TUMORS of the MALE GENITAL SYSTEM

by

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

ATLAS OF TUMOR PATHOLOGY

Second Series

Fascicle 8

TUMORS OF THE MALE GENITAL SYSTEM

by

F. K. MOSTOFI, M. D.

Chief, Genitourinary Pathology Branch Armed Forces Institute of Pathology Washington, D. C.

and

EDWARD B. PRICE, JR., M. D.

Genitourinary Pathology Branch Armed Forces Institute of Pathology Washington, D. C.

Present Address
Department of Pathology
Presbyterian Medical Center
Denver, Colorado 80218

Published by the ARMED FORCES INSTITUTE OF PATHOLOGY Washington, D. C.

Under the Auspices of
UNIVERSITIES ASSOCIATED FOR RESEARCH AND EDUCATION IN PATHOLOGY, INC.
Bethesda, Maryland
1973

Accepted for Publication 1973

For sale by the American Registry of Pathology Armed Forces Institute of Pathology Washington, D. C. 20306

ATLAS OF TUMOR PATHOLOGY

Sponsored and Supported by

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EDITOR HARLAN I. FIRMINGER, M. D.

Professor, Department of Pathology
University of Maryland School of Medicine
Baltimore, Maryland 21201
and
Scientist Associate, Universities Associated for
Research and Education in Pathology, Inc.
9650 Rockville Pike
Bethesda, Maryland 20014

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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.

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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.

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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6:427-454, 1953. For our Table III

19:1963-1988, 1966. For our figures 7, 14, 15

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30:1225-1232, 1972. For our Table IV

Appleton-Century-Crofts:

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Oxford University Press:

Carcinoma of the Scrotum in Relation to Occupation, 1946. For our figure 290 Paul B. Hoeber, Inc. Medical Division of Harper & Brothers

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8:583-602, 1960. For our Plate B, figures 2, 3

The American Association of Pathologists and Bacteriologists:

Am. J. Pathol.

12:599-624, 1936. For our figures 168, 169

43:153-173, 1963. For our figures 45, 46

U. S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health:

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Am. J. Clin. Pathol.

44:119-134, 1965. For our figures 179, 180, 200-203

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

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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 chorio-

cardinoma 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 chorio-carcinoma 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 cordiike 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 menalistic 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

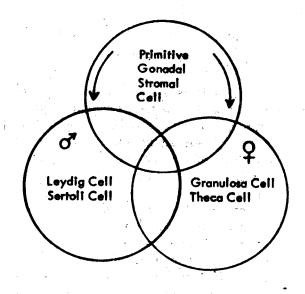


Diagram I

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 post-pubertal 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 ioin 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 (conivasculosi) 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 mitting 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.

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