IT ALL DEPENDS ON THE LIVER
We look at key problems of liver, treatments, and progress in terms of transplantation and research.

LEADER SPEAKS
Kiran Mazumdar Shaw, CMD, Biocon

PANEL DISCUSSION
Doc N Doc talks about surgery and its challenges

COLUMN
Dr Ashok Seth on total artificial heart
It all depends on the liver

Responsible for up to 500 different functions in the human body, the liver is also vulnerable to several metabolic, toxic, microbial, circulatory and malignant insults. Doc N Doc looks at some key problems of liver and their treatments, and recent progress in terms of transplantation and research. The five specialists share their experiences on tackling liver diseases, establishing India as a low-cost liver transplant destination for the world, hepatotoxicity research and ways to prevent rising liver diseases.
In the 1990s, when I was training in All India Institute of Medical Sciences (AIIMS), New Delhi, we had a very active liver unit. But most patients who needed liver transplantation were dying. The reason was that there was no recognition of brain death in India. Brain death is the complete and irreversible loss of brain function and is the only form of death that allows organs to be transplanted.

I was aware of the need for organ transplantation in India and the potential impact it could have on the quality of life for patients. I knew that the lack of organ donation was the biggest barrier to the development of a liver transplantation program in India. I decided to raise awareness about organ donation and transplantation in India.

I joined Sir Ganga Ram Hospital and set up a liver transplantation unit along with Dr S Nundy. The department conducted the first liver transplant in 2001. This was a deceased donor liver transplant. Along with Dr Nundy, I started living donor liver transplantation as the predominant form of liver transplantation. In 2004, we were doing about 10 to 12 transplants a year, but most patients were not keen to go through the process. Usually, these cases were at the last stage, and had no option but transplantation. Being last stage cases, the surgery results also varied. In 2005, I left for Hong Kong, the pioneer in the specialization. I came back and joined Apollo Hospitals in 2006.

India has come ahead since, but the journey had a lot of hurdles. Like, though the Bill was in place and there was a huge need of organ donors, society could not be motivated to donate organs. Then, in cases of paediatric transplants, till 1997, only adults could give a portion of their liver to children. Other countries were reporting breakthrough transplant surgeries, so there was knowledge. But there was also a mindset that inhibited people from donating organs.

At Apollo, what we have done differently is low-cost transplantation. We have also made changes in medications and have trained centres in handling transplant cases.
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As a society, we are aware of organ donation, but believe that such a case will not happen to us. There are many issues. Primarily, it is because of the attitude of the donor and recipient. We have given to every donor of the past as well.

Despite immense burden of liver diseases, India has limited specialists to handle the cases. As a society, we are aware of organ donation, but believe that such a case will not happen to us. There are many issues. Primarily, it is because of the attitude of the donor and recipient. We have given to every donor of the past as well.

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Pre-transplant evaluation

The pre transplant evaluation in a paediatric liver transplant includes the following issues:

- Immunisation pre transplantation: Most hospitals consider live vaccines to be contraindicated after liver transplant because of the risk of dissemination secondary to immunosuppression. It is, therefore, better to complete normal immunisations before transplant. These include BCG, DPT + Hib, hepatitis B, measles, MMR. It is suggested to give even optional vaccines such as for hepatitis A, typhoid, chickenpox, influenza rotavirus and pneumococcal vaccines. The vaccination schedule may be expedited and may differ from the normal recommendations. The target is to complete the live vaccination prior to transplant. Following live vaccination, liver transplant surgery is deferred by two-three weeks.

- In acute liver failure scenario, the doctor does not have time to look into this issue as the need for liver transplant is on an urgent basis. However, killed vaccines like tetanus, hepatitis B vaccines are given if need be.

- Management of hepatic complications: It is important to ensure that specific hepatic complications are appropriately managed while the patient waits for transplant. These include portal hypertension, oesophageal varices, ascites, hypoproteinaemia, etc.

