greater amenability to surgical excision by penile amputation. While local recurrence after excision is not uncommon for tumor of the anterior urethra, it is almost the rule for tumors located in the posterior urethra.

Death usually results from complications of the disease or therapy rather than from metastasis. Radical surgical procedures necessary to remove posteriorly situated tumor, the necessity for ureteral implantation requiring removal of the bladder, morbidity incident to urinary tract obstruction, and infection with subsequent debilitation and bronchopneumonia exact a heavy toll in patients with this disease.

TUMORS OF THE PERIURETHRAL GLANDS AND DUCTS

Three types of these rare tumors in men are generally recognized: so-called tumor of the periurethral prostatic ducts, adenocarcinoma of the urethra, and carcinoma of Cowper's glands.

Prostatic Duct Tumor (Transitional Cell Carcinoma of the Prostate)

Ende and associates described seven cases of transitional cell carcinoma and mixed transitional-adenocarcinoma of the prostate, probably derived from the mucosa of the ducts entering the prostatic urethra. Other cases of transitional cell carcinoma of the prostate have been described by Bates, by Karpas and Moumgis, by Johnson and associates, and by Rhamy and associates. This tumor presents clinically as carcinoma of the prostate, but patients are often younger than typical patients with carcinoma of the prostate. The tumor usually produces symptoms of prostatism, but in the transurethral resection material one finds a transitional cell
CARCINOMA OF PROSTATIC DUCTS
(Figures 261—263 from same case)

Several of the periurethral prostatic ducts are lined by anaplastic cells, some of which are sloughing into the ductal lumen. The inflammatory reaction at the top of the photomicrograph is secondary to a recent trans-urethral resection. X40.

carcinoma or a mixture of transitional cell carcinoma and adenocarcinoma (fig. 262) instead of the usual adenocarcinoma of the prostate. The periurethral prostatic ducts are replaced by tumor cells; sometimes central accumulation of sloughed cells produces the picture of comedocarcinoma (fig. 261). The tumor infiltrates both the prostate (fig. 263) and the base of the bladder and may produce ureteral obstruction. Proliferation and in situ carcinomatous changes may be seen in adjacent ducts and glands. This neoplasm may give rise to hematogenous and lymphogenous metastasis. It does not respond to orchiectomy or estrogen therapy, and the serum acid phosphatase levels remain normal.

Rubenstein and Rubnitz reported that hormonal manipulation was of no value in 8 of their 10 patients who died within one year. The longest survival from the time of diagnosis was 23 months. These tumors are now being recognized with greater frequency.
Anaplastic cells have replaced the mucosa of the periurethral prostatic ducts, one of which is solidly plugged by the cells. There is a suggestion of acinus formation in the latter duct. X100.
Tumors of the Urethra

Figure 263
TRANSITIONAL CELL CARCINOMA
(Figures 261—263 from same case)

The tumor has invaded the stroma of the prostate gland, and there is invasion of vascular and perineural spaces. X100.
Other authors have described atypical, hyperplastic, and dysplastic changes of the prostatic ducts as well as "carcinoma in situ" (figs. 264, 265) which may be precursors of the prostatic duct tumor (Karpas and Moumgis; Franks and Chesterman; Ullman and Ross). The number of similar cases we have observed have been too few to permit a definite correlation with subsequent prostatic duct tumors.

Figure 264
CARCINOMA IN SITU OF PERIURETHRAL PROSTATIC DUCTS
(Figures 264 and 265 from same case)
The normal lining is replaced by atypical cells completely or nearly completely filling the lumen. There is acinus formation in the epithelial lining of the duct at the top of the field. The prognostic significance of this alteration of the prostatic duct epithelium is uncertain. X90.

Figure 265
CARCINOMA IN SITU OF PERIURETHRAL PROSTATIC DUCTS
(Figures 264 and 265 from same case)
This high power view shows that the mucosa is replaced by markedly atypical cells, but the basement membrane is intact. X440.
Adenocarcinoma of Urethra

Adenocarcinoma of the male urethra is so rare that no clear-cut documentation of its clinical or pathologic features exists in the literature. The few adenocarcinomas that have been found in reviews of carcinoma of the male urethra have generally been considered of periurethral gland origin.

