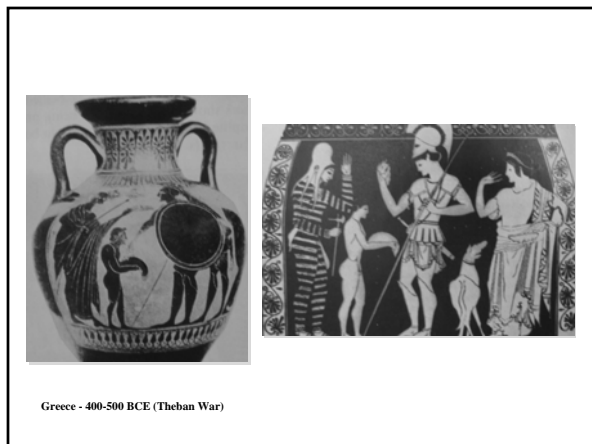
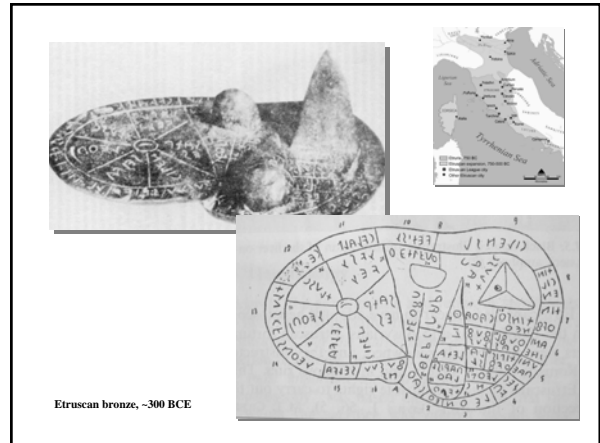
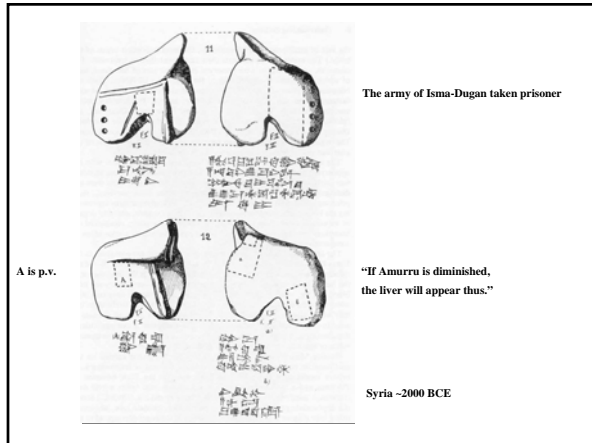
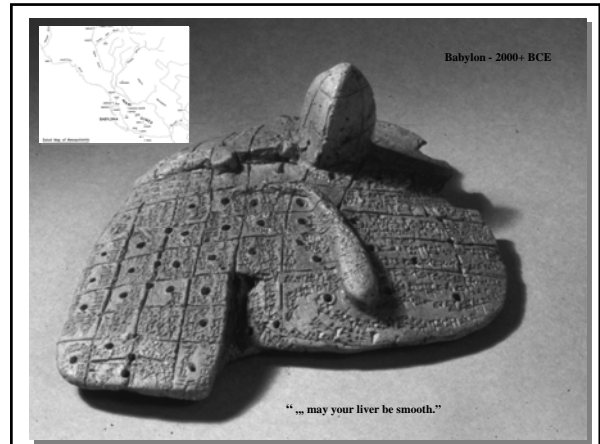


A History of Liver Tumors- [not THE History of Liver Tumors]

(or 4000+ years in 20 minutes)

Stephen A. Geller, M.D.
Department of Pathology and Laboratory Medicine
Cedars-Sinai Medical Center
Los Angeles



Aegisthus scooped the prophetic viscera up in his hands,
The liver lobe was not there.
Unhidden, the portal vein and gall-sac showed
disaster coming at him even as he peered.
His face darkened, drew down.
Euripedes: *Electra*

(Orestes then learned that Aegisthus was his father's killer; he slew him)



Kalchas, son of Thestor, inspecting an animal liver on an Etruscan bronze mirror (500-400 BCE)

“He realized what is, what will be, and what has been before.”
Homer

Prophecy in ancient Rome

The absence of the pyramidal process in an animal liver used for hepatoscopy gave advance warning of death of

Marcus Marcellus in battle against Hannibal (208 BCE)

Caligula, assassinated (41 CE)

Claudius (Caligula’s uncle), poisoned (54 CE)

For the King of Babylon stood at the parting
of the ways, at the head of the two ways,
to use divination; he made his arrows
bright, he consulted with images, he
looked in the liver.

Ezekiel 21:21

Liver disease in the Talmud (דומילת) - ~600-200 BCE

- Liver is a separate and unique organ (“it hangs from the diaphragm”)
- Flesh of the liver different from flesh (meat) found elsewhere
- Liver and brain are of equal importance
- Liver is the seat of love
- Bile (marah) is a “vital humor”
- Angel of Death kills by dropping bile into victim’s open mouth - victim turns green and dies
- Bile allays the anger of the liver
- Anatomy of liver of ritually slaughtered animals
- Regenerative powers of liver (“if the liver be torn away, but there remains the size of an olive ...”)
(? experimental hepatic resections)
- Penetrating injuries to the liver
 - Abner kills Asahel (Samuel 2)
 - Asahel’s brother Joab kills Abner (Samuel 3)
- Ingestion of vinegar can cause liver disease
- Worm abscess in animal liver
- Liver fluke in humans
- Jaundice a form of divine punishment - bile causes jaundice
- Differentiation between hepatic jaundice and jaundice associated with heart failure
- Treatments for jaundice
- Neonatal jaundice
- Cholelithiasis (“stones that are in the bile”) in animals
- Differentiation of hemoptysis (“bleeding from the lungs”) from hematemesis (“bleeding from the liver”)

Antiquity

- ~2000 BCE Babylonian liver
- ~1500 Liver and eye diseases central to Arabic medicine (Rhazes)
- 1500 Ebers Papyrus - liver diseases recognized by inspection and palpation
- 1000 China, liver stores blood and contains the soul (“father and general of the heart - king and director of the body”)
- 800 Homer (Iliad, Odyssey) - wounds to the liver are fatal
- 500 Hippocratic school - liver abscesses should be opened with a hot iron, echinococcus, ascites and jaundice (icterus) due to liver disease, choleric medicines for liver disease
- 350 Aristotle - liver and spleen “hot organs,” concerned with digestion
- 250 Herophilus recognizes portal system
- 250 Erasistratus described liver parenchyma, ascites due to hardening of the liver and treated by puncturing umbilicus

Roman medicine

- 1st C, CE Celsus - laxatives for acute liver disease, treatment of trauma to the liver
- ? 2nd C Aretaeus - pathogenesis of obstructive jaundice, hepatitis, tumors
- 119-199 Galen - liver source of natural spirits which flow to the rest of the body, structure (pig) of the liver, physiology of the liver, distinguished forms of jaundice (obstructive, hemolytic, symptomatic), founded experimental hepatology, described liver surgery using red-hot knives (cautery), jaundice: *morbus regius*



Celsus



Aretaeus



Galen

Aretaeus of Cappadocia (Κολληδοκία) -
probably lived in Alexandria (numerous references to Egyptian therapeutics)
probably lived, for a time, in Italy (familiarity with Italian wines)
probably lived 100-200 CE
 model descriptions of diabetes, gout, tetanus, epilepsy, asthma, migraine, dropsy, pneumonia, elephantiasis, diphtheria, depression, many liver disorders including various causes of jaundice and others
probably the first hepatologist

Aretaeus of Cappadocia

- Anatomy and physiology of the liver
 - Importance of the portal vein
- Hepatitis
 - Acute and chronic
- Jaundice
- Ascites
- Cirrhosis - follows hepatitis
- Liver tumors

