A History of Liver Tumors—
(not THE History of Liver Tumors)
(or 4000+ years in 20 minutes)

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“may your liver be smooth.”
The army of Isma-Dugan taken prisoner

“If Amurru is diminished, the liver will appear thus.”

A is p.v.

Syria ~2000 BCE
Etruscan bronze, ~300 BCE
Greece - 400-500 BCE (Theban War)
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.

Euripides: 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 - 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, choleretic 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-not knives (cautery), jaundice: *morbus regius*
Aretaeus of Cappadocia (Καππαδοκία) -
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**

- **Paracelcus** (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)
<table>
<thead>
<tr>
<th>language</th>
<th>Word/phrase (English translation)</th>
<th>Connotation</th>
</tr>
</thead>
<tbody>
<tr>
<td>English</td>
<td>White-livered (lacking gall)</td>
<td>Cowardice</td>
</tr>
<tr>
<td>Italian</td>
<td>Fegataccio (bad liver)</td>
<td>Arrogance</td>
</tr>
<tr>
<td>Estonian</td>
<td>Rops läeb üle maksa (the lung goes over the liver)</td>
<td>Sudden, intense anger</td>
</tr>
<tr>
<td>Monde (African)</td>
<td>Nú arô láa (his liver has laid down)</td>
<td>Satisfaction</td>
</tr>
<tr>
<td>Japanese</td>
<td>Kimo ga futoi (a hefty liver)</td>
<td>Bold, darkening</td>
</tr>
<tr>
<td>Chinese</td>
<td>Tan (gall)</td>
<td>Cowardice</td>
</tr>
<tr>
<td></td>
<td>Mei you tan tzu (having no gall)</td>
<td>Cowardice</td>
</tr>
<tr>
<td></td>
<td>Kan (liver)</td>
<td>Anger</td>
</tr>
<tr>
<td></td>
<td>Kan huo (liver afire)</td>
<td>Anger</td>
</tr>
<tr>
<td></td>
<td>Kan-tan (liver-gall)</td>
<td>Courage</td>
</tr>
</tbody>
</table>
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
- **Malphighi (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 Köölliker (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  Neubauer - 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  Rosenthal - bromsulphthalein test
• 1925  Takata - protein lability test
• 1932  Krebs, Henseleit - urea cycle
• 1937  Eppinger - “Die Leberkrankheiten”
• 1942-44  Voegt, MacCollum, Bradley - infectious hepatitis
• 1946  Rappaport - vascular (zonal) 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, Hollinger, 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** (460-377 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 consitutional cancerous diathesis
- **Thomas Hodgkin (1798-1865)** - understood nature of cancer, including metastasis
The development of cancer in the liver, as is the case in every other part of the body where the disease is met with, is limited; whenever the disease has existed for a long time, it is found to exhibit traces of decay and retrograde metamorphosis. These changes consist in fatty degeneration, as well as atrophy and shrivelling of the cancer. The cells lying in the meshes of the fibrous stroma become filled with oil globules, and present a white, opaque appearance, imparting to the morbid growth a reticulated aspect, or nodulated masses are formed, by large groups of cells at one place becoming atrophied. The fatty cells may ultimately become disintegrated into an emulsive fluid, which gradually undergoes absorption. At those places where this happens, and they are mostly the central portions of the tumors, the fibres of the reticulated stroma are densely aggregated, the meshes become smaller, and ultimately there remains only a firm, cicatrix-like tissue, from which no cancer juice can be pressed out.

The outer surface of the cancerous nodule is drawn in, and depressed, in an umbilicated manner, owing to the contractile fibrous tissue gradually becoming more and more shortened. A section made through a depressed nodule of cancer of the liver presents the following appearances:—In the centre of the nodule an umbilicated depression is observed, and beneath this the fibres of the reticulated stroma are closely compressed; the meshes at this place are contracted and partly destroyed, whilst those towards the periphery of the nodule are large and filled with cancer cells. These appearances are represented in the annexed woodcut (Fig. 11).

Fig. 11.—Section through an umbilicated cancerous nodule, projecting from the surface of the liver. The meshes found by the fibrous stroma are represented as becoming gradually smaller towards the central depression.
The bilateral tumors of the adrenal glands and its vicinity occurring in children in the form of malignant neuroblastomas of the sympathetics are not easily distinguished from a hemorrhagic, necrotic, round cell sarcoma, and often lead to enormous diffuse infiltration of the liver as well as of the bone marrow and prevertebral hepatic glands (see Landau).

**Carcinoma of the Liver.**—So-called primary carcinomas of the liver (i.e., of liver cells and of the bile duct epithelium) are quite rare and of little practical importance. Several forms occur of these two main groups.

A massive tuberosis develops isolated, or with secondary nodules in the vicinity (massive cancer, Hanot). It may reach the size of a man’s head. The author saw one (fig. 464) in the left lobe of an 83 year old

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**Fig. 464.**—Nodular primary carcinoma of l. lobe of liver of man 83 years old. Horizontal section lower aspect (pict. f. orientation Fig. 465); 1/2 nat. size (microscopy, transition of type A to B; see text below).
Liver tumors and etiologic associations

- Hepatocellular carcinoma
  - cirrhosis
  - hemochromatosis
  - hepatitis B virus
  - a-1-antitrypsin
  - androgens
  - Sabourin, 1881
  - Letulle, 1897
  - Achard 1921
  - Prince, 1970
  - Sherlock, 1970
  - Berg, Eriksson, 1972
  - Bernstein, 1971

- Cholangiocarcinoma
  - Clonorchiasis
  - Hou, 1956
  - Kartsurada, 1900

- Angiosarcoma
  - Thorotrast
  - Arsenic
  - Vinyl chloride
  - MacMahon, 1947
  - Roth, 1956
  - 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 cirrhosis” - 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 adenomatous”)
- 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-Acetaminofluorene  Wilson
- 1941  Carbon tetrachloride  Edwards
- 1943  Selenium  Nelson
- 1946  Choline deficiency  Copeland, Salmon
- 1947  Ethyl urethane  Jaffe, Jaffe
- 1948  Thioacetamide  Fitzhugh, Nelson
- 1950  Pyrrolizidine alkaloids  Cook
- 1953  Ethionine  Popper
- 1956  Dimethylnitrosamine  Magee, Barnes
- 1961  Safrole  Homberger, Long
- 1963  Cycad extracts and cycasin  Laqueur
Hepatology and Hepatopathology are founded
Hans Popper, M.D., Ph.D. (1903-1987)
“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
“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.
Classification of liver cancer

**Gross**


**Microscopic**