Carcinoma of Cowper's Gland

Carcinoma of Cowper's gland is almost equally rare; Le Duc added the eleventh case to the literature in 1962. Arduino and Nuesse recently described another case. This tumor usually presents as a perineal mass (fig. 266) generally separate from the prostate. Those in our files are poorly differentiated mucinous
Carcinoma

Figure 267
ADENOCARCINOMA OF COWPER'S GLAND
There are various sized acinar structures lined by malignant cells, which are mucin secreting. X165. (Fig. 114 from Fascicles 31b and 32, First Series; courtesy of Dr. L. V. Ackerman, Stony Brook, Long Island, N. Y.)

adenocarcinoma (fig. 267). The tumor is locally invasive and may metastasize.

SARCOMA

Most so-called sarcomas of the male urethra are considered under soft tissue tumors of the penis which is discussed on page 291. Embryonal rhabdomyosarcoma may arise in the prostatic portion of the urethra and usually has a typical botryoid appearance. This tumor is discussed in Fascicle 31, "Tumors of the Urinary Bladder."

References


TUMORS AND TUMOR-LIKE LESIONS OF THE PENIS

Neoplasms of the penis may arise most frequently from the covering epithelium, but also originate in the connective tissues that comprise the bulk of the organ. Tumors of the penile urethra are discussed under urethral tumors on page 263. In addition to carcinoma, the penile epithelium is often the site of proliferative or dysplastic tumor-like changes. Some of these changes are difficult to differentiate from carcinoma both clinically and pathologically, while others are clearly precancerous. Therefore, a discussion of these tumor-like lesions is included in this fascicle.

Proliferative lesions of the penile epithelium vary from typical condyloma accuminatum, which is benign both clinically and histologically, to invasive squamous cell carcinoma. Some epithelial proliferations occur that simulate carcinoma clinically but which lack the overt histologic features of carcinoma. These lesions appear malignant because clinically they “invade” adjacent tissues and because they usually recur and extend despite vigorous therapy.

Histologically, in addition to upward proliferation of the epithelium that occurs in typical condyloma, there is also downward proliferation causing erosion into deeper structures such as the prepuce or even the corpora of the penis. True invasion of tissues and metastasis do not occur. When possible these tumor-like lesions have been separated into specifically defined entities. In rare individual cases, however, the limits of morphologic interpretation preclude precise classification. The specific categories include pseudoepitheliomatous hyperplasia, ordinary condyloma with extensive involvement of the epithelial surfaces, giant condyloma (Buschke-Löwenstein tumor), and a group of less well defined borderline malignant lesions. The latter merge almost imperceptibly into the so-called condyloma-like (verrucous or papillary) squamous cell carcinoma, which closely resembles giant condyloma both clinically and pathologically, but in which there is actual invasion of the underlying tissues.

PSEUDOEPITHELIOMATOUS HYPERPLASIA

This epidermal proliferation is sometimes observed overlying a dermal lesion, usually inflammatory, and in the margins of a chronic ulcer. This reaction by the epidermis must be differentiated from condyloma and from verrucous squamous cell carcinoma. The histologic pattern is that of epithelial hyperplasia. The epidermis is acanthotic and greatly thickened. The rete ridges are irregular, branching, and fused with finger-like prolongations extending to variable depths into the dermis (fig. 268). The tips of these elongated processes are often pointed, unlike the rounded tips of condyloma. The proliferating squamous cells exhibit little or no pleomorphism, retain a high degree of differentiation, and maintain their continuity to the epidermis; these factors represent the chief differentiating features between pseudoepitheliomatous hyperplasia and squamous cell carcinoma. The underlying dermis usually contains a dense, chronic, inflammatory infiltrate and often, in addition, a productive fibrosis. The chief differentiating
features between pseudoepitheliomatous hyperplasia and condyloma are a greater tendency to papillomatosis, greater uniformity in depth of penetration, and acanthosis extending to the tips of the rete ridges of condyloma.

Pseudoepitheliomatous hyperplasia occurs in association with a variety of skin lesions, most often with chronic productive inflammatory processes such as bromoderma or granuloma inguinale, at the edges of chronic ulcers (basal cell carcinoma, burns, stasis dermatitis), or overlying a granular cell tumor (so-called granular cell myoblastoma).

CONDYLOMA ACUMINATUM

SYNONYMS AND RELATED TERMS: Squamous papilloma; venereal wart.

