Liver Regeneration Enables Miracle of Liver Transplantation

The liver is a unique organ due to its ability to regenerate after injury or partial removal. This special quality of the liver has been described as far back in history as ancient Greek mythology, in the story of Prometheus [1]. Prometheus, whose name means "Forethinker", was a powerful Titan, known as the supreme trickster and god of fire. He has been credited with the creation of mortals, and providing the gift of fire to mankind by stealing it from Zeus, who was the king of all the gods on Mount Olympus. As his punishment, Zeus had Prometheus chained to a mountain and sent an eagle to eat his liver (Figure 1). Prometheus' liver would regrow each night and the eagle returned every day to perpetually torture him. This agony continued for years until the eagle was killed by Hercules.

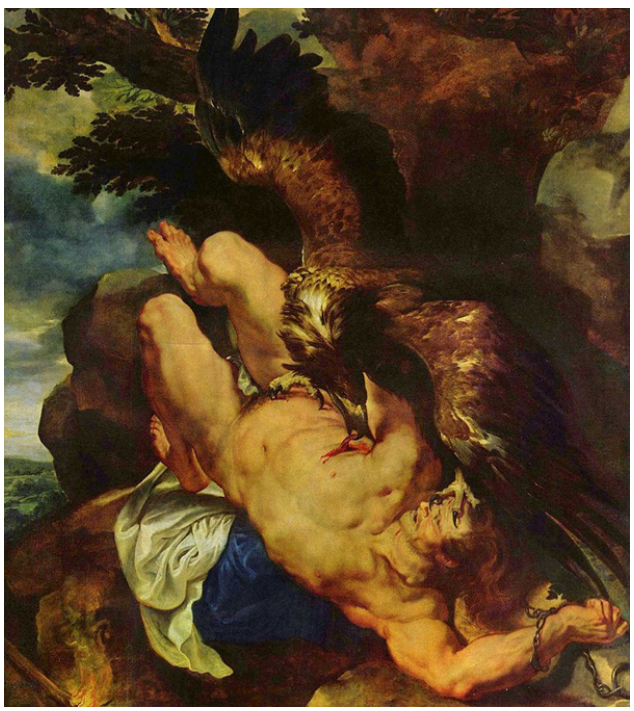

Figure 1 shows Gefesselter Prometheus by Peter Paul Rubens, 1611-1612

In modern science, the earliest studies on liver regeneration were pioneered by Higgins and Anderson in 1931. [2] They removed two-thirds of the liver in rats, and demonstrated subsequent enlargement of the remnant liver until the original liver volume was restored within 7 days after surgery. The phenomenon of liver regeneration after destruction or loss of liver mass has been observed in all vertebrate species including humans [3]. It is postulated that we have evolved the ability to regenerate our livers in order to protect one of the most important organs in our bodies.

The liver is a large organ which sits in the upper right side of the abdomen (Figure 2). It has a right lobe and a left lobe. Its anatomy

Figure 2 shows human liver, located at the upper right of abdomen.

is distinctive from the standpoint of its blood supply. Unlike most organs which only receive their blood supply from our hearts via an artery, the liver receives additional blood directly from the intestine via the portal vein. This blood is rich in nutrients recently digested and absorbed by our intestines. One of the important functions of the liver is to process and metabolize nutrients including carbohydrates, protein and lipids into products which can be used by our bodies for sustenance. The liver also produces bile - which is important for fat digestion, and clotting factors - which prevents us from excessive bleeding. Toxins and drugs are cleared by the liver and it plays a crucial role in the regulation of blood sugars and body temperature.

Since the liver is essential for survival, its regenerative capability is important after partial removal or destruction in order to maintain adequate function. In adult rats, mature liver cells will begin replicating within 24 hours of surgery, followed closely by bile ducts cells. This process occurs in an orderly and well-orchestrated manner where liver cells will both increase in size and number. At the cellular level, regeneration is postulated to be triggered by changes in the blood flow and concentration of growth factors and local hormones within the remnant liver [3].