European Renaissance

- **Paracelsus (1493-1541)** **chemical changes of tissues**
 "...because the liver is a source of many diseases, and is a noble organ that serves many organs, almost all of them; so it suffers, it is not a small suffering, but a great and manifold one."
- **Van Helmont (1514-1564)** **chemical changes of tissues**
- **Vesalius (1514-1564)** ***De fabrica ... (1543)***
- **Servetus (1511-1553)** **pulmonary circulation**
- **Colombo (1510 - ?)** **circulatory physiology**
- **Harvey (1578-1657)** **structure of liver**
circulation of liver
cirrhosis as clinicopathologic entity
- **Cesalpino (1590-1603)** **attacked Galen circulatory concept**

Hundt M. Anthropogium. Leipzig, 1501

Andreas Vesalius (1514-1564)

Metaphors

Language	Word/phrase (English translation)	Connotation
English	White-livered (lacking gall)	Cowardice
Italian	Fegataccio (bad liver)	Arrogance
Estonian	Rops läheb üle maksa (the lung goes over the liver)	Sudden, intense anger
Monde (African)	Nú aóá láa (his liver has laid down)	Satisfaction
Japanese	Kimo ga futoi (a hefty liver)	Bold, darking
Chinese	Tan (gall)	Cowardice
	Mei you tan tzu (having no gall)	Cowardice
	Kan (liver)	
	Kan huo (liver afire)	Anger
	Kan-tan (liver-gall)	Courage

Hepatic encephalopathy precipitated by protein intolerance



(Sir Andrew about himself)

Methinks sometimes I have no more wit than a Christian or an ordinary man has; but I am a great eater of beef, and I believe that does harm to my wit.

Twelfth Night, Act 1, Sc. iii

17th Century

- Aselli (1581-1625) lacteal vessels
- Pequet (1622-1674) thoracic duct
- Rudbeck (1632-1702) intestinal lymphatics drain to thoracic duct
- Glisson (1597-1677) distribution of vessels of the liver
liver capsule
first book devoted to the liver
- Sydenham (1624-1689) epidemiology of icteric diseases
- Malpighi (1628-1694) circulation of the blood
lobular architecture of liver
portal vein as principal blood supply of liver
bile flow from acini to ducts to gallbladder
- Sylvius (1614-1672) bile salts



Antoni van Leeuwenhoek (1623-1723)

18th Century

- Morgagni (1682-1777) yellow atrophy of the liver
gummata of liver
cirrhosis
calculi
tumors
"De sedibus et causis" - 1761
- von Haller (1708-1777) experimental liver physiology
- Saunders (1743-1817) first English language liver text
- Baillie (1761-1823) clinical picture of cirrhosis
("which is most commonly seen in drinkers")



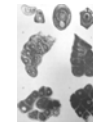
19th Century (selected)

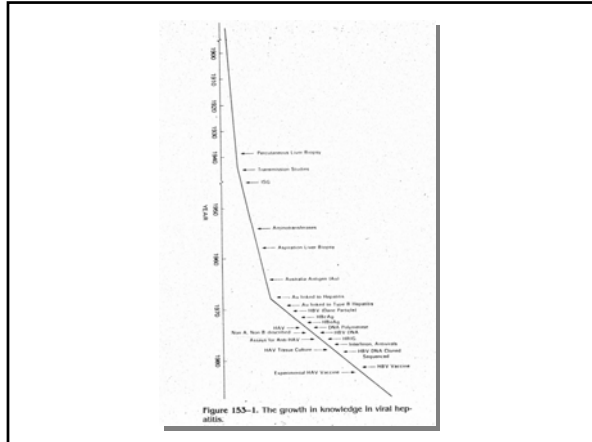
- Karl von Rokitansky (1804-1878) acute yellow atrophy
- Rudolf Virchow (1821-1902) use of microscope in pathology
disease begins in the cell
- Friederich von Frerichs (1819-1885) pathology of cirrhosis - 1855
textbook of liver diseases
- Kiernan (1800-1874) microscopic anatomy of liver - 1833
- Claude Bernard (1813-1878) glycogenic function of liver - 1843
- George Budd (1811-1880) first modern English text of liver disease - 1845
- von Kölliker (1817-1907) hepatic hematopoiesis - 1846
- Joseph von Gerlach (1820-1896) liver cords, bile canaliculi - 1849
- Remak (1815-1865) limiting plate - 1855
- Hering canalicular structure - 1872
- Hanot (1844-1896) primary biliary cirrhosis - 1875
- Kupffer reticulo-endothelial cells - 1876
- Paul Ehrlich (1854-1915) bile tests, liver biopsy (trocar) - 1883
- Charles Sabourin HCC, nodular hyperplasia - 1884
- von Recklinghausen (1833-1910) hemochromatosis - 1889



Liver biopsy

- ~1884 Paul Ehrlich - first liver biopsy (described in von Frerichs text)
- 1895 Lucatello - describes diagnostic liver biopsy
- 1907 Schupfer - 2mm diameter needle
- 1923 Bingel
- 1930 Martin and Ellis - fine needle aspiration biopsy
- 1938 Silverman
- 1939 Iversen and Roholm
- 1958 Menghini





20th Century

- 1901 Kelling - first laparoscopy
- 1903 Neuhauer - Ehrlich's urobilinogen assay as liver test
- 1906 Bauer - galactose assay as liver test
- 1902-13 Embden - glycogenesis
- 1913 van den Bergh (Snapper) - bilirubin assay
- 1923 Kalk - systematic use of laparoscopy
- 1924 Rosenhal - bromsulphalein test
- 1925 Takata - protein lability test
- 1932 Krebs, Hensleit - urea cycle
- 1937 Eppinger - "Die Leberkrankheiten"
- 1942-44 Voegt, MacCollum, Bradley - infectious hepatitis
- 1946 Rappaport - vascular (portal) structure of the liver
- 1947 MacCollum - "hepatitis A" for infectious hepatitis, "hepatitis B" for serum hepatitis
- 1949 American Association for Study of Liver Diseases (AASLD) founded in Chicago
- 1952 Grassman, Hannig - protein electrophoresis
- 1955 Wroblewski, Karmen, LaDue - transaminase
- 1955 Popper, Schaffner - "Liver: Structure and Function" - first modern liver text
- 1960's Krugman - epidemiology of infectious hepatitis
- 1965 Blumberg - Australia antigen
- 1968 De Groote et al - systematic classification of chronic hepatitis
- 1970 Dane et al - ultrastructure of hepatitis B virus
- 1973 Feinstone et al - ultrastructure of hepatitis A virus
- 1976 Purcell, Deinhard, Prince et al - hepatitis B immunization
- 1977 Rizzetto - Delta hepatitis
- 1978 Alter, Tabor, Hellingger, Prince - transmission of non-A, non-B hepatitis to chimpanzee
- 1989 Houghton et al - molecular cloning of hepatitis C virus

Liver tumors

Primary carcinoma of the liver - historical background

- Rigveda (~4000 BCE) - oldest Indo-European book - Hindu Sanskrit - alludes to malignant tumors
- Ramayana (~2000 BCE) - Indian epic alludes to malignant tumors
- Ebers-Smith papyrus (~1500 BCE)
- Hippocrates (46-377 BCE) - introduces the word "cancer" or "carcinoma" as a descriptive term for all new tissue formations which could not be cured - distinguished "scirrhus," a hard type of tumor, from open "carcinoma" - classic descriptions of breast and skin cancers
- Galen (129-210) - early description of liver cancer
- Aretaeus (~2nd C) - regarded liver cancer as result of hepatitis
- Morgagni (1682-1711) - founder of pathologic anatomy - described "steatomata" or "hard" tumors of the liver - first autopsy description of cancers of the liver, almost certainly metastatic