Typical condylomas are essentially squamous papillomas, closely related to verruca vulgaris, and occur on the moist mucocutaneous regions of the external genitals in both males and females. They may also arise from vaginal, anal, or urethral mucosa. In males, they are usually found in the preputial sac arising from the lining of the prepuce, the coronal sulcus of the glans penis, the epithelium about the urethral meatus, or rarely on the penile shaft. The soft, verrucal, or warty masses are generally pink and vascular. They are caused by a filterable virus, and aggravated by the presence of a prepuce, warmth, moisture, and irritating discharges. Typical condylomas usually remain localized and superficial; they respond to therapeutic treatment, including the application of podophyllin, particularly if the aggravating factors are removed or corrected.

Histologically, typical condyloma is characterized by marked acanthosis and by hyperplasia of the prickle cell layer (fig. 269). The stratum corneum may be slightly thickened,
This low power photomicrograph shows the epithelium is acanthotic, but with orderly maturation of the cells. The rete ridges, the tips of which are rounded, extend for a short but uniform depth into the corium. X55.

The rounded end of a rete ridge is composed of orderly epidermal cells exhibiting a normal maturation pattern. X130.
and parakeratosis is present as it is normally on mucosal surfaces. The rete ridges are elongated and may be branching, although usually the deep surface of the papillae is broad and rounded. The growth pattern is characteristically upward toward the surface rather than downward into the tissues. The bases of the acanthotic papillae all extend to approximately the same depth, and there is no hyperplasia of the basal cell layer (fig. 270). The entire picture is one of orderly proliferation of epithelial cells with maintenance of the usual stratification of the skin or mucosa. The presence of clear vacuolization of some of the prickle cells is considered by some to be characteristic. The dermis beneath the lesion is usually moderately edematous, and there is often a dense, chronic inflammatory infiltrate.

Condyloma is usually a localized lesion, but some extensive condylomas display a tendency to spread out and involve a large area. The fact that this lesion tends to remain superficial without extension into underlying tissues distinguishes it from the giant condyloma of Buschke-Löwenstein.

GIANT CONDYLOMA

SYNONYMS AND RELATED TERMS: Giant condyloma acuminatum; condylomatoid carcinoma; carcinoma-like condyloma; Buschke-Lowenstein tumor.

Giant condyloma has been separated from the more typical variety because it fails to respond to podophyllin and radiation, and displays a progressive and recurrent invasive growth pattern, indistinguishable clinically from that of carcinoma. Histologically, it may show some nuclear atypicality and with occasional reports of metastases, it is questionable whether this lesion is truly condyloma or well differentiated carcinoma. Giant condyloma is found in the preputial sac of middle-aged, uncircumcised men; rarely, the tumor has been reported in the perianal region (Knoblich and Failing). However, this case is considered a squamous cell carcinoma. The lesion forms large, grotesque, cauliflower-like, warty masses over extensive areas (fig. 271). Ulceration and secondary infection often occur. A characteristic feature is the downward growth of the lesion into underlying tissues in addition to the upward growth of typical condyloma (fig. 272). This downward growth is apparently expansion of the lesion and not true invasion, as seen in carcinoma, with the base of the lesion being pushed downward by the overlying, proliferating, prickle cell layer. The tissues beneath the giant condyloma are compressed and ultimately destroyed. The lesion often perforates the prepuce, then ulcerates and spreads. The warty growths may extend

Figure 271
GIANT CONDYLOMA
The preputial sac is filled with an extensive warty or cauliflower-like growth in which there has been ulceration and secondary infection. The lesion appears to invade the underlying tissue and cannot be distinguished from verrucous carcinoma clinically.
onto or beneath the skin of the penile shaft; in the latter instance, multiple fistulae may form with protrusion of warty masses through the fistulous openings. The prepuce and glans are always extensively involved and often destroyed. Giant condyloma is very resistant to treatment; it does not respond to podophyllin, and radiation therapy is ineffective. Usually, extensive surgical excision and occasionally, partial amputation of the penis is required. Recurrence is common, but the lesion does not metastasize.

