1 From Promethean to Modern Times

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From myths to mysteries

In the dark ages of our ancestors, liver surgery was inexistent and the organ was a source for myths, legends, and spirituality. During the Babylonian era (~3000–1500 BC), the liver was thought to bear the soul. Priests used hepatoscopy in animal livers as a tool for divine connection, predicting the future. Clay models of sheep livers, probably used for teaching or divination, still exist from this period.

The famous legend of Prometheus was written by Hesiod (750–700 BC), recounting very ancient times (Figure 1.1). Prometheus stole fire from Zeus, the godfather of ancient Greece, and gave it to mankind. For this infringement, the angry Zeus chained him to a rock and sent an eagle to devour his liver. Prometheus was captured in eternal pain. The liver regenerated and gained its normal size overnight, and the hungry eagle returned daily to its victim. Over 2000 years later, the amazing regenerative capacity of the liver is no longer a mystical tale, but the basis for current hepatobiliary surgery and a promising topic of surgical research [1].

Probably the first anatomist to describe the liver was the Alexandrian Herophilus (330–280 BC). Although his written work has not survived, another famous scientist cited him. This was the Greek Galen (130–200 AD), who dominated medical literature for the following centuries. He made accurate descriptions of the lobar anatomy and the vasculature, interpreting the liver as the source of blood. In contrast to his empirical anatomic insights, he propagated a humoral basis of medicine. Originating from the theories of Hippocrates (460–380 BC), diseases were based on an imbalance of the four humors: black and yellow bile, blood and phlegm. However, in the following years and centuries of the Middle Ages, theories became traditions and knowledge moved forward very little. Brilliant exceptions were Leonardo da Vinci's drawings of the extra- and intra-hepatic portal and venous vessels.

Malignant Liver Tumors: Current and Emerging Therapies, 3rd edition. Edited by Pierre-Alain Clavien.

In 1640, Johannis Walaeus, from Leiden, Netherlands, reported a common tunic, surrounding the branches of the choledochal duct, the celiac artery, and the portal vein. In 1654, Francis Glisson, from Cambridge, England removed the liver parenchyma by cooking the organ in hot water and explored the hepatic blood flow with colored milk [2]. He discussed the intrahepatic anatomy and topography of the vasculature (Figure 1.2). The growing knowledge of liver anatomy was one of the substantial preconditions for the development of liver surgery. However, this was still far from realization, and the liver remained a fragile bleeding mystery. We would like to refer to the comprehensive overview by McClusky *et al* for the fruitful interaction between anatomists and pioneers of liver surgery [3].

Of inquisitive anatomists and courageous surgeons

In 1842, Crawford W. Long used ether as a surgical anesthetic for the first time in the United States. This was a fundamental step in the development of abdominal surgery. In 1867, Joseph Lister from Glasgow, Scotland, introduced antiseptic techniques against bacterial infections after Louis Pasteur, from Paris, France, had discovered the dangers of bacteria.

Before this period, only anecdotal records exist of descriptions about the removal of protruding liver tissue after trauma. Among these surgeons were Ambroise Paré from Paris, France, J.C. Massie from the United States, Victor von Bruns from Germany, and many others. However, liver trauma at this time was generally managed without operation. It took many years before any courageous surgeon was successful in the first attempt of a planned liver resection.

Carl Langenbuch from Berlin, Germany (Figure 1.3), who was among those to perform the first cholecystectomy, reported the first elective and successful hepatic resection in 1888 [4]. William W. Keen from Philadelphia performed the first liver resection in the United States in 1891. He used the "finger-fracture" technique to divide the liver parenchyma. By 1899, the first case series were being reported in the

Figure 1.1 Prometheus bound to a rock, with an eagle eating out his liver. 550 BC.

Figure 1.2 Intrahepatic vasculature as illustrated in Francis Glisson's *Anatomia Hepatis* (1654). (Reproduced from Glisson [2], with permission.)

United States [5]. The most striking challenge at this time was the control of intraoperative bleeding. In 1896, Michel Kousnetzoff and Jules Pensky introduced a continuous mattress suture above the resection line for bleeding control [6]. In 1908, J. Hogarth Pringle from Glasgow, Scotland described a method of temporary compression of the portal ligament in a small series of patients [7]. However, it took 70 years before tolerance of this maneuver – exceeding 20 min – was shown [8].

