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EDITORIAL

NOBEL LAUREATES WHO CONTRIBUTED TO TRANSPLANTATION

The Nobel Prize in Physiology or Medicine, administered by the Nobel Foundation, is awarded once a year for outstanding discoveries in the fields of life sciences and medicine. Nobel was personally interested in experimental physiology and wanted to establish a prize for progress through scientific discoveries in laboratories. The Nobel Prize is presented to the recipient(s) at an annual ceremony on 10th December, the anniversary of Nobel's death, along with a diploma and a certificate for the monetary award.

Across the XX century many scientists have focused on the field of transplantation. Achievement of few of them was awarded with the Nobel Prize. One of them whose achievement was awarded with the Nobel Prize was **Alexis Carrel**. He was born on 28 June 1873 near Lyon, France. Carrel's interest in transplantation was first manifested in 1902 in Lyon, when he transplanted a kidney from a dog's abdomen to its neck. The kidney produced urine immediately and the animal died after a few days from an infection. In 1904, Carrel left France after failing in several examinations to qualify for a faculty position there. He moved to Chicago, where he partnered with the physiologist Charles Guthrie. They collaborated for barely 12 months, but during this time, they successfully transplanted the kidney, thyroid, ovary, heart, lung, and small bowel, averaging one publication on this work every 14 days. Carrel's success with organ grafts was not dependent on a new method of suturing but on his use of fine needles and suture materials, his exceptional technical skill, and his obsession with strict asepsis. Carrel and Guthrie developed the so called Carrel's patch for kidney transplantation. In 1906 Carrel moved from Chicago to the Rockefeller Institute in Chicago. Next few years Carrel focused on surgical procedures on the heart. He did the world's first coronary artery bypass graft, suturing one end of a long segment of canine carotid artery to the aorta and the other to a coronary artery. Carrel was rewarded for his groundbreaking work by receiving the Nobel Prize in Physiology or Medicine in 1912, "in recognition of his work on vascular sutures and the transplantation of blood vessels and organs". At the age of 39 years, he was also the youngest Nobel Laureate. When he reached age of 65, he was forced to retire, so he came back to France..

Carrel noticed that vascular grafts, he used did not survive too long, but nobody had any idea why. Thanks to the work of **Sir Frank MacFarlane Burnet** and **Peter Brian Medawar** who shared the Nobel Prize in 1960 for discovery of acquired immunological tolerance.Sir Frank Macfarlane Burnet was born at Traralgon, Victoria, Australia, on September 3rd, 1899 and completed his medical course at the University of Melbourne. In 1944 he became Director of this Institute and Professor of Experimental Medicine in the University of Melbourne. His work on the agglutinins of typhoid fever was followed by the work on viruses for which he is nowadays justly famous. His greatest work described concepts of immune tolerance and clonal selection. He died from colorectal cancer in 31 August, 1985.His partner in the Nobel Prize was Peter Brian Medawar. Medawar researched on tissue culture, the regeneration of peripheral nerves and changes in shape of organisms that occur during this development. In 1956 he published monograph exploring the parameters of both tolerance and immunity to allogeneic transplants, and showing they were 'cell mediated' rather than humoral. His research career was prematurely interrupted in 1969, on account of a stroke. In 1986, he published his autobiography, a year before his death.

The Nobel Prize in Physiology and Medicine in 1980 was awarded jointly to **Baruj Benacceraf**, **Jean Dausset** and **George D. Snell** for their discoveries concerning genetically determined structures on cell surface that regulate immunological reactions. G. Snell was the founder of the scientific journal titled 'Immunogenetics', and served as its first editor. Dausset was also interested in immune-hematology techniques applied on red blood cells (Coombs test). He described the first leukocyte antigen, now called HLA-A2.In 1947 Benacerraf switched from clinical medicine to research. Over the next decade or so, he continued his research into the mechanisms of the immune system. The breakthrough came when Benacerraf noticed that a proportion of guinea pigs injected with particular antigens failed to mount an immune response. He did further breeding experiments to show that the animals' responsiveness to these antigens was controlled by dominant autosomal genes that he termed immune response genes.