Despite its clinical resemblance to carcinoma, histologically giant condyloma has the same regular and orderly arrangement of cells as typical condyloma. The stratum corneum may be thicker than that of simple condyloma, and parakeratosis is present. There is striking acanthosis with papillomatosis (fig. 273) and marked hyperplasia of the prickle cell layer. Epithelial cells of the papillae are supported by delicate fibrovascular cores. The bases of the papillae generally are rounded and extend to approximately the same level (fig. 274). In contrast to typical condyloma, however, the papillae of giant condyloma extend deeply into underlying tissues. Mitoses are present in the basal and prickle cell layers, but they are rarely numerous. Despite the degree of epithelial proliferation and depth of penetration by the epithelium, the cells maintain their normal stratification and retain their normal polarity. The basement membrane is intact. The tissues surrounding the penetrating epithelial papillae are compressed and ultimately destroyed; there is marked congestion of the blood vessels, and a dense chronic inflammatory infiltrate is present. If fistulae have formed and there is secondary
Figure 273
GIANT CONDYLOMA
The epidermis is markedly acanthotic, and there is hyperplasia of the prickle cell layer. The rounded tips of the rete ridges often extend deeply into the corium, but generally to the same level. X50

Figure 274
GIANT CONDYLOMA
(Figures 272—274 from same case)
Despite the downward proliferation of the epidermis, the cells are orderly and exhibit a normal maturation pattern. X115.
Infection, the inflammatory reaction may be purulent. A clear distinction between giant condyloma and verrucous carcinoma is impossible, and there are some who regard the two lesions as synonymous (Kraus and Perez-Mesa; Smith et al.). We believe it preferable, however, to reserve the term giant condyloma for well differentiated, papillary, squamous cell tumors in which there is no true invasion, and hence no capability for metastasis. The term verrucous carcinoma should be used for those tumors in which there is invasion with truly disconnected islands and groups of invading cells and potential metastasis.

Why certain condylomas display this penetrative and persistent growth pattern has never been satisfactorily explained. The lesion is nearly always associated with a tight or narrow prepuce which, in some way, apparently stimulates growth of the cells. Whether or not a true invasive carcinoma capable of metastasizing develops from giant condyloma is also uncertain; if it does occur, however, it is rare. Examples of malignant change in giant condylomas have been reported in the literature (Machacek and Weakley; Dawson et al.; Davies), but the possibility has not been ruled out that the lesions were condyloma-like carcinomas from the outset rather than carcinomas developing in a condyloma.

Penile lesions characterized by dysplasia can usually be classified into a specific, well recognized entity, either erythroplasia of Queyrat or Bowen's disease. If the lesion cannot be readily classified, it should be coded as acanthosis with dysplasia, nonspecific (fig. 275). Some pathologists use the clinical term "leukoplakia" for such lesions; however, these lesions are not white and since pathologic definitions of leukoplakia vary widely, the term is unsuitable for pathologic diagnosis for these lesions.

Figure 275
NONSPECIFIC ACANTHOSIS WITH FOCAL DYSPLASIA
Some pathologists code a lesion of this type as "leukoplakia." X85.
Erythroplasia of Queyrat is a dysplasia usually occurring on the glans and prepuce. It has also been reported on glabrous skin, vulva, lips, tongue, and oral mucosa. It presents as a red, velvety plaque, usually about 1.0 cm. in diameter, which may be elevated, papillary, or ulcerated. Most patients with erythroplasia are uncircumcised. The age range in Graham and Helwig’s series was from 20 to 80 years, with a mean age of 51. Because of the marked similarity between the histologic picture of erythroplasia and Bowen’s disease, some have regarded erythroplasia as Bowen’s disease of the mucosa (Andersson et al.; Lever). Erythroplasia of Queyrat is different from Bowen’s disease of the skin because it lacks any significant association with the development of systemic cancer or other cutaneous cancer which so frequently occurs in patients with Bowen’s disease (Helwig and Graham). However, erythroplasia is a pre-cancerous lesion with infiltrating squamous cell carcinoma developing in approximately 10 percent of patients.

Histologically, erythroplasia presents as an acanthotic plaque in which there is diminution of the keratin layer, parakeratosis, irregular acanthosis and sometimes papillomatosis and infiltration of inflammatory cells in the upper corium (fig. 276). The thickened epidermis is composed of atypical cells with loss of both normal polarity and normal maturation pattern; many of the cells are vacuolated and there are numerous mitoses throughout the epidermis (fig. 277). These changes involve all layers of the epidermis, and these, plus prolongation and extension of the rete ridges into the underlying stroma closely resemble the histologic pattern of Bowen’s disease. Differences between the two include hypokeratosis, fewer multinucleated and malignant dyskeratotic cells, and a pronounced plasma cell component of the inflammatory infiltrate in erythroplasia.