Our improved understanding of liver regeneration coupled with advances in surgical techniques and peri-operative care have led to the development of safe liver surgery to treat malignant and benign diseases of the liver. The risk of death associated with liver surgery has been reduced from 50% in the 1970s to <5% currently in most large-volume liver centres in the world [4]. The regenerative capacity of the liver is even more crucial in the setting of liver transplantation - where the entire diseased liver is removed and replaced with a healthy liver (deceased donor liver transplantation),

Figure 3 shows what happens during Living Donor Liver Transplantation (LDLT)

and regeneration is especially critical when only part of a healthy liver is donated (living-donor liver transplantation).

Liver transplantation is an important treatment option for patients with chronic liver disease, acute liver failure, and primary liver cancer. The first successful liver transplantation in humans was performed by Thomas Starlz in 1967. [5] Since then the field of transplantation has expanded due to improvements in surgical techniques, peri-operative management, preservation solution and immunosuppression regimens which prevent rejection of donated organs.

Liver transplantation is indicated in the treatment of acute and chronic liver failure not responsive to maximum medical treatment. Patients with primary liver cancer who may not be candidates for liver surgery due to poor liver function may benefit from liver transplantation which is then the best option for cure of both the cancer and the liver failure.

Due to the increasing number of patients on the transplant waiting list coupled with a lack of deceased donor organs, the evolution to transplantation of partial liver grafts from living donors began with the first successful LDLT in 1989. Living donor liver transplantation (LDLT) is particularly common in Asia due to low rates of deceased donor organ donation. The success of this technique is enabled by the regeneration of the partial liver in both donor and recipient.

During LDLT, both the donor and recipient will undergo their respective operations simultaneously. A portion of the liver is removed from the donor (for an adult recipient, this is most commonly the right lobe of the liver) and sutured into the recipient after the recipient's original diseased liver has been completely removed (Figure 3).

At the Asian American Liver Centre, prior to liver transplantation, the potential recipient and donor will need to undergo an extensive evaluation process whereby their indications and fitness for surgery and post-operative care are examined. Potential donors will undergo 3-D imaging scans of their livers to assess anatomy and ensure the volume of the liver is adequate for both recipient and donor (Figure 4). We ensure that our donors will have at least 30% of liver volume remaining after surgery, which is consistent with most international standards.

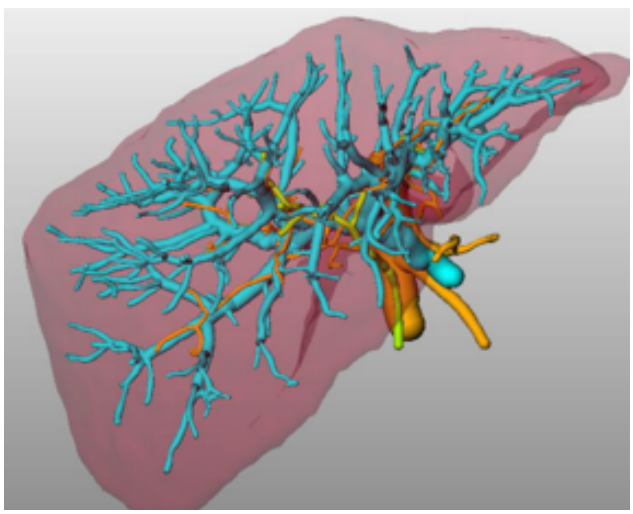

Figure 4 shows 3-D imaging of donor liver revealing blood vessels and bile ducts within liver

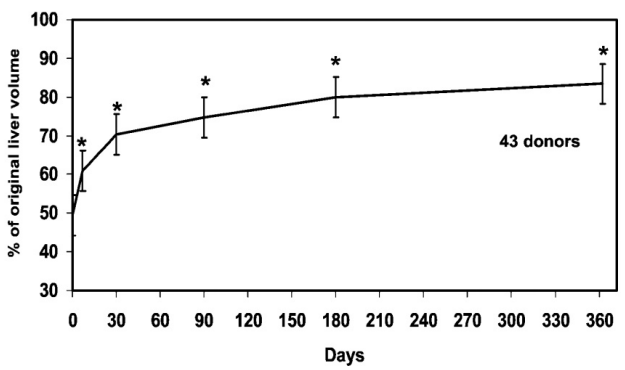

Figure 5 shows the overall donor remnant liver regeneration [8]