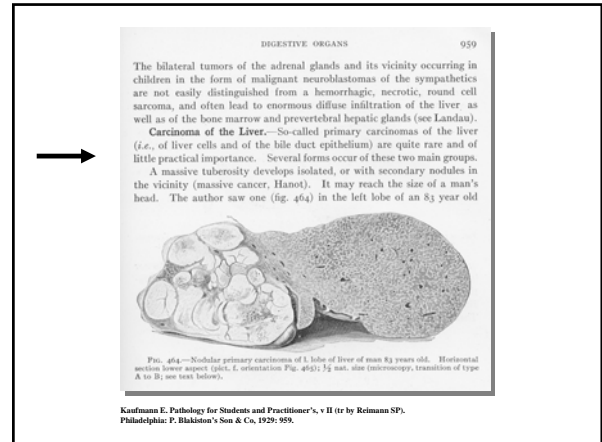
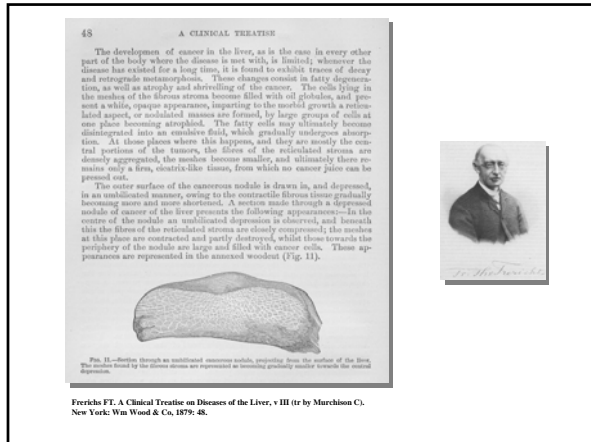
Liver cancer is associated with tumors in the stomach and spleen, and is metastatic.

Giovanni Battista Morgagni (1682-1771)

Primary carcinoma of the liver - Morgagni forward

- Morgagni (1682-1711) - founder of pathologic anatomy - described "steatomata" or "hard" tumors of the liver - first autopsy description of cancers of the liver
- Matthew Baillie (1761-1823) - extended Morgagni's work - described "large white tubercles" in the liver, comparing them with "scirrhus" in other organs - could not distinguish neoplasia from tuberculosis, syphilis and other diseases
- Gaspard Bayle (1774-1816) - first clear description of cancer of liver - showed that "steatomata" of Morgagni and "white tubercles" of Baillie were true cancers, similar to cancer of breast - thought that metastasis represented a constitutional cancerous diathesis
- Thomas Hodgkin (1798-1865) - understood nature of cancer, including metastasis





Liver tumors and etiologic associations

- Hepatocellular carcinoma**
 - cirrhosis Sabourin, 1881
 - hemochromatosis Letulle, 1897
 - Achard 1921
 - hepatitis B virus Prince, 1970
 - Sherlock, 1970
 - a-1-antitrypsin Berg, Eriksson, 1972
 - androgens Bernstein, 1971
- Cholangiocarcinoma**
 - Clonorchiasis Katsurada, 1900
 - Hou, 1956
- Angiosarcoma**
 - Thorotrast MacMahon, 1947
 - Arsenic Roth, 1956
 - Vinyl chloride Creech, Johnson, 1974
- Liver cell adenoma**
 - Oral contraceptive Baum, 1973

Primary carcinoma of the liver - histopathology

- Rudolf Virchow (1821-1902) - defined primary and metastatic
- Kelsch and Kiener (1876) - two cases of primary liver cancer
- Sabourin (1881) - benign primary liver tumors from malignant
- Hanot and Gilbert (1888) - classification of primary liver cancer (gross: "massive," "nodular," "cancer with cirrhotic" - microscopic: "trabecular epithelioma" "alveolar epithelioma")
- von Hansemann (1890) - incidence of primary liver cancer low
- von Heukolom (1894) - introduced term "adenocarcinoma" for primary liver cancer
- Eggel (1901) - modified Hanot/Gilbert to add "diffuse" - separated into two histologic types ("carcinoma solidum," "carcinoma adenomatiform")
- Katsusaburo Yamigawa (1911) - "hepatoma" and "cholangioma" (benign and malignant)
- Goldzieher, von Bokay (1911) - "hepatocellular carcinoma" and "cholangiocarcinoma"
- James Ewing (1866-1943) - "Neoplastic Diseases"
- Edmondson and Steiner (1954) - grading of hepatocellular carcinoma
- Hugh Edmondson (1958) - first AFIP fascicle on liver tumors

Experimental hepatocarcinogenesis - milestones

- 1932 O-Aminoazotoluene Yoshida
- 1935 p-Dimethylaminoazobenzene (butter yellow) Sasaki, Yoshida
- 1941 2-Acetylaminofluorene Wilson
- 1941 Carbon tetrachloride Edwards
- 1943 Selenium Nelson
- 1946 Choline deficiency Copeland, Salmon
- 1947 Ethyl urethane Jaffe, Jaffe
- 1948 Thioacetamide Fitzhugh, Nelson
- 1950 Pyrrolidizidine alkaloids Cook
- 1953 Ethionine Popper
- 1956 Dimethylnitrosamine Magee, Barnes
- 1961 Saffrole Homberger, Long
- 1963 Cycad extracts and cycasin Laqueur

Hepatology and Hepatopathology are founded



Hans Popper, M.D., Ph.D. (1903-1987)

- Pathologist
- Clinician
- Biochemist
- Physiologist
- Anatomist
- Geneticist
- Molecular biologist
- Experimentalist
- Hepatologist
- Nephrologist
- Author
- Editor
- Historian
- Scholar
- Academician
- Mentor
- Chairman
- Dean
- Medical center president
- Academic politician
- Health care planner
- Medical innovator
- AASLD founder
- IASL founder
- President, USCAP
- first "Distinguished Pathologist," USCAP
- Visionary
- Educator
- National leader
- International leader

“Hans Popper, the founder and reigning monarch of modern hepatology, died on May 6, 1988. He was a man of colossal intellect, boundless energy and encyclopedic knowledge who dominated the field of liver disease for nearly a half century.”

Hepatology 1989; 9:669-674



Hans Popper, Hyman Zimmerman, Kamal Ishak - 1983

“Let me teach you something.”

Hans Popper

First published paper at age 22

814 published papers

- 40+ in the three years after he died, topics including:
 - carcinogenicity of woodchuck hepatitis
 - HBV carrier state and hepatocellular carcinoma
 - hepatocellular carcinoma in Eskimos
 - regulatory modulation
 - porphyrias
 - drug injury
 - mechanisms of cell necrosis in cirrhosis
 - delta hepatitis
 - the liver and aging
 - others

Primary liver cancer is far less frequent than metastatic cancer



Hansmann D. Über den primären Krebs der Leber. Berl Klin Wochenschr 1890; 27:353-356.

Classification of liver cancer

Gross

Hanot V, Gilbert A. Études sur les maladies du foie. Asselin et Houzeau, Paris, 1888.

Eggle H. Über das primäre Carcinom der Leber. Beitr z path Anat z allg Path 1910;30:506-604.

Microscopic

Yamagiwa K. Primary parenchymatous carcinoma of the liver (hepatoma). Gann 1911;5:225-282.

Goldzieher M, Bokay Z. Der primäre Leber Krebs. Virchows Arch [A 1911;203:75-131.

Edmondson HA, Steiner PE. Primary carcinoma of the liver. A study of 100 cases among 48,900 necropsies. Cancer 1954;7:462-503.



History of Renal Neoplasia

Brett Delahunt MD FRCPA FRCPATH

Department of Pathology and Molecular Medicine, Wellington School of Medicine and Health Sciences, University of Otago - Wellington, Wellington, New Zealand

Early Observations

The earliest reference suggestive of tumor arising in the kidney was made by Daniel Sennert in his text *Practicae Medicinae*, first published in 1613.¹ In this Sennert states; “Moreover the hard swelling of bad kidneys which has the capacity to throw a person into cachexia and dropsy, is for the greater part incurable”.