- Nutritional support: It has been demonstrated in several studies that nutritional status at liver transplant is an important prognostic factor in survival, i.e., better outcome is seen in patients with good nutritional status. The patient needs to be on a high calorie diet (150-200 per cent calories good protein intake) with two times the RDA of multi vitamins, and in patients with cholestasis, supplementation with fat soluble vitamins is done. In patients with cholestasis MCT oil is also given. The indications of liver transplantation in children are different from adults. They are mostly secondary to structural changes such as biliary atresia, whereby birth the bile duct, which transmits bile from liver to intestine, is not formed, or functional changes where there is a lack of an enzyme or a factor required to carry out important steps in the metabolism of food such as carbohydrates, fats and proteins. Occasionally, liver may fail due to acute viral infections such as viral hepatitis A, B, C, E or due to side effects of certain drugs such as tuberculosis, antiepileptics and paracetamol poisoning. Liver tumours may also be the cause of liver failure.

Usually, in a child, left lobe or left lateral lobe is used. However, in older children and adolescents, right lobe of the donor may also be used. The minimum graft should be 0.8-1 per cent of the body weight of the child. In a small baby even left lateral segment may be too large for the small size vessels that the patient has. Therefore, after removing a part of the liver (usually left lateral) a bench surgery is performed to reduce the weight and make it apt to the weight and needs of the child. This is called reduced graft.

A pioneer in paediatric gastroenterology, hepatology and liver transplantation, Dr Neelam Mohan, director, Department of Pediatric Gastroenterology, Hepatology and Liver Transplantation, Medanta-The Medicity, Gurgaon, is credited with establishing the busiest paediatric liver transplant programme in India, with nearly 150 transplants, including world’s first living related liver transplant in a baby with factor VIII deficiency, world’s youngest domino liver transplant and world’s first interlinked three paediatric living related transplant with two donors. She shares her experience in the specialisation with Doc N Doc."
Post-transplant care of paediatric patients has to be by specialised paediatric intensivists and nurses. In patients may require prolonged ventilation and ICU stay. Also, as a lot of patients have Roux en Y surgery for bile ducts, feeds are delayed till around third day post-op. Their need for analgesia is also a bit higher.

Dr Neelam Mohan, part of the therapy else lungs would develop collapse consolidation.

Children who survive liver transplant will usually achieve a normal lifestyle despite the necessity for continuous monitoring of immunosuppressive drug levels. They attend normal school and participate in sports and other activities. Most children are able to resume after three months of transplant and sport after three to six months of transplant.

Majority of paediatric patients being post Kasai (post biliary atresia surgery), there are no significant issues related to mortality after this. Patients usually lead a normal life and take part in sports and other normal activities. There have been examples of children who have even climbed mountain peaks.

There is a common need to exchange recipients—giving the liver to an unknown, but compatible individual. The donors can provide two patients with healthy livers, which was technically more difficult and required much more expertise, as the blood vessels and bile duct in a child are much smaller than those in an adult liver transplant in children.

Majority of the donor pool can be increased for paediatric liver transplant cases by using split livers, i.e. a single deceased (cadaveric) donor liver is divided into right and left portions that are implanted into two recipients simultaneously. Usually, the right lobe in adults and left/left lateral lobe is given to children. ABO incompatible donors may occasionally be used in children, as antibodies are not developed in young age and, thus, the chances of rejection are less. In ABO incompatible liver transplants, usually few sessions of plasmapheresis are carried out a week prior to the transplant and the cost of transplant would accordingly increase.

Another option of increasing the donor pool is swap donor, which means when the same blood group donors are not available, donors of two different patients with similar blood type can be matched and donate to each other. In a paired donor exchange, also known as a liver swap, two liver recipients are matched and follow up with a doctor to monitor the function of the organs and side effects of immunosuppressive medications. The team confronted with the daunting task of a complex liver surgery by coordinating the donate transplant chain that saved the lives of the three children. The team started with Tejasree, her donor and Anees’s operations. Then Ansa’s and another donor’s surgeries started simultaneously. Usually, the right lobe in adults and left/left lateral lobe is given to children. ABO incompatible donors may occasionally be used in children, as antibodies are not developed in young age and, thus, the chances of rejection are less. In ABO incompatible liver transplants, usually few sessions of plasmapheresis are carried out a week prior to the transplant and the cost of transplant would accordingly increase.