Figure 1.3 Carl Langenbuch (1846–81).

Bleeding control remained a major limiting factor in the development of hepatic surgery for many years. The fine work of anatomists provided the key insights to overcome major bleeding. In 1888, Hugo Rex from Germany [9], and in 1897 James Cantlie from Liverpool, England [10], revisited the accepted anatomic division of the liver by the falciform ligament. Using corrosion studies, they separated the liver by the branches of the portal vein and defined an avascular plane through the gallbladder bed. Today, the plane passing through the gallbladder bed towards the vena cava and through the right axis of the caudate lobe along the middle hepatic vein is known as the Rex–Cantlie line. Walter Wendell from Magdeburg, Germany [11] and Hans von Haberer from Graz, Austria [12] were the first surgeons at the beginning of the 20th century to apply resections along this anatomic plane.

Following World War II, Carl-Herman Hjortsjo from Lund, Sweden [13] and John E. Healey from Huston, United States [14] further refined hepatic anatomy by their description of the intrahepatic biliary duct system and the vascular tree. In 1954, Claude Couinaud from Paris, France (Figure 1.4) published his seminal work on the segmental architecture of the liver [15, 16]. Based on the branches of the portal vein, he separated the liver into eight well-described segments. Before this time, liver resections were mostly performed in a "blindly manner." The findings of Carl-Herman Hjortsjo, John Healey, and Claude Couinaud had a major impact on surgical technique and related mortality. The rapidly evolving era of liver surgery had begun.

In 1950, Ichio Honjo from Kyoto, Japan reported the first "anatomic" liver resection [17]. Jean-Louis Lortat-Jacob from Paris, France in 1952 [18], followed by Julian. K. Quattlebaum, from Georgia, United States in 1953 [19], reported the first resections in Europe and the United States. Subsequent, descriptions of the procedure were provided by Alexander Brunschwig [20] and George T. Pack [21] in New York, United States, and later by William P. Longmire and Samuel A. Marable [22] in Los Angeles, United States.

At this time, George T. Pack documented the regenerative potential of the human liver after a major hepatectomy [23]. A few years later, Tien-Yu Lin and Chiu-Chiang Chen from Taipei, Taiwan described the decrease of regenerative capacity of the cirrhotic liver [24]. The knowledge about liver regeneration in humans was preceded by animal experiments years before. In 1879, Hermann Tillmanns from Leipzig, Germany [25] demonstrated regeneration in rabbit livers. In 1883, Themisocles Gluck from Berlin [26], and later Emil Ponfick from Breslau, Germany, demonstrated liver regeneration after major resections in animals.

In the 1960s, perioperative mortality rates up to 50% were common after right hemihepatectomy. Furthermore, serious concern was growing over hepatic nomenclature, and notably, liver surgeons throughout the world used different, sometimes confusing, terms [27]. In 2000, a group of international liver surgeons proposed a standardized nomenclature, which was introduced at the bi-annual meeting of the International Hepato-Pancreato-Biliary Association (IHPBA) in Brisbane, Australia. The terminology for hepatic anatomy was subsequently called the Brisbane nomenclature [28]. Nomenclature in hepatic surgery is discussed in detail in Chapter 2.

Over the years, growing anatomic and physiologic knowledge, and ongoing specialization in experienced centers, have significantly lowered mortality from liver resections to below 5% [29]. We would like to refer to the comprehensive overviews by Joseph G. Fortner and Leslie H. Blumgart [30], and James H. Foster [31], for an in-depth coverage of liver surgery in the 20th century.

The era of liver transplantation

A giant leap forward and a driving force in the rapid development of hepatobiliary surgery was the onset of the transplantation era. In 1955, Cristopher S. Welch from Albany, United States, published the first heterotopic liver transplantation in a dog [32]. Others, such as J. A. Cannon, Thomas E. Starzl, and Francis D. Moore, followed with orthotopic liver transplantations (OLT), also in dogs, and established the basis for transplantation in humans [33]. In 1963, Thomas E. Starzl (Figure 1.5) made the first attempt to transplant a human liver in Denver, United States [34]. However, the patient died during the operation. Another attempt by Francis D. Moore in Boston also did not succeed

Figure 1.4 Claude Couinaud working with his collection of liver casts at the School of Medicine in Paris, 1988.