Rayer in the introduction to his series of renal tumors published in 1841, discussed the significance of these observations and suggested that Sennert’s comments referred to sclerosing chronic inflammation of the kidney rather than malignancy.² Rayer also reviewed two earlier reports, previously considered by Chopart (1791) to be renal carcinoma. The first case, described by Seger in 1673, was a renal tumor that appeared to be an abscess complicating nephrolithiasis. The other case, published by Thomas Bonet in 1679, noted that the kidney was turned into a sort of pocket; the patient experienced intermittent hematuria, and the likely diagnosis was carcinoma of the renal pelvis.

The earliest unequivocal case of renal carcinoma was published by Miril in 1810.³ He described the case of Françoise Levelly, a 35 year old woman, who presented to Brest Civic Hospital on April 6, 1809, supposedly in the late stages of pregnancy.

The first classification of renal tumors based on a macroscopic morphology was published by Koenig in 1826, who divided the tumors into scirrhus, steatomatous, fungoid and medullary forms.⁴ In his series of thirteen cases, Rayer² classified renal tumors into three groups based on clinical and gross pathological findings.

In 1842, Cruveilhier published his *Atlas of Anatomical Pathology*, which included a case of renal carcinoma antedating those illustrated by Rayer in his Treatise and Atlas of 1837-1841. The patient was a 53 year old woman who had been admitted to the Maison Royale de Santé on June 9, 1828, in a debilitated and emaciated state.

Following publication of Rayer’s series, other authors examined the tissue of origin for renal carcinoma. Robin⁵ thought that the tumor was derived from renal tubular epithelium. Kuppfer suggested in 1865 that renal tumors were not of renal tubular origin but resulted from malignant change of intrarenal Wolffian rests.³ Waldeyer thought that the tumor was derived from renal tubular epithelium, an observation accepted by Klebs in 1876 and Lancereaux in 1889.⁶

The Hypernephroma Controversy

The pathogenesis of renal epithelial tumors has provided one of the most enduring controversies of modern surgical pathology. The debate was initiated by Paul Grawitz when in 1883, he published his observations on the morphology of small, yellow predominantly subcapsular renal tumors that had previously been described as lipoma.⁷ Grawitz compared

these small tumors to the normal adrenal gland and cortical hyperplasia of the adrenal, and concluded that they represented small ectopic adrenal rests (*struma suprarenalis aberrata*). He postulated that these adrenal rests were the source of small subcapsular renal cortical tumors that were not usually malignant in character.

Grawitz's theory stimulated considerable interest and was widely accepted, in part because of its concurrence with Cohnheim's cell rest theory.³ Chiari, in 1884, gave his support to the concept in a case report of a 44 year old man with a large pelvic tumor of probable renal origin that recurred following surgical removal.

Grawitz consolidated his theory in 1884 with further illustrations of intrarenal ectopic adrenal tissue, and concluded that only alveolar tumors were of adrenal origin, whereas papillary tumors were derived from renal tissue.⁸

The first serious challenge to Grawitz arose in 1893 when Sudeck published descriptions of renal tumors in which he identified atypical features within renal tubules and noted a gradation in atypicality between these tubules and neighboring malignant tumor.⁹ The publication of Sudeck's paper stimulated further interest, although the majority of subsequent reports favored Grawitz's concept. Lubarsch in 1894 supported the adrenal rest theory by coining the term *hypernephroid tumor*,¹⁰ later amended by Birch-Hirschfeld¹¹ to *hypernephroma*, to describe these tumors.

Reports published in the following 14 years continued the debate, with the majority of authors preferring an adrenal gland or adrenal rest origin for these tumors, although there were occasional dissenting reports, such as that of Kelynack, who believed the tumors to be of renal epithelial origin.¹²

Vigorous criticism of Grawitz was provided by Stoerk in 1908, who considered the adrenal origin of renal tumors to be unproved. He compared the relative frequency of renal tumors with the scarcity of malignant epithelial tumors of the adrenal gland and commented on the lack of histological similarity between hypernephroma and adrenal carcinoma.¹³

Despite these compelling arguments, the term hypernephroma, with its associated adrenal connotation, persisted in the literature.

Newcomb, after a careful study of 5,201 autopsies, suggested a renal origin for Grawitz tumors, as did Karsner, who proposed the terms renal carcinoma and malignant nephroma to describe these malignancies.³

Foot and Humphreys, and Foote et al. introduced the term *renal celled carcinoma* to emphasize a renal tubular origin for these tumors.¹⁴ Their designation was slightly altered by Fetter in the discussion section of the latter report to the now widely accepted *renal cell carcinoma*.

Convincing evidence to settle the debate was offered by Oberling et al. in 1959 who studied the ultrastructure of clear cells from eight renal carcinomas.¹⁵ They found that the tumor cell cytoplasm contained numerous mitochondria and deposits of glycogen and fat. They identified cytoplasmic membranes inserted perpendicularly onto basement membrane with occasional cells containing microvilli along the free borders. They concluded that these features indicated that the tumors arose from the epithelial cells of the (renal) convoluted tubule, thus finally settling one of the most debated issues in tumor pathology.

Renal Adenoma

The term renal adenoma has been included in most classifications of neoplasms of the renal tubules, but its definition and relationship to renal cell carcinoma has been controversial.

The designation “renal adenoma”, referring to benign tumors of the renal parenchyma, was first used in the classifications proposed by Sturm¹⁶ in 1875 and by Klebs³ in 1880. Sturm distinguished between solitary and multiple adenomas of the kidney, and postulated that in time, “benign” adenomas could show transformation into carcinomas. Renal adenomas were subsequently classified into papillary and alveolar types by Weichselbaum and Greenish,¹⁷ whereas Sabourin¹⁸ described two forms of multiple renal adenomas that were differentiated by the presence of cuboidal or cylindrical cells. In these early reports, the authors distinguished between adenomas and their malignant counterpart on the basis of tumor size and circumscription, and the absence of metastases.

Burkhardt¹⁹ considered adenomas to have a malignant potential being the precursor lesions of malignant tumors of the renal parenchyma, whereas Green and Brooks²⁰ were unable to differentiate between adenomas and hypernephromas on histological grounds and considered that most of the tumors previously described as adenomas should be reclassified as hypernephromas. A continuum between benign renal adenomas and carcinomas was also postulated by Stoerk¹³ in 1908, Gerlach and Gerlach²¹ in 1915 and Arkin²² in 1926.

The frequency of occurrence of renal adenomas varied considerably in early reported series. Prior to 1883 renal adenomas were considered to be rare; however, Grawitz⁸ reported finding three examples in routine post-mortems over a 5 week period. A year earlier, Weichselbaum and Greenish¹⁷ found adenomas in 10% of postmortem subjects over 70 years of the age, whereas Zehbe collected 250 cases of which 40% were solid and 60% had a papillary or alveolar pattern.²³ Hefke found 45 papillary and 8 alveolar adenomas in addition to 8 adrenal rests in 500 consecutive autopsies.²⁴

In 1938 Bell²⁵ reclassified renal tumors, basing his observations on the results of 30,000 autopsies. He grouped adenomas and adenocarcinomas into one group and differentiated between these and multiple adenomas associated with atherosclerotic kidneys, for which he claimed there was no clinical evidence of malignant potential. Bell was unable to distinguish histologically between benign and malignant forms in his adenoma-carcinoma group. He divided the tumors according to size and noted that only one tumor <3cm in diameter had metastasized. He concluded his classification with the statement that “although the size of the tumor is not a certain criterion as to malignancy ... we may say that tumors not over 3cm in diameter have rarely formed metastases”. In his enlarged series, 65 tumors <3cm in diameter were found to have undergone metastatic spread. Despite these conflicting results, Bell arbitrarily classified all solid tumors <3cm in diameter as adenomas but qualified this by stating that all solid adenomas appeared to be small carcinomas.²⁶

The concept that tumors <3cm were adenomas was widely embraced and was not formally dispelled until publication of the Heidelberg/Rochester Classification in 1997.