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Interview

“Virtual liver is a milestone in hepatotoxicity research”

Strand Life Sciences, founded by computer science and mathematics professors at the Indian Institute of Science (IISc), Bangalore, was awarded a patent in the US in February for its two-year-old virtual liver product, used by pharmaceutical companies globally to test new drug toxicity in the liver. Virtual liver, a ready-to-use software simulation, mimics normal liver functions and generates likely outcomes of new drugs before the drug is tested on animals and humans. Dr Kalyanasundaram Subramanian, chief scientific officer, Strand, in an email interview with Jyoti Verma of Doc N Doc, talks about the journey and company’s plans ahead. Excerpts:

How has been the journey from the concept, research and pilot studies to the patent? The journey from the start of the project conception to the patent has been seven years. We began by conceptualising the idea. We then started small parts of the model to see if indeed a complex biological system could be modelled. Once that was established, a larger team was built, we acquired funds to work on the problem and began the study. As the research continued, we kept looking for examples in literature to validate the concept. So, along the journey the concept was continually being validated by other literature studies. Finally, once the model took shape, the next challenge we faced was to perform the laboratory experiments—the pilot studies—so to speak. This proved challenging as we were not able to get the work done, although we collaborated with an academic institute and later with a contract research organisation (CRO). None was able to deliver the work. Eventually, we reverse outsourced the lab work to California where it was performed. But the costs were challenging and we felt that we could not offer this as a service to the industry at competitive rates using CA costs. We were then helped by Department of Biotechnology (DBT), Ministry of Science and Technology, that provided us support to build a laboratory and run pilot studies with the industry. This brings us to the present, where we have the patent now, laboratory expertise and a unique service offering to the industry.

What challenges did you face? There were several challenges. At the conceptualisation stage, it was really blue-sky thinking, so it was not clear that we would be able to do what we set out to do. To address this challenge, we tried to structure the project into smaller pieces, each that had specific validation bars to meet. This allowed us to build a foundation to work on. The other major challenge was that this was a long-term project and costly for a small company such as ours. The management supported the initial work and that enabled us to get the support from World Bank and then DBT. The last challenge was getting the experimental work done—we could not find labs in India capable or willing to do it and ended up outsourcing the work abroad which brought its own challenges of cost. Ultimately, we set up our own lab to be able to do the work. Now the challenge ahead of us is to really spread this approach through the industry and make a major part of the workflow of pharmaceutical, cosmetic and chemical companies.

Please tell us about the application of virtual liver. Pharmaceutical and FMCG companies invest millions of dollars every year to develop drugs or raw material for their food or cosmetic products. However, only a few drugs qualify for clinical trials and enter the market. At times, drugs are subject to post-marketing withdrawal due to their toxicity. This leads to significant loss of effort and capital for pharmaceutical companies. To minimise such losses, the virtual liver platform can be used for pursuing research on hepatotoxicity or toxicity in general, using which companies can efficiently advance their drugs through the pipeline at a lower cost.

How important is the patent for India? What’s your next move? Affordability of research infrastructure to assess the toxicity of drugs is a major impediment for drug discovery in India and other developing countries. The virtual liver platform will significantly bring down the costs associated with toxicity research. In addition to this, our proposal is ethically very significant, since it reduces animal usage for pharmaceutical development.

We are already working with top global pharma and FMCG companies to study the hepatotoxicity of their compounds. Now with the US patent being approved, we expect more business.