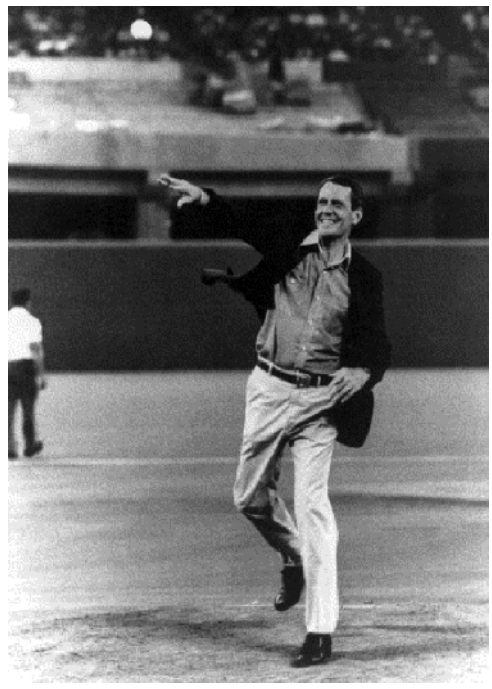

Figure 1.5 Thomas E. Starzl has the honor of the first pitch at the Three Rivers Stadium in 1983, Pittsburgh. (Reproduced from the *Pittsburgh Post-Gazette*.)

[35]. The first series of successful OLTs was reported in 1968 by Thomas E. Starzl [36].

A year later, Sir Roy Calne performed the first OLT in Europe in Cambridge, England [37]. However, although many patients initially tolerated the transplantation well, most did not survive OLT longer than a few weeks or months.

Another quantum leap was the discovery of cyclosporine A (CyA) by Hartmann F. Stähelin and Jean-Francois Borel from Basel, Switzerland, in 1972. Seven years later, Sir Roy Calne reported the first use of CyA in OLT patients with a dramatic improvement in long-term survival [38]. Before the introduction of CyA, 5-year survival after OLT was less than 20% and improved to 60% or more with the introduction of CyA [39]. In the late 1980s, Thomas E. Starzl introduced FK-506 (tacrolimus) as a new and promising immunosuppressant at the University of Pittsburgh. The introduction of effective immunosuppressants such as polyclonal antilymphocyte antibodies, anti-CD3 antibodies in the 1980s, or mycophenolate mofetil (MMF) in the early 1990s, and rapamycin in the late 1990s offered further alternatives in the management of patients after OLT.

Already in the early stage of solid organ transplantation, it was recognized, that success could only be achieved with adequate preservation of the organs. Cold preservation was described as early as 1912 by the French surgeon Alexis Carell, who preserved and transplanted vessels, skin, and connective tissues in dogs [40]. Together with the famous aviator and engineer Charles A. Lindberg, he constructed a perfusion pump and successfully preserved thyroid glands [41]. Years later, in the era of liver transplantation, the relevance of cooling the donor organ was recovered during animal experiments by Francis D. Moore [33]. Lawrence Brettschneider from Denver, United States used cooling of the animal donor organ and intraportal infusion with a balanced, cooled electrolyte solution, buffered to pH. The organ was additionally perfused after harvesting, but this technique was much too complex for clinical application [42]. For many years, storage in cold Collins solution was the standard for organ procurement [43]. A landmark advance was the development of the University of Wisconsin (UW) solution by Folkert O. Belzer and James H. Southard in 1988 [44], representing an important growth of knowledge in the pathophysiology of ischemia/reperfusion injury. This solution contains colloids to prevent cell swelling, the oxygen scavengers allopurinol and glutathione, and adenosine to facilitate adenosine triphosphate (ATP) production.

In 1983, a National Institutes of Health (NIH) Consensus Conference considered liver transplantation as an accepted therapy for patients with end-stage liver disease. The consequence of this statement was a rapid increase in the numbers of patients on waiting lists in the following years, resulting in a dramatic shortage of available donor organs for transplantation. The development of new concepts was therefore crucial.