Classification of Renal Tumors

The resolution of the question regarding the tissue of origin of renal cell carcinoma gave rise to a rational bias for the classification of renal epithelial neoplasia. In many of the early classifications malignant tumors were grouped together regardless of their histologic architecture.⁴ As late as 1981, the first edition of the WHO classification simply divided

carcinomas of the renal parenchyma into *renal cell carcinoma* and *others*.²⁷ Despite this failure to acknowledge the existence of different morphotypes of renal neoplasia by the WHO in 1981, important advances in our understanding of the diversity of these tumors were being made. In 1976 the first series of papillary renal cell carcinoma was reported²⁸ and in the same year a series of 13 cases of renal oncocyoma was published.²⁹ In 1985 Thoenes' group described chromophobe renal carcinoma³⁰ and a year later this was incorporated into the Mainz Classification,³¹ which was based upon the morphology and the putative tissue of origin of each tumor group. The recommendations of Mainz Classification were reinforced by studies that showed each of the tumor morphotypes to have differing cytogenetics, and with minor modifications were endorsed by the Heidelberg (1996) and Rochester (1997) Consensus Classifications.^{32,33} An important feature of both of these consensus classifications was the acknowledgement that diagnostic criteria should be rigidly adhered to and if tumors exhibit atypical features these should be classified as *renal cell carcinoma unclassified*.⁴ The application of this recommendation has led to the identification of several novel forms of renal cell neoplasia, with mucinous tubular and spindle cell carcinomas³⁴ and translocation carcinomas,³⁵ being added to the 2004 edition of the WHO classification of renal tumors.³⁶ Since then other novel morphotypes of renal carcinoma have been described and it is anticipated that these will be recognized in the next edition of the WHO classification.

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Ovarian Tumors and Those who Wrote About Them:

Brief Notes

Robert H. Young, M.D.

James Homer Wright Pathology Laboratories, Massachusetts General Hospital,
Harvard Medical School, Boston, Massachusetts

In this brief summary I endeavor to give some sense of the time-line and major individuals who have brought our knowledge of ovarian tumors to its current state. Comments of a biographical nature on the various individuals who have contributed are kept to a minimum but the reader is referred to cited tributes which cover this aspect and appropriate comments of a biographical nature will be given in the spoken version. I am well aware that what follows is incomplete and, in particular, as of this time I have not had time to review the older foreign language literature to the degree I would wish and would be appropriate. Nonetheless, I believe most of those who have contributed significantly are noted below. As is generally customary in matters of this nature I do not consider those of very recent times, whose story is for another day.

Ovarian tumors have of course been a human affliction since the dawn of time but for practical purposes knowledge in this area only began to evolve with the work of the great Morgagni (1). He is credited for the first significant mention of ovarian tumors in the earliest book I have been able to find with the words ovarian (or ovary) and pathology in the title, Dr. Charles G. Ritchie's publication of 1865 (2). Ritchie's work is indispensable in providing information about contributions made before 1865, many of those mentioned by him not being easily available for review. He notes the 1762 English translation of a book by Astruc (3), consulting physician to the King of France, entitled "A treatise on the diseases of women". In it ovarian diseases are considered under six headings, but it did not advance knowledge much although Ritchie's concluding generous remark reads "such as it was, Astruc's treatise seems to have been for some time the best guide to ovarian pathology in the English language".

At around this same time Morgagni's work appeared with description in it of dermoid cysts. He referred to ovaries having "vesicles filled with grumous material" and a tumor that was "evidently bony." Another giant of anatomic pathology, Matthew Baillie, also recognized dermoid cysts, mentioning in his 'Morbidity Anatomy of the Human Body', published in 1793, "the ovaria changed into a fatty substance with hair and teeth"(4).

The 19th century saw a significant increase in exposure of surgeons and ultimately pathologists to ovarian tumors because of the advent of surgical exploration of the abdomen and what we now know as oophorectomy, known at that time as ovariectomy. Dr. Ephraim McDowell (5) performed the first ovariectomy on Christmas Day in 1809, in Danville, Kentucky. That was over 30 years before anesthesia was introduced so the skill of Dr. McDowell and courage of the patient need no elaboration. The story of the slow acceptance of operative removal of the ovary and the pioneering surgeons who blazed the trail is the domain of surgery more than pathology so is not considered here. I will note in this essay only those such as the British stalwarts Spencer Wells (6) and Lawson Tait (7) who had a major interest in pathology.

The third and fourth decades of the 19th century saw two giants best known for other contributions enter our story. In 1829, Dr. Thomas Hodgkin (8) read a paper before the Medico-Chirurgical Society entitled "Upon some adventitious structures". In his comments on serous cysts he notes that they may be solitary or can "reproduce themselves ad infinitum". Some of the second group which he refers to as "proliferous" were noted by him to be found in great abundance in the ovary. 1838 saw the publication of a report on abdominal tumors by Dr. Richard Bright (9), whose greater fame is for his contributions to renal disease. Two of his four categories of pelvic tumors he attributed to ovarian abnormalities. He noted

as follows: "by far the most frequent form of ovarian tumor, is essentially a specific disease assuming all the varieties of structure which result in the numerous modifications of that morbid action called malignant". That comment is one of the first to herald the now well-known great diversity of morphology seen in ovarian tumors.

A little later (1854) Sir James Paget (10) made his contributions to the area in his lectures on surgical pathology. In his 23rd lecture he gives ovarian tumors detailed consideration. He generously acknowledges the prior contributions of Hodgkin by the following comment, "the principle varieties of the complex ovarian cysts have been described to the very life by Dr. Hodgkin, to whom we are indebted for the first knowledge of their true pathology". He goes on to say that "I will more briefly say that according to his arrangement, we may find in the proliferous ovarian cysts two principle or extreme forms of endogeneous cysts". According to the descriptions and illustrations that follow, he appears, and Hodgkin likewise, to be categorizing the tumors into what we would not recognize as mucinous and serous groups. Mixed forms are referred to and he notes "but a lecture would not suffice to describe, even briefly, the variety of forms into which these ovarian proliferatous cysts may deviate." Paget comments on what were probably Krukenberg tumors (11).

In 1870 Heinrich Waldeyer (12) (of eponymous fame for other reasons) wrote a lengthy paper on epithelial ovarian tumors, being one of the first to suggest a histogenesis similar to that now widely accepted for the most common form of ovarian cancer. The early 1870's also saw the publication of two major books on the ovary. The first was E. Randolph Peaslee's "Ovarian Tumors: Their pathology, diagnosis, and treatment, especially by ovariectomy" (13). It begins with a helpful time-line listing prior contributions, including many of those already referred to here and present in Ritchie's summary. This book is divided into two parts, the first deals largely with clinical aspects but the second is entitled "Ovarian Tumors - Their Classification and Pathological Anatomy". A particularly striking illustration (his Figure 21) is a drawing of what may well have been a serous cystadenoma and surface papilloma of borderline malignancy. The "polycystic lesions" appear for the most part to have been mucinous cystic tumors. He concludes with relatively detailed consideration of dermoid cysts, knowledge of which was better developed at the time than was that of other ovarian neoplasms.