The Nobel Prize in 1990 was shared by **Joseph E. Murray** and **E. Donnall Thomas** for their achievement in organ and cell transplantation. Joseph Eduard Murray was born on April 1, 1919 in Milford, Massachusetts. He was of Irish and Italian descent. After graduating with his medical degree Murray was inducted into the Medical Corps of the U.S. Army. He served in the plastic surgery unit which cared for thousands of soldiers wounded on the battlefields of World War II, working to reconstruct their disfigured hands and faces. His interest in transplantation grew out of working with burn patients during his time in the army. After his military service, Murray completed his general surgical residency and joined the surgical staff of the Peter Bent Brigham Hospital. On December 23, 1954, Murray performed the world's first successful renal transplant between the identical Herrick twins, an operation that lasted five and a half hours. He suffered a stroke at his home on Thanksgiving and passed away on 26 November 2012, at the Peter Bent Brigham Hospital at the age of 93. It was in this same institution that he performed the first successful kidney transplant.

E. Donnall Thomas known as "Don" to his friends, was born in a small town – Mart in central Texas, USA on 15 March 1920. He entered Harvard Medical School in 1943 and received his M. D. in 1946. Don Thomas developed his interest in bone marrow and leukemia during medical school. Inspired by the successes of Sydney Farber with antifolate therapy for acute lymphoblastic leukemia, he initially studied marrow-stimulating factors. Many patients had been cured of leukemia using this technique by the late 1970s. Since then Don Thomas and his colleagues improved their success rates significantly. In addition to leukemia and other cancers of the blood, bone marrow transplants are used to treat certain inherited blood disorders and to aid people whose bone marrow has been destroyed by accidental exposure to radiation. He was President of 'American Society of Hematology' and served on the editorial boards of eight medical journals. E. Donnall Thomas died at the age of 92 on 20th October 2012 in Seattle.

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Patients with end stage liver disease who have failed standard medical therapy are the usual candidates for liver transplantation. A number of acute and chronic diseases of the liver can result in end stage liver disease. Other than this, liver transplantation is also considered for various hepatic malignancies. Currently up to 10-20% of all liver transplants performed are for hepatocellular cancer (HCC). There is no controversy that hepatoblastoma is an excellent indication in pediatric patients with unresectable tumors. Similarly, liver transplantation for HCC in the adult population yields good results for patients whose tumor masses do not exceed the Milan criteria. It remains to be determined whether patients with more extensive tumors can be reliably selected to benefit from the procedure. Adjunctive procedures like radiofrequency ablation, chemoembolization, or cryotherapy might be indicated to limit tumor progression for patients on waiting lists. Epitheloid hemangioendothelioma is also an appropriate indication for liver transplantation. Metastatic liver disease is not an indication for liver transplantation, with the exception of cases in which the primary is a neuroendocrine tumor, for which liver transplantation can result in long-term survival and even cure in a number of patients.

HEPATOCELLULAR CARCINOMA

Liver transplantation was originally conceived as an ideal therapy for advanced hepatic malignancy because it eliminates the primary liver tumor and the potential for recurrence in the liver remnant, compared with standard hepatic resection. Several attempts to implement this strategy in the 1960s, 1970s, and 1980s led to poor results, and as such transplantation for both primary and metastatic tumors was largely abandoned. In 1996, Mazzaferro and colleagues reported a novel strategy for surgical treatment of hepatocellular carcinoma—performing liver transplants in cirrhotic patients with *early*-stage malignancy.In their study, liver transplantation was evaluated in 48 patients with HCC, apparently meeting the preset criteria of either one tumor <5 cm or up to three tumors <3 cm, the now called Milan criteria. This approach has markedly changed organ allocation and established standardized indications for transplant, with excellent long-term results. More than 60 percent of liver transplant patients with advanced liver cancer are still alive after five years, compared to nearly zero survival for those patients who did not undergo transplant, In addition to the favorable five-year survival rates, the survival rates have increased steadily over the last decade, suggesting that criteria for patient selection established by other experts may assist physicians in selecting those patients most likely to respond well to the procedure.