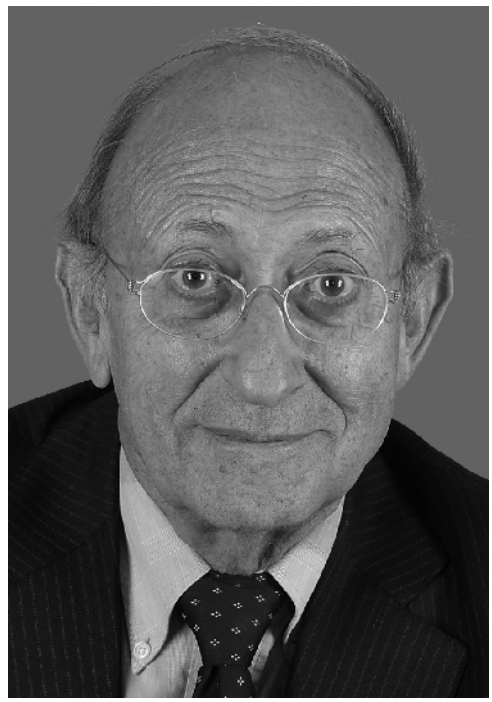

Figure 1.6 Henri Bismuth.

The shortage of size-matched liver donors for pediatric patients was responsible for a high death rate on the cadaveric pediatric waiting list. This stimulated the development of technical innovations based on the segmental anatomy of the liver. Reduced liver graft, split graft, and living donor liver transplantation were such innovative techniques. In 1984, Henri Bismuth (Figure 1.6) from Paris, France, performed the first OLT using a left hemiliver [45]. In 1988, Rudolf Pichlmayr from Hannover, Germany extended the concept of partial liver graft transplantation and published in 1988 a report of a split graft, where the right hemiliver was transplanted to an adult, and the left to a child [46]. Two years later, Christoph E. Broelsch published the first patient series of split liver transplantation in Chicago, United States [47]. The introduction of living donors was a critical step in the further evolution of liver transplantation [48]. In 1989, Silvano Raia from Sao Paulo, Brazil [49], and one year later Russell W. Strong from Brisbane, Australia [50], reported the first living donor liver transplantations using the left hemiliver. In 1994, Yoshio Yamaoka from Kyoto, Japan used the right hemiliver for transplantation, expanding this procedure also for adults [51]. The first series of patients was published by Christoph E. Broelsch in Chicago [52], later by Chung-Mau Lo in Hong Kong [53].

Nowadays, patient survival after one year has reached 80–90% in many contemporary series of OLT [54]. Conse-

quently, donor criteria are still expanding under the pressure of an insufficient donor pool. Beside end-stage liver disease and acute liver failure, selected patients with primary liver cancer [55] and early stage hilar cholangiocarcinoma [56] have become accepted indications for OLT (see also Chapter 26 for indications of OLT in treatment of liver tumors).

A potential approach to solve the shortage of donor organs was the use of steatotic donor organs and this was shown to have a favorable outcome by McCormack *et al* [57]. Donor risk scores and appropriate matching to selected recipients may further improve the outcome [58]. Thus, extending donor criteria, improvement of allocation procedures, and finally, translation of knowledge from basic research about donor organ protection into clinical application, may help to overcome the problem of donor organ shortage in the near future.

Surgical oncology: breaking down the limits

Parallel to the progress in the field of liver transplantation, liver surgery, mostly for oncologic diseases, became more sophisticated. In 1983, William P. Longmire from Los Angeles, California, published the results of 138 patients after major resections with a 30-day mortality of 10% [59]. In the 1990s, Jacques Belghiti from Paris, France reported – in a large series of 747 patients – a mortality of 1% in patients with normal liver parenchyma [60]. Leslie H. Blumgart from New York, United States [61] and Sheung Tat Fan from Hong Kong [62] published similar results. However, the presence of cirrhosis [63], portal hypertension [64], and liver steatosis [65] were identified as important risk factors for perioperative morbidity and mortality.