One of the giants of ovarian surgery, Spencer Wells, contributed a work on the ovary almost synchronously with Peaslee, the edition of his book "Diseases of the Ovaries: Their Diagnosis and Treatment" available to me (the American one) being published one year after Peaslee's (14). Two of the 20 chapters concern pathology, the second entitled "Morbidity and Pathology of the Ovaries"

and the third, on dermoid cysts. The latter stands the test of time particularly well. He considered other ovarian tumors in three groups: adenoid, fibrous, and malignant with the first category being further subdivided into simple cysts, multiple cysts, and proliferous cysts. His description of proliferatous cysts and use of the word “budding” suggests that at least some would now be considered serous papillary tumors of borderline malignancy. The discussion of fibrous tumors appears to refer largely to tumors that today would be considered in the fibroma group but he also makes perhaps the earliest reference to a smooth muscle tumor of the ovary and compares their rarity in the ovary to their frequency in the uterus. He notes having seen two ovarian examples and that in both there was a large quantity of fluid in the peritoneal cavity. In his discussion of malignant tumors, Wells states “every kind of cancer infesting other organs is in turn reproduced in the ovary”. Most of the cases summarized in the section on cancer of the ovary read as if they were probably cases of serous carcinoma. One case of “encephaloid cancer” from a 14-year-old girl cannot be confidently classified but it is suspect for dysgerminoma. The attention he gave to extraovarian tumors mimicking ovarian tumors on clinical, and even sometimes pathologic evaluation is noteworthy. There is detailed consideration of tuboovarian cysts and mention of cysts of Wolffian derivation.

1873 also saw the publication of a book containing consideration of ovarian tumors by someone whose name is, for various reasons, linked with that of Spencer Wells, Lawson Tait, another giant of 19th century surgery (15). The two men initially were on good terms but subsequently had a bitter row and sadly can fairly be said to have been "sworn enemies" but we shall not dwell on that unfortunate situation. One of the six chapters in Tait's book is entitled: Ovarian Tumors and Conditions Which Simulate Them. It is the longest chapter, 101 pages, and accounts for close to one third of the book. However, it is even more difficult than in the case of Wells' book judging how lesions described by Tait would be classified today, problems being compounded by the limited illustrations and charming, but at the same time, sometimes confusing, wording. He may have been referring to the common problem of invagination of epithelium into stroma that often complicates the interpretation of serous borderline tumors when he remarks "by the growth of subsequent cysts, these papillary remains are often forced into irregular and very complex folds, the apparent complexity of which may be greatly increased by the accidents of the section". The association of ovarian tumors with a number of interesting clinical manifestations, notably amenorrhea is referred to.

Two additional influential British surgeons of the late 19th century who had considerable interest in pathology were Alban Doran and John Bland Sutton (16). Each wrote books on the ovary. Doran's book, published in 1884, had 12 chapters

accounting for 175 pages and 32 illustrations (17). Two of the major chapters were on dermoid cysts and "solid tumors" of the ovary. Bland Sutton's "Surgical Diseases of the Ovaries and Fallopian Tubes" published in 1891 (18), runs to 488 pages divided into 42 chapters with 119 black and white illustrations and five color plates. Bland Sutton is critical of previous writers for recording largely their own personal experiences in his firmly worked preface and indicates his own intent that "full justice is done to the original work of other surgeons". Aspects which struck me as of interest are as follows. There are some comments which I took to refer to the imprecise line between inclusion cysts and neoplastic cysts, as well as a few pages concerning the association of dermoid cysts and mucinous cystic tumors. The chapter on dermoids reflects amongst other things Bland Sutton's interest in the teeth of dermoids, a matter he had studied in great detail and indeed made a presentation about to the Odontological Society of Great Britain in 1890. The chapter on "solid tumors" considers them under four headings: fibromata, myomata, sarcomata, carcinomata. When dealing with sarcomas it is stated that "both ovaries are frequently affected primarily" but a few pages later when discussing secondary tumors of the ovary the following remark appears "it is quite possible that in some cases described as primary sarcoma or carcinoma of the ovary, the growth in the ovary was really secondary to cancer of some other organ". Other comments in the section on secondary tumors that stood out were

mention of the frequency of bilaterality and the striking lobulation of metastatic breast cancer which, along with uterine cancer and melanoma, are the three secondary tumors considered. One chapter pertains to ovarian tumors in infancy and childhood. It begins with the discussion of neonatal cysts, presents a case of a tumor of uncertain type in a 7 month fetus, has a table of cases in the literature of tumors in girls under 15 years of age (most of them dermoids), mention some dermoid cysts with associated malignant components (? Yolk sac tumor, ? dysgerminoma) and concludes with a two page long discussion of “oophoromata” and based on an illustration they are suspicious for dysgerminoma. The next chapter is noteworthy because the discussion and illustrations under the heading of “wartlike ovarian cysts”, almost certainly refer to serous papillary tumors including the borderline forms. Bland Sutton's work is advanced for its time.

It is around this time that the famous “Krukenberg tumor”, arrived on the scene resulting from Friedrich Krukenberg’s description in 1896 of six cases (19). The work was carried out in the laboratory of Felix Marchand, eminent amongst other things for his work on trophoblastic disease (20), in Marburg. Krukenberg believed the tumors he described were primary in the ovary and his description of the gross characteristics as translated by Speert (21) “Unevenly knobby, firm areas alternate with rather myxomatous ones – larger, smooth-walled cysts may develop as a result of progressive softening of the myxomatous tissue” will resonate with

all who have had experience with this tumor. The familiar stromal proliferation of this tumor tricked Krukenberg into considering it a fibrosarcoma, albeit one with prominent mucin, despite the fact that it appears some had been correctly interpreted when initially examined as “fibrocarcinoma”. He appears to have concluded as he did because of the lack of an apparent epithelial origin despite noting that the tumor cells appeared epithelial. Only six years later Schlagenhauser firmly established the secondary nature of the Krukenberg tumor (22).

In the last decade of the 19th century major contributions were made by the German investigator Herman Johannes Pfannensteil. Writing in the famous German book “Veit’s Handbook of Gynecology” in 1898, he segregated, more clearly than Waldeyer had, the tumors arising from the surface epithelium (23). He was probably the first to introduce the general concept of neoplasms intermediate between those that are unequivocally benign and those that are overtly malignant in his comment on papillary tumors that “are not really malignant but they have clinical features that stand on the border of malignancy.” He was also likely the first to clearly distinguish between serous and mucinous tumors and wrote on pseudomyxoma peritonei amongst other topics within the field of ovarian neoplasia. In 1929 Dr. Howard C. Taylor of New York expanded on Pfannensteil’s concept of tumors intermediate in behavior between benign and malignant (24). Three years later he authored another important paper on

spontaneous regression of the peritoneal implants of serous ovarian tumors (25), and a career-long interest in “borderline” ovarian tumors is exemplified by the fact that 30 years later he wrote another significant contribution on the topic (26).

The waning years of the nineteenth century saw the emergence of a second famous eponymous ovarian tumor, the Brenner tumor (27). Dr. William B. Ober’s masterful telling of the story of the Brenner tumor (28) is recommended reading as is Dr. Harold Speert’s consideration of it (29). Despite the priority of other workers it was Fritz Brenner who became immortalized because of his 1907 paper and the fact that when Robert Meyer (see below) clearly distinguished the Brenner tumor from the granulosa cell tumor in 1932 (30) he perpetuated the association of Brenner’s name with the tumor Brenner had described 25 years earlier. Brenner’s paper “Das oophoroma Folliculare” concerned three cases, two of them autopsy findings, and the descriptions and illustrations leave no doubt as to the nature of the tumors (27). Brenner had thought his tumor arose from the Graafian follicle, the same explanation for the granulosa cell tumor (folliculoma) described by von Kahlden in 1895 (31). In Germany this led to the two folliculomas (of Brenner and von Kahlden) being qualified as “Al Typhus Brenner” and “Al Typhus von Kahlden” until Meyer’s classic paper of 1932. The eminent British pathologists Drs. Harold Fox and Fred Langley (33) in their book (one of many strengths of which is good consideration of the historical background to the entities they

discuss) credit the great Rokitansky with perhaps first describing what we now know as the granulosa cell tumor. It was not until 1895, however, that von Kahlden (31) described the histologic features of this tumor in detail and the designation “granulosa cell tumor” was only introduced in 1914 by von Werdt (34). In addition to being the subject of many papers, this tumor has been the subject of two monographs, one by Schiller in 1934 (35) and another by Varangot in 1937 (36).