Figure 276
ERYTHROPLASIA OF QUEYRAT
The lesion forms an acanthotic plaque beneath which the corium is heavily infiltrated by chronic inflammatory cells. X55.
**Bowen's disease** is a carcinoma in situ of the skin in which there is a predilection for the development of other cutaneous dysplasias, malignant neoplasms, and of other primary carcinomas in the viscera (Graham and Helwig). A lesion of Bowen's disease occurs in a variety of cutaneous locations, including the shaft of the penis and the scrotum. While predominantly a disease of Caucasians, it is also found in other races. Although it has been described as occurring in the genital region of both males and females in the third, fourth, and fifth decades, our experience shows that it usually occurs in middle and old age. Its gross appearance is variable, but plaque formation with crusting and ulceration are usually present. The lesions average about 1.3 cm. in diameter.

Microscopic features resemble those of carcinoma in situ with replacement of thickened epidermis by abnormal, often markedly atypical cells. The lesion forms a plaquelike acanthosis, sometimes with papillomatosis, but the basement membrane remains intact (fig. 278). Usually, the dermal-epidermal junction is sharp, but it may be obscured by a dense, prominent, inflammatory infiltrate in the upper corium composed of lymphocytes, histiocytes, and plasma cells. Normal polarity of the cells is lost as is normal maturation of the cells from the basal layer to the surface. The proliferating epidermal cells are variable in size and shape. There is considerable nuclear variation with hyperchromatism and prominent nucleoli (fig. 279). Mitotic figures may be very numerous, and at times abnormal. Multinucleated cells, vaculated cells, and malignant dyskeratotic cells are also present. These changes involve the full thickness of the epidermis. Hyperkeratosis and parakeratosis may be marked, with corresponding increase or loss of the granular layer.

Invasive squamous cell carcinoma develops at the site of the lesion in about 5 percent of patients; adequate surgical excision may prevent this complication. About 40 percent of patients with Bowen's disease ultimately develop other premalignant and malignant lesions of the skin, and more than 25 percent ultimately develop a primary visceral carcinoma.
The lesion forms an acanthotic plaquelike area on the shaft of the penis. There is marked papillomatosis, but the epidermodermal junction is sharply defined. X90.

Bowen’s disease represents carcinoma in situ of the epidermis with replacement of the epidermis by atypical cells in which mitoses are present at all levels. There is parakeratosis and absence of a granular layer. X260.
CARCINOMA

Carcinoma of the penis accounts for about one percent of all malignant tumors in the male (Buddington et al.). While the tumor is found occasionally in young men, the highest incidence occurs in the seventh decade; 80 percent of patients are past the age of 50. The disease has been reported in all races, but is more common in Asia and Africa than in the United States or Europe. The lowest incidence rates are reported for those races or societies in which circumcision is a common practice.

While the etiology is unknown, there is general agreement that circumcision performed in infancy gives almost 100 percent protection against the disease. Although rare, penile carcinoma has occurred in patients circumcised in infancy (Melmed and Pyne). Circumcision performed later in life gives less protection. Retained secretions in the preputial sac thus appear to play an important role in the genesis of penile cancer. The possible role of venereal disease is less well defined, but many patients with carcinoma of the penis have had prior venereal disease. The precancerous nature of penile dysplasia, Bowen's disease, and erythroplasia of Queyrat has already been noted.

Many carcinomas of the penis are large and well advanced by the time the patient consults a physician, and the precise site of origin on the penis may be difficult to determine. With early and smaller lesions, however, the site of origin is nearly always on the glans or inner surface of the prepuce; origin from the penile shaft is rare.

Clinically, the tumor may present as an ulcer (fig. 280), nodule, verruca, or as a large, fungating lesion. With ulceration or secondary infection, the lesion may be associated with a foul discharge which may be purulent or blood-tinged. The presence of a prepuce, often phimotic, may obscure the tumor until it is well advanced. In addition to the penile lesion, inguinal adenopathy is the next most common finding. This may be due to reactive hyperplasia and/or chronic lymphadenitis or to metastatic carcinoma. Reactive hyperplasia and lymphadenitis are difficult to distinguish from metastatic carcinoma by clinical examination. Clinical staging of carcinoma of the penis is, therefore, difficult. In general, the larger node is more likely to contain metastatic carcinoma, and the smaller penile lesion is less likely to metastasize (Frew et al.; Buddington et al.; Staubitz et al.).