The survival rate following transplantation is both significantly better than with hepatic resection and comparable with the survival rate following liver transplantation for other indications. Milan criteria is most commonly used to determine the candidature of a patient with HCC for performing liver transplant. Detection of HCC in the cirrhotic liver provides a seemingly highly appropriate indication for LDLT. Since hepatic dysfunction in these individuals is typically modest, the transplant can be planned as a semi-elective procedure, yet more expeditiously than is usually possible with deceased-donor transplantation. LDLT appeared to provide a distinct advantage over deceased-donor liver transplantation. Survival rates for patients undergoing LDLT versus deceased-donor liver transplantation were 86% and 71% (at 1 year) and 68% and 42% (at 5 years), respectively.

It is a common perception that the Milan criteria may be too stringent and may be excluding some patients who might benefit from the procedure from consideration for transplantation. Several other guidelines are available, more popular amongst these are the UCSF guidelines.UCSF criteria (one tumor ≤6.5 cm, three or fewer nodules with the largest lesion ≤4.5 cm and total diameter ≤8 cm) has shown results comparable with that in the patients undergoing transplantation based on the Milan criteria.

HILAR CHOLANGIOCARCINOMA

Initial experience in patients undergoing Liver Transplantation for Cholangiocarcinoma was unsatisfactory due to early disease recurrence and poor long term survival. Treatment of patients with hilar Cholangiocarcinoma by liver transplantation has gained attention in recent years. Neoadjuvant chemo radiation in combination with liver transplantation for highly selected patients with hilar Cholangiocarcinoma has shown impressive results with 5-year survival rates of approximately 76% to 82%. This is similar to other standard indications for liver transplantation, including hepatocellular carcinoma. The Mayo Clinic has published data on the largest series of patients with hilar Cholangiocarcinoma to have undergone liver transplantation. Rigorous diagnostic criteria have been implemented to ensure the best outcome including tumor size less than 3 cm in radius, the findings of a malignant-appearing stricture confirmed by biopsy or cytology, an elevated CA 19-9 level more than 100 IU/mL, or evidence of aneuploidy in tissue samples. Unresectability is predicated based on technical considerations or the presence of intrinsic underlying liver disease. Exclusion of regional lymph node and peritoneal involvement is required by operative staging after completion of Neoadjuvant therapy.The protocol includes pretransplant external-beam irradiation followed by transcatheter irradiation and 5-fluorouracil (5-FU) followed by oral Capecitabine. An exploratory laparotomy is performed to exclude extrahilar lymph node disease, following which the patient is activated on the waiting list.

HEPATIC EPITHELOID HEMANGIOENDOTHELIOMA

Epitheloid hemangioendothelioma is a disease affecting mainly younger females and resulting from a malignant transformation of vascular endothelium. An association with oral contraceptives has been suggested but not completely established. Clinical presentation may be with abdominal pain, but more frequently the lesion is an incidental finding. Since the tumor is often widespread within the parenchyma, complete resection may not be possible, even in the non-cirrhotic liver. The results after liver transplantation are quite acceptable, being comparable with those after OLT for viral-induced cirrhosis.

HEPATOBLASTOMA

Hepatoblastoma is the most common malignant tumor of the liver in the pediatric population, affecting mostly young boys age less than 3 years and accounting for 75% of primary liver tumors in childhood. Diagnosis is usually at a late stage. The introduction of chemotherapy with cisplatin and doxorubicin has changed the treatment success of hepatoblastoma substantially, and despite a large tumor mass at presentation, a combined surgical and chemotherapeutic approach has yielded a 5-year survival rate of approximately 80%. Liver transplantation plays a role in those patients whose tumors cannot be completely resected after appropriate chemotherapy. The most complete report of liver transplantation was published by Otte et al. who reviewed the results of 147 patients from several European pediatric centers. The overall survival rate at 6 years post-transplantation was 82% in patients who had not undergone pretransplant-attempted liver resections, versus 30% at 6 years for patients who underwent liver transplantations after failed resections.