Is similar research on other organs and areas expected? We may create a similar model for the heart because that’s another organ affected by drug toxicity. But we are expecting the industry to take the lead and partner with us on the next steps. Diagnostics research is another area that we work on. We have developed targeted genetic panels that enable doctors to diagnose diseases that run in the family or to choose proper cancer treatment. We expect to patent these panels.
Liver cancer is the third most frequent cause of cancer deaths in India. Over a period of past two decades, there is a gradual rise in liver cancer patients in the country. A distinguished surgeon of international acclaim, Dr Saumitra Rawat has extensive world-class experience in gastrointestinal and HPB surgery and has pioneered advanced laparoscopic GI cancer surgery in India. The chairman and head of surgical gastroenterology and liver transplant, Sir Ganga Ram Hospital (SGRH), New Delhi, speaks to Nikunj Shama of Doc N Doc about various aspects of the disorder. Excerpts:

How big is liver cancer for India? How frequently do we see the cases being reported?
Liver cancer is the third most frequent cause of cancer deaths in India. Over a period of past two decades, there is a gradual rise in liver cancer patients in the country. The foremost reason for liver cancer is Hepatitis B and C, alcohol consumption, obesity, and diabetes mellitus. Cases of liver cancer due to hepatitis B is rampant in India. Basically, liver cancer occurs in two forms, primary and secondary (metastatic). Nowadays, about 40 per cent of the cases are diagnosed at an early stage. This was not the case two decades ago when only about 10 per cent cases were curable, as they were reported at a late stage. This percentage has now increased to 30-40 per cent, thanks to growing facilities and awareness.

What is the latest treatment/surgery available in India to treat these?
Resection is the most important surgery for cases in early stage, but for late stage procedures trisegmentectomy, embolisation, RF ablation, chemo-embolisation and cryosurgery are the preferred treatment alternatives. Embolisation involves shrinking of the original tumour size followed by the application of radiotherapy. In cryosurgery, we freeze the cells, while in ablation we heat the affected site.

“I was in the UK for 17 years before I joined SGRH, and from my past one and a half year stay and many visits across India, I can say that the top five super-specialty and multi-super-specialty facilities in the country are at par with the West. Robotic surgery is an advance technique and offers several advantages in surgical procedure for liver cancer, such as smaller scars, fast recovery and improved intra-operative visualisation.”

SGRH is one of the largest centres for gastrointetinal and liver cancer treatment in India.

Are there any procedures to treat cancer at an early stage?
If the cancer is detected early then we can perform laparoscopic procedure, but we need latest equipment to do this and the surgeon must be well-trained. Robotic surgery is also an advance technique and offers several advantages in surgical procedure for liver cancer, such as smaller scars, fast recovery and improved intra-operative visualisation.

“Liver cancer is a ticking time bomb in India”
Liver cancer is the third most frequent cause of cancer deaths in India. Over a period of past two decades, there is a gradual rise in liver cancer patients in the country. A distinguished surgeon of international acclaim, Dr Saumitra Rawat has extensive world-class experience in gastrointestinal and HPB surgery and has pioneered advanced laparoscopic GI cancer surgery in India. The chairman and head of surgical gastroenterology and liver transplant, Sir Ganga Ram Hospital (SGRH), New Delhi, speaks to Nikunj Shama of Doc N Doc about various aspects of the disorder. Excerpts:
Robot can also enhance surgical precision, which leads to reduced blood loss and better patient outcomes. Recently, doctors at SGRI successfully treated a large cancerous tumour in the liver using laparoscopic technique.

How do you visualise the role of advanced technologies (such as robotic) in overcoming conventional hurdles? Do these present new challenges too? The main challenge with advanced surgery is scarcity of well-trained professionals to operate such complex procedures with the help of advanced tools. SGRI took a note of the issue and started providing training to several medical professionals across the country. The endeavour aims to help both, the medical fraternity and patients in addressing the problem. Robot has a role in liver surgery as it enhances precision. In esophagus, low rectal and GI surgeries, robotic is quite helpful. In the UK, a nationwide scheme was launched back in 2005 to train doctors and now the region has around 30-40 per cent of its workforce trained in GI and liver cancer procedures. In India, less than 5 per cent of liver specialists are performing laparoscopic GI cancer surgeries, which is quite less compared to the number of patients registering for the procedure across India. Recently, I delivered a keynote lecture in Patna Medical College, and found that out of 200 attendants no one was performing laparoscopic GI cancer surgery. The situation is quite alarming, and it seems that the people of this region are not aware of the benefits of laparoscopic GI cancer surgery.