Carcinoma of the penis is nearly always squamous cell; initially, it develops as a small ulcer, nodule, or verruca on the glans or inner surface of the prepuce. More advanced tumors usually are large, fungating, and centrally ulcerated; they may involve an extensive area of the penis. Carcinoma of the penis rapidly invades underlying tissue and
Tumors of the Penis

may destroy the glans, the prepuce, and a portion or all of the shaft. Ultimately, Buck's fascia is penetrated, and the tumor invades the corpora cavernosa. Large fungating and papillary tumors are often termed **verrucous carcinoma**; these must be differentiated from giant condyloma of Buschke-Löwenstein (fig. 281).

Histologically, squamous cell carcinoma of the penis is usually well to moderately well differentiated and resembles squamous cell carcinoma occurring elsewhere. Papillary or verrucous tumors usually exhibit marked acanthosis and papillomatosis with hyperkeratosis and parakeratosis. In many areas of the tumor, the cells may be orderly like those of giant condyloma (fig. 282). However, there are foci where the cells are disorganized, with variation in size and shape of cells and their nuclei, loss of normal maturation and polarity, and excessive numbers of abnormal mitoses (fig. 283). Infiltration of the dermis may be focal (fig. 284), and differentiation from giant condyloma may require multiple sectioning of the tumor. The more solid or nodular tumor is usually clearly infiltrative and tends to be less well differentiated than the verrucous type (fig. 285). Squamous cell carcinoma invades the dermis and deeper tissue in irregular strands or cords, or small clumps.

Despite the vascularity of the penis, the spread of penile carcinoma by way of the blood vessels is rare. A few cases demonstrate vascular invasion with embolization through the prostatic plexus of veins, pelvic veins, and vena cava. In rare instances, the dorsal vein of the penis is invaded and the cells may be carried by way of the vertebral

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**Figure 281**

**VERRUCOUS CARCINOMA (CONDYLOMA-LIKE CARCINOMA)**

(Figures 281—284 from same case)

The lesion closely resembles the giant condyloma of Buschke-Löwenstein, but contains foci of dysplasia and of microinvasion not seen in this photomicrograph. X7.
Figure 282
CONDYLOMA-LIKE AREA IN VERRUCOUS CARCINOMA
(Figures 281—284 from same case)
An area such as this cannot be differentiated from giant condyloma. X70.

Figure 283
VERRUCOUS CARCINOMA
(Figures 281—284 from same case)
A focal area of dysplasia is seen in a verrucous carcinoma. Such areas are not found in giant condylomas. X100.
Tumors of the Penis

Figure 284
VERRUCOUS CARCINOMA
(Figures 281—284 from same case)
This shows a focus of early true invasion of the corium in a verrucous carcinoma. Such areas are not found in giant condylomas. X80.

Figure 285
SQUAMOUS CELL CARCINOMA
This is a moderately well differentiated, invasive squamous cell carcinoma of the penis. X50.

veins of Batson. Carcinoma of the penis usually metastasizes by way of the lymphatics to the inguinal lymph nodes, often with bilateral involvement. Distant metastasis from carcinoma of the penis is rare and occurs in only about 10 percent of cases.

Prognosis for carcinoma of the penis is fairly good with about one half of the patients surviving. The survival time varies with age (see bar graph).
MISCELLANEOUS EPITHELIAL TUMORS

A few recorded examples of basal cell carcinoma of the penis have been reviewed by Hall and associates. According to Hayes and Young, 146 cases of metastatic carcinoma of the penis are recorded in the English language literature. In 1961, Abeshouse and Abeshouse presented an extensive review of the literature concerning secondary penile carcinoma. The bladder, prostate, and kidney are the most frequent primary sites of these tumors. Malignant melanoma of the penis is also quite rare; Ellis and White found 23 reported cases and added one of theirs. Prognosis is grave; of these cases reviewed, there were only two long-term survivors. Fronstin and Hutcheson found reports of 25 malignant melanomas of the penis in the literature and reported two additional cases.