METASTATIC NEUROENDOCRINE AND COLORECTAL CANCERS

Neuroendocrine tumors are usually hormone producing (serotonin, insulin, gastrin, glucagon, etc.), but also may present as a nonfunctioning mass lesion. The clinical presentation is diverse, depending upon the hormone secreted. These tumors typically metastasize to the liver, and some patients note pain, resulting from capsule distention, as a first symptom. Even after metastasizing, these tumors often remain slow growing so that approximately one-third of the patients survive for 5 years after the development of liver metastases. Because of the somewhat indolent nature of their liver metastases, these patients are considered appropriate candidates for liver transplantation. Liver resection resulted in a 5-year survival rate of 67%, but a disease-free survival rate of only 29%. Liver transplantation resulted in a 5-year survival rate of 70% and recurrence-free survival rate of 53%.Patients with hepatic metastases from neuroendocrine tumors may have prolonged survival, especially under the ideal selection criteria: age less than 46 years, limited liver tumor burden with favorable histology, and no extra hepatic disease. Such patients often have good overall survival and quality of life.

Transplantation for metastatic liver disease secondary to colorectal metastasis is currently a controversial subject. In the pilot study from the Oslo Transplant Center, Hagness et al reported their experience with liver transplantation in 21 patients performed over a 4.5-year time interval. The 5-year overall survival rate was 60%, with a 1-year disease-free survival rate of 35% and no patients had long-term disease-free survival. The status of Liver Transplantation for Colorectal metastasis to the Liver at this time is investigational.

LIVER TRANSPLANTATION AT RGCIRC

RGCIRC is a Government certified liver transplant center and it successfully started its liver transplant program in September this year. Patient was a case of CLD (HCV related) with portal hypertension with HCC with tumor thrombus in right portal vein, diagnosed 2 years back . Initially he had undergone TACE at RGCIRC 2 years back and was on sorafenib. Lately for 6 months he was having signs of liver decompensation, so liver transplant was planned. His daughter agreed to donate his part of liver and he underwent right lobe living donor liver transplant on 26 september 2019. Both donor and recipients recovery was uneventful and they are doing well.

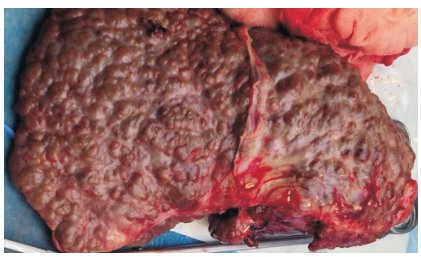

Fig.1 Explanted Liver

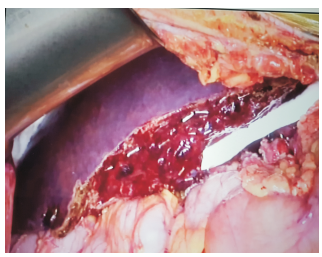

Fig. 2 Liver Graft after Implantation

Donor(Left) with Recipient

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SCREENING FOR BREAST CANCER

Screening modalities — Screening mammography has been shown to lower deaths from breast cancers. Mammography (digital or film) is the primary modality for breast cancer screening in average-risk women. Other techniques, such as ultrasound and magnetic resonance imaging (MRI), are useful for further evaluation of findings on mammography or for screening of women at a higher risk for breast cancer. Breast examination by the clinician or by the patient is not recommended as the only screening method, and it is controversial as to whether clinician breast exam or patient breast self-exam (BSE) are beneficial as an adjunct to mammography. But it is important to educate women about breast awareness and to encourage women to report any breast concerns. Following are the recommendations by different societies for routine mammographic screening in women at average risk.