At what stage are we in terms of awareness and infrastructure? Well, in terms of awareness, I would admit that we lack right from hepatitis B vaccination to regular check-ups, as most of the patients we diagnose are in the advanced stage of the disease. Besides, unfortunately, come a bit late stage and at times at the failure stage. This is an area where we can improve through awareness and education. The cost cannot be brought down beyond a specific limit. In the case of corporate hospitals, the cost of liver transplantation is about 2.25 lakh. There are options such as SGRI, which provide treatment at a lower cost. The best solution is to go for preventive healthcare such as regular check-ups, hepatitis B vaccination, protected sex and a healthy lifestyle. Liver cancer is a ticking time bomb, as the situation after 10 to 20 years is going to be worse.

PROGENITOR CELLS CAUSING LIVER TUMOURS ISOLATED

A University of California research team, which includes an Indian-origin scientist, has isolated and characterised the progenitor cells that give rise to the most common form of liver cancer—malignant hepatocellular carcinoma (HCC). The study’s lead author Michael Karin, PhD, professor of pharmacology and pathology, and colleagues reported that HCC progenitor cells (HcPC) take form within dysplastic or abnormal lesions found in damaged or cirrhotic livers. Study co-author Debanjan Dhar said that their study showed that HcPC are likely derived from dysplastic lesions, can progress to malignant tumours and further demonstrate that their malignant progression to cancer depends upon the environment that surrounds them. A number of factors, including genetic mutations, environmental exposures and lifestyle choices, can contribute to the development of liver cancer. In India, less than 5 per cent of specialists are performing laparoscopic GI cancer surgeries. The cost of liver transplantation is about 2.25 lakh. There are options such as SGRI, which provide treatment at a lower cost. The best solution is to go for preventive healthcare such as regular check-ups, hepatitis B vaccination, protected sex and a healthy lifestyle. Liver cancer is a ticking time bomb, as the situation after 10 to 20 years is going to be worse.

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Non-alcoholic fatty liver disease is quietly on the rise among the adult population, writes Dr Vibha Varma, consultant, liver transplant, hepatobiliary and pancreatic surgery, Kokilaben Dhirubhai Ambani Hospital.

Non-alcoholic fatty liver disease (NAFLD) is the most frequent liver-related disease worldwide and is becoming a public health issue because of its increased prevalence. This is because of obesity (15-30 per cent) and insulin resistance/type-2 diabetes (7-15 per cent) in most industrialised countries. NAFLD is a spectrum of disease which ranges from those with simple fat accumulation in the liver (fatty liver) to inflammation along with fat (non-alcoholic steatohepatitis or NAH) to full-blown cirrhosis (scarring of liver). This liver disease occurs in those who drink little or no alcohol (See figure).

Prevalence of NAFLD is about 15-30 per cent in the Western population, about 58 per cent in overweight subjects, and about 75-98 per cent in those who are obese or non-diabetic and obese. The exact prevalence of NAH is difficult to report as it requires an invasive test in the form of a liver biopsy for diagnosis. However, it is approximately 10-15 per cent of those with NAFLD. About 25 per cent of those with NAFLD progress to develop fibrosis (early scarring) and about 25 per cent of them progress to develop cirrhosis. A minority of these patients with cirrhosis (two to three per cent) progresses to end stage liver disease and liver failure. Patients with NAFLD can develop hepatocellular carcinoma (liver cancer) in less than three per cent (reported on 20 years follow-up) without developing cirrhosis and in those with cirrhosis due to NASH the risk is approximately two to three per cent every year.

### Problems in diagnosis

Patients who have fatty liver alone are generally asymptomatic and the problem is incidentally diagnosed on imaging (ultrasound/computed tomography scan/magnetic resonance imaging). These patients when subjected to liver function tests are found to be abnormal. Patients with NASH and early cirrhosis (fibrosis) are also ‘silent’; it is only in the advanced stage of cirrhosis that these patients show symptoms of weakness, weight loss, fluid accumulation in the tummy, swelling of feet, loss of muscle mass, jaundice, blood vomiting, etc. It is important to diagnose these patients in the early stage when the disease is reversible (fatty liver, NASH and fibrosis), but once there is cirrhosis or liver cancer, the case becomes irreversible and advanced, making the treatment difficult.