SOFT TISSUE TUMORS

Fifty-four cases of sarcoma of the penis were reviewed by Ashley and Edwards, who added an additional case of leiomyosarcoma. Dehner and Smith have recently reviewed mesenchymal and neurogenic tumors of the penis listed in the files at the Armed Forces Institute of Pathology; 24 were benign and 22 were malignant. They included tumors that were classified as follows: 19 vascular, 12 benign and 7 malignant; 10 neurogenic, 8 benign and 2 malignant; 5 smooth muscle, 3 benign and 3 malignant; 4 fibrous, I benign and 3 malignant; 2 malignant lymphoma; and 5 unclassified miscellaneous, all malignant. Nine of the vascular tumors were capillary hemangioma; 1 was sclerosing hemangioma; 1, glomus tumor; and 1, lymphangiomia. There were 4 cases of Kaposi's sarcoma, and 3 malignant hemangioendotheliomas. The malignant hemangioendotheliomas were fairly well circumscribed, spongy, hemorrhagic masses, 1 to 3 cm. in diameter, located in the subcutis or attached to the corpus cavernosum or ischiocavernosus muscle. Despite the malignant histologic pattern of these tumors (figs. 287, 288), their clinical course was benign. Waugh, however, reported Kaposi’s sarcomas located on the
Tumors of the Penis

Figure 286
KAPOSI'S SARCOMA
This section is from one of two wartlike growths on the penile shaft which had been present for two years, with rapid growth for about one week. X300.

Figure 287
MALIGNANT HEMANGIOENDOTHELIOMA
(Figures 287 and 288 from same case)
Irregular vascular spaces are lined with malignant-appearing endothelial cells which are separated by sheaths and cords of similar-appearing cells. X280.

Figure 286

Glans or prepuce (fig. 286); in cases in which the penile lesion was solitary, the patients were living and well from 2 to 10 years after excision. Hutcheson and associates recently reviewed 11 cases of leiomyosarcoma of the penis, including those in the Armed Forces Institute of Pathology series. These tumors characteristically arise in the penile shaft, are histologically of low or intermediate grade malignancy (fig. 289), and have a tendency to recur locally. Only 2 of 11 patients developed metastases. Fibrosarcoma of the penis is rare. Of the 3 cases in the Armed Forces Institute of Pathology series, one patient died of metastasis one and a half years after treatment, one was lost to follow-up, and the third patient, whose lesion was dermatofibrosarcoma protuberans, was living and well more than 10 years after excision.
References


Gersh, L. Giant condylomata acuminata (carcinoma-like condylomata or Buschke-Löwenstein tumors) of the penis. J. Urol. 69:164-172, 1953.

TUMORS OF THE SCROTUM

The scrotum is covered by pigmented skin of the usual composition. The dermis contains hair follicles, sebaceous glands, and sweat glands. Beneath the dermis is a thin layer of smooth muscle, the dartos tunic, which produces furrowing or wrinkling of the skin when it contracts. Deep to the dartos tunic are several layers of fascia containing some adipose tissue and some striated fibers of cremasteric muscle. The inner lining of the scrotum is composed of mesothelium constituting the parietal layer of the tunica vaginalis. Tumors of the latter structure are discussed on page 168.

Tumors arise more often from the skin while those of mesenchymal origin occur occasionally. The scrotum may be the site of any neoplasm originating from epidermis or adnexal structures (see Fascicle 2, First Series, "Tumors of the Skin"). All tumors of the scrotum are rare, and only those that occur occasionally will be discussed here. The most common epithelial tumors or tumor-like lesions are pigmented nevi and epithelial inclusion cysts or sebaceous cysts. Inasmuch as the cysts are not true neoplasms, they will not be discussed in this fascicle. The occurrence of carcinoma of the scrotum has declined over the past two decades. Malignant melanoma is rare. Tumors of mesenchymal origin are very rare; lipoma and hemangioma occur least rarely. Leiomyoma arising from the dartos tunic or from vascular channels is seen occasionally.

CARCINOMA

INCIDENCE AND ETIOLOGY. Carcinoma of the scrotum has been investigated by many authors primarily because of its relationship to industrial carcinogenic agents. It was the first human neoplasm to be clearly associated with certain hydrocarbons found in soot, oils, and paraffin. A definite occupational incidence was established among chimney sweeps, mule spinners, and paraffin workers. With elimination of potential industrial hazards, carcinoma of the scrotum has become quite rare. Occasionally, it is discovered in someone who has had no known contact with carcinogenic agents (Tucci and Haralambidis). Patients are usually from the lower socioeconomic class. This tumor occurs most often during the fifth and sixth decades, indicating an extended latent period between the time of exposure to carcinogenic agent(s) and its clinical appearance. The reported incidence of carcinoma of the scrotum is high in Caucasians and low in Blacks (Tucci and Haralambidis).