Group (year)	Frequency (years)	40 to 49 years of age	50 to 69 years of age	≥70 years of age
US Preventive Services Task Force (2016)	Two	Individualize*	yes	Yes, to the age of 74
American Cancer Society (2015)	One year age 45 to 54 One to two years age ≥55	Individualize* through age 44 Yes, start age 45	yes	Yes$^{\Delta}$
National Comprehensive Cancer Network (2018)	One	yes	yes	yes

* Women should be counseled about the harms and benefits of mammography; individualized decisions should include shared decision-making based on risks, benefits, patient values and preferences. Δ If in good health and life expectancy >10 years.

Above average risk or high risk of breast cancer is associated with personal history of breast, ovarian, tubal, or peritoneal cancer or family history of breast, ovarian, tubal, or peritoneal cancer. Other factors associated with high risk of breast cancer are family history of hereditary breast and ovarian cancer syndrome (eg. Mutations of *BRCA1* or *BRCA2, PTEN, TP5)* in self or relative. The screening in this population should begin 10 years prior to the youngest family member with breast cancer but not before the age of 25-30 years. The other group of patients at high risk of developing breast cancer is those with prior history of chest irradiation between age 10-30 years. These patients should be started on screening protocols beginning 10 years after radiation therapy. Both annual mammogram and breast MRI are recommended for screening of high risk patients. The risk and benefits of screening should always be discussed at length with the individual as this can lead to overdiagnosis, anxiety and more biopsies that were not needed.

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Transplantation would not have developed without discovery of the immunosuppressive drugs. The first step for sure was steroid treatment, but synthesis of azathioprine was the real breakthrough. Nobel Prize Committee in 1998 awarded **Gertrude B. Elion** and **George H. Hitchings** for discovery of this drug. Hitchings and Elion successfully synthesized two compounds—diaminopurine and thioguanine. For the first time, a treatment that could interfere with the formation of leukemia cells and induce remission. In addition to 6-MP, Elion went on to discover a series of drugs that attack the life cycle of nucleic acid, including allopurinol—which inhibits uric acid synthesis, making it a viable treatment for gout—and azathioprine (Imuran), an effective immunosuppressive drug. Her discovery of azathioprine was extremely important to transplantation, because it made possible for people to receive organ transplants without their body rejecting them. In the 1960s Hitchings and Elion determined that infectious diseases could be fought if drugs could be targeted to attack bacterial and viral DNA. This work resulted in pyramethamine, which was used to treat malaria, and trimethoprim, which was used to treat meningitis, septicemia, and bacterial infections of the urinary and respiratory tracts. In 1967, Hitchings became Vice President incharge of Research of Burroughs Wellcome. Hitchings suffered from Alzheimer's disease and died on February 27, 1998 in Chapel Hill, North Carolina, USA.

The last described Noble Prize winner was **Ralph N. Steinman**. He was born in Ashkenazi Jewish family on 14 January 1943. In 1973, Steinman and Cohn discovered dendritic cells, a previously unknown class of immune cells that constantly formed and retracted their processes. This discovery changed the field of immunology. He and his colleagues established that dendritic cells are critical sentinels of the immune system.He also showed that dendritic cells are the main initiators of T cell-mediated immune responses. Diagnosed with pancreatic adenocarcinoma in March 2007, Steinman believed that dendritic cells had the potential to fight his aggressive tumor. Ralph N. Steinman died on 30 September 2011, three days before his Nobel Prize was announced. Unaware of his death at the time of its announcement, the Nobel Committee made an unprecedented decision that his award would stand.

Despite the enumerable advances in transplantation in surgical and medical fields, very few have been crowned the Nobel Prize. I hope that the XXI century will be more fruitful for transplantation and the Nobel Prize Winners involved in this part of science.

Dr. A. K. Dewan
Director - Surgical Oncology

Architect's Impression of RGCIRC (post expansion)

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