An important step for the improved outcomes was the understanding that these complex diseases must be treated in specialized, interdisciplinary centers [66]. A higher caseload in such hepato-pancreatico-biliary (HPB) centers translates into more experience, an important factor for favorable outcomes [67, 68].

In the last decades, basic research provided new insights into liver physiology and pathophysiology [69–71]. Interleukin-6 [72], tumor necrosis factor α [73], platelet-derived serotonin [74], and bile salts [75] were identified as central mediators of liver regeneration. Explorations of mechanisms of ischemic damage and cell death provided novel perceptions of liver injury [76–79]. However, only few new strategies, such as ischemic preconditioning, made the transition into clinical practice [80].

Diagnostic accuracy improved due to the availability of computed tomography (CT) scans and magnetic resonance (MR) tomography. Masatoshi Makuuchi, from Tokyo, Japan, introduced the concept of routine intraoperative ultrasonography for liver surgery [81]. He was also among the first to use portal vein embolization to increase the future liver remnant prior to major resection [82], although the mechanism of selective portal occlusion and subsequent contralateral hypertrophy was already known since 1920 [83]. For the treatment of unresectable tumors, radiofrequency was introduced as an alternative treatment [84–86].

The complex treatment strategies for metastatic liver disease are illustrative examples of the progress of HPB surgery [1]. In 1940, Richard B. Cattell, in Boston, United States, performed the first resection of a metastatic tumor [87], although resection of colorectal liver metastases remained controversial until the early 1980s. The survival of patients after resection was 21%, but the operative mortality still reached 17% [88]. Today, resection for liver metastasis, especially of colorectal origin, provides favorable outcomes compared to the natural history [89]. In a series of 1001 consecutive patients, the 5-year survival rate was 37% [1, 90]. In selected patients with unresectable and multifocal metastases, a two-stage hepatectomy combined with chemotherapy was recognized as an effective and safe treatment strategy [91]. In 2004, promising survival rates for patients treated with two-stage procedures, combined with portal vein ligation, were published [92]. Down-staging of previously unresectable colorectal liver metastases could also be achieved by portal vein ligation combined with intra-arterial chemotherapy [93]. Multistage procedures are currently recognized as effective strategies for patients with otherwise unresectable tumors [1].

In conclusion, liver surgery has enjoyed a dramatic development during the last three decades. Surgical experience and outcomes after major surgery improved as a result of progress in many fields. Furthermore, multidisciplinary patient management became a mainstay of care in recognized HPB centers. Today, liver surgery no longer carries the high risk that it did in its infancy. In experienced hands, liver surgery became reliable and effective, and consequently saved the lives of many patients.

Self-assessment questions

1. Name the surgeon who performed the first successful liver resection.
2. Name the surgeons who performed the first major liver resections.
3. What was a prerequisite for safe major liver surgery?
4. What was the major innovation making OLT a successful treatment?
5. A great problem was the availability of size-matched donor organs for children. Who found the solution, which had also a major impact on later developments?

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Self-assessment answers

1 Carl Langenbuch, a German surgeon, performed the first successful liver resection in 1888 in Berlin.
2 Ichio Honjo reported the first "anatomic" liver resection in 1950 in Kyoto, Japan. In 1952, Jean-Louis Lortat-Jacob from Paris, France reported the first resection in Europe, followed by Julian K. Quattlebaum from Georgia, who reported the first resections in the United States in 1953.
3 The fine work of Carl-Herman Hjortsjo from Lund, Sweden, John E. Healey from Huston, United States and Claude Couinaud from Paris, France revealed the complex anatomy of intrahepatic structures, a fundamental basis for safe liver surgery.
4 Before the advent of cyclosporine A, discovered in 1972 by Hartmann F. Stähelin and Jean-Francois Borel from Basel, Switzerland, the prognosis after OLT was poor. Cyclosporine A improved the outcome of these patients significantly.
5 The segmental anatomy of the liver was the key to the problem. Henri Bismuth from Paris, France performed the first OLT using a left hemiliver in 1984. Later, Rudolf Pichlmayr from Hannover, Germany performed a split graft, where the right hemiliver was transplanted to an adult, and the left to a child. This principle was also the basis for living related liver transplantation.