CLINICAL FEATURES. Carcinoma of the scrotum initially appears as a papillomatous or wartlike nodule or as an area of hyperkeratosis. It may occur anywhere on the scrotum, but is usually found on the inferior-anterior area. Pruritis may be an early symptom, but as the lesion enlarges, its margins become raised and hard, and central ulceration usually occurs. When ulceration and secondary infection occur, it may become painful. The lesions are occasionally multiple (fig. 290). Although not a frequent early finding, inguinal adenopathy often occurs in tumors of more than 9 to 12 months duration. Enlargement of the inguinal nodes presents the same problem in scrotal cancer as in penile carcinoma, since it is often impossible to determine clinically whether enlargement is due to reactive hyperplasia and/or chronic lymphadenitis or to metastatic carcinoma.
Tumors of the Scrotum

 Figure 290
 CARCINOMA

 This is a carcinoma of the scrotum at the junction of the scrotum with the penis. A smaller second lesion is seen on the right scrotum. The patient was a corkstone maker, aged 65. (Fig. 128 from Fascicles 31b and 32, First Series; also from Henry, S. A. Cancer of the Scrotum in Relation to Occupation. London: Oxford University Press, 1946.)

 Figure 291
 CARCINOMA

 (Figures 291 and 292 from same case)

 Junction between nonneoplastic epithelium at top and invasive tumor is evident. Marked chronic inflammatory exudate in dermis is usual. X100. (Fig. 129 from Fascicles 31b and 32, First Series.)
PATHOLOGIC FINDINGS. Carcinoma of the scrotum is nearly always of squamous cell type, either well differentiated (grade 1) or moderately well differentiated (grade 2). Histologic structure and modes of growth and infiltration are identical to squamous cell carcinoma of other areas of the skin (figs. 291,292). While there may be extensive local invasion, perforation of the tunic is rare. Metastasis is nearly always to inguinal lymph nodes, and bilateral involvement of these nodes is the rule. Distant metastasis is rare.

COURSE AND PROGNOSIS. Carcinoma of the scrotum has only a fair prognosis with a 5-year mortality rate of 50 to 60 percent. Death usually results from large, extensively ulcerated, necrotic lesions producing inanition and sepsis, and sometimes massive hemorrhage. With modern surgical therapy and chemotherapy and the availability of blood for transfusions as needed, survival rates should improve considerably because patients rarely die from metastases.

OTHER EPITHELIAL TUMORS

Pigmented nevi, usually of the junctional or compound type, occur only occasionally (fig. 293). Epithelial dysplasia and carcinoma in situ (Bowen’s disease) are equally rare. The clinical and pathologic features of these lesions on the scrotum are similar to those occurring on other epithelial surfaces (see Fascicle 2, First Series, “Tumors of the Skin”).
Tumors of the Scrotum

Figure 293
ANGIOKERATOMA
Note phlebectasia and marked atrophy of dartos muscle. X40 (Fig. 4 from Imperial, R., and Helwig, E. B. Angiokeratoma of the scrotum (Fordyce type) J. Urol. 98:379-387, 1967.)

Figure 294
HEMANGIOMA
Numerous thin walled, dilated, engorged blood vessels are seen in the dermis extending to the epidermal margin. X55
MISCELLANEOUS TUMORS

Capillary hemangioma (figs. 294, 295) and, rarely, lymphangiomatous tumor of the cystic hygroma type occur in the scrotum. Angiokeratoma, Fordyce type, is a vascular, warty, tumor-like lesion of the scrotum that represents a telangiectasia of the venules associated with acanthosis and elongation of the overlying rete ridges of the skin (Imperial and Helwig). Grace recorded the eighth case of scrotal leiomyoma, and a case of leiomyosarcoma was reported by Immergut and associates. We have observed rare examples of scrotal lipoma, and Waller reported a liposarcoma.

Figure 295
CAPILLARY HEMANGIOMA
This high power view shows a well circumscribed and uniformly cellular benign lesion with many small blood vessels throughout. X395. (Fig. 135 from Fascicles 3lb and 32, First Series.)

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