Several groups have published studies on liver regeneration in donors and recipients after LDLT. At 3 months after LDLT when the right lobe was donated, donors regenerated almost 80% of their ideal liver volume, whereas recipients had attained 103.9% [6]. Recipient liver volume tends to decrease after 2-3 months, reaching 90% at 1 year post transplant [7]. Overall right lobe donor liver regeneration at 1 year post donation was 83.3% of original liver volume; the fastest rate of regeneration occurred during the first week post operation (Figure 5) [8]. Even though the donor livers did not return to 100% of original volume, the majority of liver donors attained normal liver

function within 1 week post donation, which suggests that livers can function adequately without regenerating to 100%.

Liver transplantation is a major surgical procedure with significant operative risks. The perioperative risk of death is 5-10%, depending on severity of liver disease and the presence of other diseases. Complications may occur in up to 30% of cases including bleeding, acute rejection, and infections. Long-term outcomes from LDLT have improved since its' inception and current 5-year survival rates reach >80% [9]. Long-term survival rates are slightly lower for recipients who receive a liver transplant for primary liver cancer due to risk of cancer recurrence.

Even though the donor operation has lower complication rates compared to the recipient operation, any risk is considered significant as the donor derives no benefit from their operation except for the emotional reward of a magnanimous gesture. The perioperative risk of death for donors is 0.1- 0.5% whereas complication rates can reach up to 15%. After initial recovery from the operation, however, liver donation does not shorten the donor lifespan or put them at increased risk of liver dysfunction compared to a person without liver donation [10].

In conclusion, the ability of the liver to regenerate has enabled us to develop advanced surgical techniques such as living donor liver transplantation to treat complex diseases of the liver including liver failure and liver cancer. It would have been unlikely for these patients to survive without liver transplantation once regular medical therapies have been exhausted. Liver regeneration therefore enables one of the miracles of modern medicine – the ultimate life-saving gift of a liver.

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About the Author

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A Board Certified surgeon of the American Board of Surgery, Dr Cheah Yee Lee specialises in liver transplantation and hepatopancreatobiliary surgery (surgery of the liver, pancreas and bile ducts).

Dr Cheah began her surgical career in 2000 with a medical degree from the Royal College of Surgeons, Ireland, and obtained her Associate Fellowship of the Royal College of Surgeons, Ireland, in 2003. From 2003 to 2008, she completed her general surgery training at the prestigious Ivy League General Surgery Residency Program at Brown University in Rhode Island, USA, where she was appointed Executive Chief Resident of General Surgery in 2008. Dr Cheah also received the Dean's Teaching Award in 2007 and the Haffenreffer Outstanding Resident of the Year Award in 2008 at Brown University.

Dr Cheah underwent advanced training in liver transplantation and hepatopancreatobiliary surgery under the mentorship of Professors Elizabeth Pomfret and Roger Jenkins at the Lahey Clinic in Massachusetts, USA. She completed her American Society of Transplant Surgeons (ASTS) accredited fellowship in 2010. She returned to Asia and joined Khoo Teck Puat Hospital (KTPH), Singapore, as Consultant Surgeon and was instrumental in developing its hepatopancreatobiliary surgery programme until 2014, when she left KTPH to join Asian American Liver Centre.

Dr Cheah's clinical interests are in living donor liver transplantation, surgery of the liver, pancreas and bile ducts for benign and malignant disorders, and nutrition support and therapy of surgical patients. Her main research interests are in the areas of living donor safety, and disorders of the liver, pancreas and bile ducts. Dr Cheah was appointed Clinical Instructor at Brown University and Tufts University, USA, from 2003 to 2010. She is a founding member of the Hepatopancreatobiliary Association of Singapore. In addition, she has served in the Vanguard and Membership Committees of the International Liver Transplant Society (ILTS) since 2011. Dr Cheah has given presentations at local national and international surgical, transplant and nutrition meetings and conferences.