This brings us to Dr. Robert Meyer truly one of the titans of ovarian pathology (32). Apart from his clearly delineating the Brenner tumor as a distinctive neoplasm separate from other tumors with an insular pattern such as the granulosa cell tumor he elaborated on the various morphologic features of the granulosa cell tumor to a degree greater than before. Meyer also introduced the term “arrhenoblastoma” (37) for the often masculinizing tumor known most widely now as Sertoli-Leydig cell tumor. Although tumors that can retrospectively be recognized as Sertoli-Leydig cell tumors are present in the older literature, Meyer’s work on these neoplasms brought knowledge of them to a new level. His subclassification of them into well differentiated, intermediate, and poorly differentiated forms remains the major subcategorization of these tumors that is of practical importance.

One can discern examples of dysgerminoma in the older literature under the designation "medullary carcinoma", but they had been first referred to in appreciable detail by Chevassu in his famous thesis describing the seminoma and described in detail as an ovarian neoplasm by another French investigator, Marcel Chenot, in 1911 (38) and by Pierre Masson (39) a year later, although both the latter authors used the seminoma designation. It was Meyer who coined the term "disgerminoma", the change to dysgerminoma being made soon after.

In 1925 Dr. John Sampson, referred to as "the Father of Endometriosis", described the association of ovarian endometriosis with carcinoma resembling the common endometrial carcinoma and delineated the nature of ovarian endometriotic cysts. His career has been elegantly reviewed elsewhere quite recently (40).

The Danish pathologist Dr. Gunnar Teilum contributed significantly to knowledge concerning both sex cord tumors and germ cell tumors but it is for his work on one tumor in the latter family that he will be most remembered. His observations elucidating the germ cell nature of the yolk sac tumor of the ovary (and elsewhere) represents one of the most astute in the study of human neoplasia. In 1944 he wrote the first of many English language papers on this neoplasm (41) and over the ensuing years (42), culminating in his book published in 1971 (43), established the yolk sac tumor (which he referred to as "endodermal sinus tumor") as a distinctive variant of primitive germ cell tumor and described most of its now

well known patterns. In 1939, Dr. Walter Schiller, an Austrian pathologist who had immigrated to the United States (44), had reported a series of ovarian tumors under the designation “mesonephroma ovarii (45).” It became slowly apparent that within it were cases we now recognize as clear cell carcinoma (see below) and yolk sac tumor. In the last decade of his life Teilum wrote papers on the localization of alpha-fetoprotein in the tumor cells (46) and relating the morphology of the tumor to alpha-fetoprotein production (47). In one of the most striking examples of the benefit of comparative morphology, Teilum had noted that the papillary structures of the yolk sac tumor morphologically resembled the endodermal sinuses of the rat placenta. This was the result of a visit to an embryologist in Paris who showed him slides of the rat placenta. The placental structures in the rat had been designated “endodermal sinuses” by M. Duval in the 19th century and were known to be of yolk sac origin, resulting in Teilum's application of the now famous eponym “Schiller-Duval bodies” for these structures in yolk sac tumors. Tributes to Dr. Teilum, one of which lists all his papers, are available (48,49).

A neoplasm related to the yolk sac tumor is the polyembryoma, containing as it does yolk sac epithelium as a component of the embryoid bodies, myriads of which constitute the polyembryoma. In 1939 a French histologist, Albert Peyron (50), described these enigmatic and picturesque structures within a testicular

teratoma and polyembryomas were subsequently described in the ovary and even at extragonadal sites. They arguably are the most photogenic of all gonadal tumors.

Dr. Lars Santesson of Sweden (51) was a major figure in the International Federation of Gynecology and Obstetrics (FIGO) and in conjunction with the pioneering gynecologic oncologist Professor Hans L. Kottmeier, had a major influence in the development of the modern classification of ovarian tumors. Santesson, with Kottmeier, was responsible for the organization of a meeting at the Radiumhemmet in Stockholm in August 1961, which produced the first classification of the surface epithelial stromal tumors which closely approaches that used today. Others participating were: Dr. Lauren V. Ackerman, Dr. Georg Gricouroff, Dr. H. Hamperl, Dr. Arthur T. Hertig, Dr. J.H. Muller, Dr. Claud W. Taylor, Dr. Herbert C. Taylor, and Dr. Teilum. Dr. Santesson reported on 660 primary ovarian cancers that had been treated at the Radiumhemmet through 1940 and divided them into the serous, mucinous, and endometrioid groups, this being the first large series in which endometrioid carcinomas were separately categorized (52). His observations provided the framework for the proposal of that conference that endometrioid tumors be considered a separate entity and that an association with endometriosis, although common, was not required for the diagnosis as it had generally been until then. Endometrioid carcinomas quickly became established as

a separate entity (53). Santesson and Kottmeier introduced the low malignant potential terminology (a well-known synonym for the borderline tumor group). In the words of Dr. Robert E. Scully “he (Santesson) can be truly called the father of the modern classification of the epithelial tumors of the ovary” (Scully RE, personal communication, January 2004). Santesson also contributed excellent papers on dysgerminoma (54) and yolk sac tumor (55).

Santesson was one of those to first appreciate that clear cell carcinoma, (or as it was still being called at that time, mesonephroma), was related to the endometrioid carcinoma, his belief being clearly stated by Kottmeier in a review of ovarian tumors (56). The occurrence of clear cells in ovarian adenocarcinomas began to receive attention (57) soon after Schiller’s paper on "mesonephroma" and although the histogenesis was debated, a mesonephric origin was still favored until the late 1950s when De Santo and colleagues (58) indicated a probable origin from mullerian epithelium. Subsequently Dr. Laman A. Gray (59) put forth a similar opinion. The matter was put firmly to rest in 1967 when Scully and Barlow (60) unequivocally demonstrated a mullerian origin. The existence of true mesonephric ovarian neoplasms (wolffian tumors) was sporadically acknowledged by various earlier workers, and by the time this writer began working with Dr. Scully in July 1979 it was clear that Dr. Scully had a clear opinion on their morphology based, in part, on earlier work on broad ligament examples and diagnosed ovarian examples

of wolffian tumors sporadically as these rare tumors were submitted in consultation. Dr. Peter Hughesdon reported the first series in 1982 (61) and Dr. Scully's experience was reported a year later (62).

A major development in ovarian tumor pathology was the publication of the World Health Organization (WHO) classification of ovarian tumors in 1973 (63). This was the culmination of work carried out over more than a decade by numerous major figures in the field of gonadal tumor pathology. That undertaking began when the FIGO Ovarian Cancer Committee subdivided the surface epithelial tumors of the ovary into five major categories based on cell type, subdividing each category into three groups, benign, malignant, and an intermediate group designated "atypical proliferating tumors of low-malignant potential." In 1956-1957 the WHO requested that its cancer committee classify tumors of various sites including the ovary. Dr. Humberto Torloni, editor of the series of WHO tumor classifications, was contacted by FIGO, which requested a joint meeting of representatives of its committee and the ovarian WHO group. At that meeting, held in Geneva in 1963, Dr. H. Hamperl of Germany was Chairman of the FIGO group; Dr. Santesson of Sweden, Dr. Teilum of Denmark, and Dr. Gricouroff of France were additional members of both committees and Dr. Fred Langley, Dr. Antonio Luisi, and Dr. Robert Scully were members of the WHO group. Dr.