One also needs to rule out secondary causes of fatty liver (excessive alcohol consumption, certain medications, nutrition problems, excessive weight loss, starvation, parenteral nutrition, toxins, etc.).

### Diagnosis

**Risk factors:** The exact cause for NAFLD is difficult to pinpoint, however, it is associated with certain medical disorders. Overweight, obesity, high body mass index (above 30), type-2 diabetes, cardiovascular disorder, and patients who have metabolic syndrome are more likely to have NAFLD. Metabolic syndrome is diagnosed when any three of the risk factors are present. The incidence is on the rise because of modern Western nutrition, sedentary lifestyle and genetic predisposition. Initially, there was some observation that NAFLD was more prevalent in urban as compared to rural population, however, this is not true always.

**Blood tests:** Liver function tests will reveal abnormalities (raised liver enzymes).

**Imaging:** Ultrasonography, CT scan and MRI of the abdomen will reveal presence of fat in the liver, diagnose cirrhosis, liver cancer with cirrhosis in the advanced stage of the disease spectrum. There are indices for diagnosing fatty liver.

**Other modalities:** Fatty Liver Index is a score based on four parameters (BMI, waist circumference, triglycerides and gamma glutamyltransferase-a liver enzyme) and is calculated to confirm or to rule out the presence of NAFLD.

Liver biopsy is the gold standard for diagnosing the whole spectrum of liver diseases associated with NAFLD. The invasive nature of the procedure is a disadvantage though.

### Staging of NAFLD

NAFLD fibrosis score (NFS) utilises six factors: age, blood sugar level, BMI, platelet count, serum albumin (a form of protein), and the liver enzymes ratio (AST/ALT). It rules out advanced fibrosis/scarring which is irreversible; this helps in planning the treatment.

FibroMeter is used to confirm advanced stage of fibrosis/scarring. This is based on the analysis of seven parameters (age, weight, fasting sugar, liver enzymes-AST and ALT, ferritin-measure of iron store in the body, and platelet count).

Fibroscan is another non-invasive tool to determine the liver stiffness/stage of fibrosis/scarring.

All these non-invasive measures to assess liver fibrosis are useful before planning for a liver biopsy, which is performed only in those patients where the test is ambiguous.

### Treatment

The goals of treatment in patients with NAFLD are to reverse and improve fatty change and prevent fibrosis/scarring. This is achieved by lifestyle modifications and medical treatment. Lifestyle modifications include weight reduction (about 7-10 per cent weight loss) by physical exercise and dietary changes (plant-based diet rich in fruits, vegetables, whole grains and healthy fats). It improves the liver enzymes, glucose control is better in diabetics, and on liver biopsy the inflammation also regresses.

Medical treatment is required in a subset of patients with NAFLD in the form of anti-oxidants vitamin E and C (prevents progression of fibrosis), and drugs used to treat diabetes (improves insulin sensitivity and liver functions). However, the treatment needs to be given with caution as there are conflicting reports (improvement versus risks) associated with their consumption.

Other therapies include using bile salts, omega-3 polyunsaturated fatty acids, cholesterol lowering agents (statins), prebiotics (non-digestible carbohydrates) and probiotics (liver micro-organisms). These help in taking care of obesity, dyslipidemia, cardiac problems, insulin resistance and intestinal microflora.

Bariatric surgery is used to treat morbidly obese patients (BMI>40 or BMI>35 with comorbidities). It improves the fatty change and the inflammation (NASH) in the liver.

Surgical treatment in patients with NAFLD is a challenge and requires good perioperative care to prevent cardiac and chest complications, which is very common in these obese patients. Definitive treatment in the form of liver transplantation is required in patients with advanced cirrhosis leading to liver failure or when there is liver tumour in a cirrhotic liver.