Hamperl and his associates urged the members of the WHO committee to accept with no more than minor modifications the FIGO classification of surface epithelial tumors to avoid the chaos that might result if it were to be substantially altered. Dr. Scully subsequently served as co-chairman of the further meetings of the WHO group along with Professor S.F. Serov of Russia. Dr. Mikhail Glazunov, a Russian pathologist, who had written a book on ovarian tumors, had been appointed chairman of the WHO group, but died suddenly before the first meeting and was succeeded by his younger associate, Professor Serov, whose primary interest had been bone and soft tissue tumors. The subsequent meeting of the WHO ovarian group was held in St. Petersburg (at the time Leningrad) in 1965. Slides were circulated amongst the various participants and discussed at a series of meetings that took place between 1967 and 1971. Finally the classification (and selected cases) were reviewed by a second small group of pathologists, and the final classification was adopted and published in 1973 as one of the familiar "blue books" of the International Histologic Classification of tumor publications. Major differences between the FIGO and the WHO dedications were that the latter preferred by a very close vote "tumors of borderline malignancy" over "tumors of low malignant potential", and also classified all other ovarian tumors and tumor-

like lesions. The classification was used in the second series fascicle "Tumors of the Ovary and Maldeveloped Gonads" authored by Dr. Scully (64) and the excellent British contribution of Drs. Harold Fox and Fred A. Langley, "Tumours of the Ovary" published in 1976 (33).

Dr. Robert Scully's work in the WHO meeting having just been considered it is now appropriate to conclude these notes with comments on other contributions of this remarkable investigator, who with Dr. Meyer, in my opinion is one of the two above all others who dominate the history of ovarian tumors.

A lifelong interest in functioning tumors of the ovary was stimulated by Dr. Scully's collaboration with a gynecologist, Dr. John McLean Morris, on the book "Endocrine Pathology of the Ovary," published in 1958 (65). A year before Drs. Scully and Morris had drawn attention to the phenomenon whereby tumors that are not normally associated with endocrine manifestations sometimes have such features because of the development of lutein cells in their stroma (66). They introduced the term "ovarian tumors with functioning stroma", a now familiar term. Dr. Scully rapidly became known as a consultant for unusual cases in ovarian pathology and developed a remarkable collection which lent itself to many important investigations by him and various fortunate collaborators over the years. Although others share the stage with Dr. Scully in the author listing of these many papers, all will acknowledge that he was the individual who recognized the various

entities, including such now well-known neoplasms as the sclerosing stromal tumor, sex cord tumor with annular tubules, juvenile granulosa cell tumor, strumal carcinoid, small cell carcinoma of hypercalcemic type, and retiform Sertoli-Leydig cell tumor. Dr. Scully's contributions are legion and the reader is referred to a detailed appreciation of him for more detailed comments than space allows here (67). One need only review his classic 1970 paper on gonadoblastoma (68) to get some sense of the remarkable diligence and painstaking care that he took with his academic contributions, just as he did with his review of individual cases. To have worked with him on some of these, and on his second ovary fascicle (69) (also co-authored by Dr. Philip B. Clement of Vancouver, Canada, one of Dr. Scully's most illustrious and distinguished trainees), has been a treat of the highest order and those who have had the good fortune to spend any significant amount of time working closely with Dr. Scully will feel firm that he is truly a giant not just of gynecologic pathology but of pathology in general given his remarkable constellation of talents.

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TUMORS OF SELECTED ORGANS AND WHO WROTE ABOUT THEM

THE THYMUS

Juan Rosai, M.D.

**Centro Diagnostico Italiano, Milan, Italy
Genzyme Corp., New York, NY**

The most important advances that have been made during the past 50 years concerning the neoplastic pathology of the mediastinum are the following:

- The realization that thymoma is a specific tumor of the thymic epithelial cells;
- The realization that the lymphocytic component which is often present in thymomas and that sometimes dominates the microscopic feature is of non-neoplastic and immature T-cell nature;
- The realization that there is a range of differentiation in thymomas, which embraces thymic carcinoma;
- The reaching of an international agreement on the histologic classification of thymomas using a letter-number system, which has been sanctioned by the WHO;
- The confirmation of the fact that the most accurate prognostic indicator of thymoma is the clinical/surgical staging using the Masaoka system or any of its modifications;
- The confirmation of the fact that the histologic typing of thymomas correlates closely with prognosis, but that this correlation loses much of its significance when evaluated within the confines of a given clinical stage;
- The realization that, despite their rarity, there is a marked morphologic variation among the cytologically malignant thymomas, i.e., those tumors traditionally known as thymic carcinomas and designated as type C thymomas in the previous version of the WHO classification,
- The realization that the tumor originally described as granulomatous thymoma by James Ewing and further elaborated by Elizabeth Lowenhaupt represents Hodgkin's lymphoma of the thymus, and that this is nearly always of the classic type, nodular sclerosis subtype;
- The documentation of the fact that the tumor formerly diagnosed as "compartmentalizing large cell tumor of the thymus" is a large B-cell lymphoma of this organ, and that it has distinctive clinical, immunophenotypic and genotypic characteristics which suggest a specific origin from thymic B-cells. Fibrosis is a conspicuous feature of this tumor. Some B-cell markers such as CD19 and CD20 are consistently present, but Ig and HLA class I and II molecules are frequently expressed only incompletely or not at all. CD10 and CD5 are also absent, whereas there may be a weak expression of CD30. At the genetic level, Ig rearrangements are present. The karyotype is hyperdiploid, often with gains in 9p,

amplification of the REL gene, and overexpression of the MAL gene. There are no BCL2, BCL6 or MYC rearrangements.

- The documentation of the fact that the old Sternberg's sarcoma, which then became Lukes' convoluted cell lymphoma, is a precursor T-lymphoblastic lymphoma, an entity closely related to T-lymphoblastic leukemia. This tumor has been stratified into different stages of intrathymic differentiation according to the number and sequence of antigens expressed;
- The realization that the thymus is yet another place where so-called MALT-type lymphoma can develop;
- The realization that there is a whole gamut of thymic tumors exhibiting neuroendocrine differentiation in the thymus, from the well-differentiated thymic carcinoid to the highly malignant small cell neuroendocrine carcinoma, and that their classification scheme mirrors that of the corresponding neuroendocrine neoplasms of the lung. It has also been ascertained that a high proportion of thymic carcinomas (type C thymomas) exhibit some degree of neuroendocrine differentiation, whereas this is almost never the case for types A and B thymomas;
- The documentation of the fact that the old germinomatous thymoma is a seminoma of the thymus. The close anatomic connection of this tumor type with the thymus (the relationship being much more specific than that usually implied when stating "mediastinal" or "midline" location) and its almost exclusive occurrence in males are two intriguing facts in search for a biologic explanation;
- The realization that a certain morphologically distinctive type of mediastinal tumor formerly thought to be a subtype of spindle (type A) thymoma is actually the mediastinal counterpart of the pleural lesion once known as solitary fibrous mesothelioma and now designated as solitary fibrous tumor;
- The acceptance of the fact that multilocular thymic cyst is the thymic expression of a theme which repeats itself at several places in the head and neck region, and which is characterized by proliferation and cystic dilatation of epithelial branchial pouch-derived structures as a result of stimulation by a reactive lymphocytic component. In the thymus, these lymphocytes may be the expression of an idiopathic "thymitis", HIV-infection, or congenital syphilis, or may be accompanying Hodgkin's lymphoma, seminoma, and other tumors of the thymus;
- The documentation of the fact that tumors arising from thymic and related branchial pouch derivatives can occur at several locations in the neck (often in close anatomic relationship with the thyroid gland), some of them having a distinctive appearance not seen at the thymic orthotopic site, as in the case of ectopic hamartomatous thymoma and so-called SETTLE (spindle epithelial tumor with thymic-like elements).

As one looks back at this list of developments, one cannot help but concluding that some real progress has been made. Among the many people responsible for this achievements, I would like to single out the following (listed in alphabetical order, and leaving out those from the current generation): Benjamin Castleman, Raffaele Lattes, Robert Lukes, Gerald Levine, Akira Masaoka, and Hans K. Müller-Hermelink.