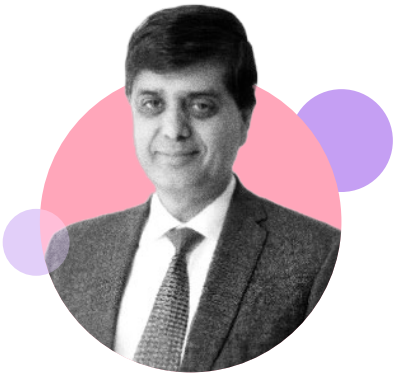

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> **When I left India, there were no transplants happening there, but the UK was doing very well**

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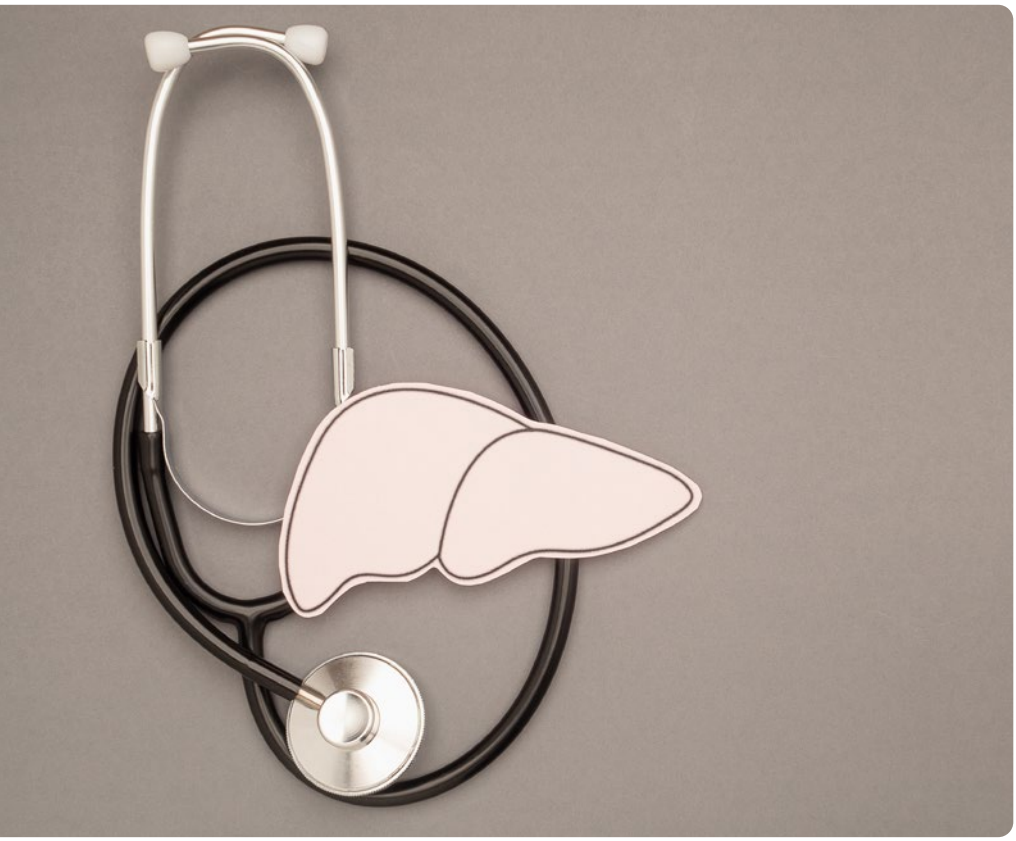
Q1 You have had an extensive and impressive career in hepatology to date, particularly with regard to paediatric hepatology. What was it that led you to specialise in this field in particular?

I started in paediatric hepatology in 1992, when I got a placement at King's College Hospital, London, UK. I graduated in India as a medical student, and then did my postgrad in paediatrics at the Post Graduate Institute of Medical Education and Research, Chandigarh, India. After that, I was exposed to the field of liver disease in that hospital in India. Then I arrived at King's College Hospital, which was, and continues to be, one of the premier level disease centres in the world, for children particularly, as there are very few children's liver centres in the world, even today. The UK is also the only country in the world that specialises exclusively in liver disease in children; other countries have gastroenterology and hepatology as one training programme.

When I started here, I realised that was the field which was progressing, as liver transplantation had just started in the late 1980s. I really embraced hepatology, and realised that this is where the innovations were happening, or would happen in the future. I was also very lucky to have been welcomed by people at Kings, and so, the rest is history.

Q2 How has paediatric liver transplantation changed over the course of your career, both in terms of the treatment itself, and the attitudes around it in hospitals today?

In the 1960s, Thomas Starzl started doing liver transplantation in Denver, Colorado, USA. He was successful, technically, but unfortunately, some of the patients did not survive, so there was a pause. However, in 1984, liver transplantation was accepted by the National Institute of Health (NIH) as a clinical treatment. The problem that children faced before, when transplantation had just started, was that they could only receive whole livers as grafts. This meant that a lot of children died while on the waiting list, as they could not get the right size graft. So, when the techniques to reduce the whole liver to fit in a child, and



> **Now, you can perform a transplant without opening up the patient's abdomen**

subsequently splitting one liver for two patients got established, that made a big difference in reducing wait list mortality.

At the same time, we began to consider who needed a transplant. Previously, we were only doing transplants for children who were going to die in a few months' time, but as a result of the improved transplantation survival rates, we became more liberal. Quality of life became one of the factors when we started deciding who qualified for liver transplantation. If the child was suffering from extreme itch, or if medicines were not helping the child, then they were accepted for transplantation. Then, as we gained more experience, we became even more liberal; previously, we excluded children at high risk, for example, if they had a cardiac problem. Afterwards, even those at high risk could get a liver transplantation. However, the big breakthrough was for children with liver cancer. Previously, the mortality rate for children with liver cancer was >90%. After transplantation was introduced, the survival rate became >90%. We introduced transplantation because chemotherapy was not enough in itself in eradicating the tumour, or making the tumour resectable.

We then started offering liver transplantations for conditions that are not life-threatening in the short-term, but where treating them could improve the patients' quality of life. We also started looking at conditions that are not liver-based, but where a problem in the liver causes problems somewhere else. These patients have a liver that looks normal if you do liver tests, but treatment can protect the brain, or protect the kidneys. For example, in conditions like Crigler–Najjar syndrome, patients have to lie under the lights for 12–18 hours per day, sometimes more. Can you imagine the effect of that on somebody's quality of life? Maybe for a young child, you can leave them, but if they are 10, 15, or 20 years old, what is going to happen? So, that became an indication for liver transplantation. Transplantation over the last 10–15 years has become a very 'well accepted' procedure.

Other innovations have come in as well, like using living donor transplantation. If you look at the countries where organ donation is not very well established, for either logistical or religious reasons, such as in Japan, Korea, China, or India, living donation is the most common mode for transplantation.

For some time, I called liver transplant a 'disease' in itself and not a 'cure'. What we do is we change one disease into another. We take a life-threatening or life-limiting condition; or a condition that is interfering with quality of life, such as itching, or yellow discoloration of the eyes; and we give patients a transplant. But transplantation comes with its own set of problems, the biggest being a lifelong commitment for immunosuppressive medication, because we do not have enough data to show that you can stop it safely. These medications also come with their own side effects. So, the liver transplant recipient is a patient forever again, and I believe we have to support these people with their day-to-day

living. A lot of these adults and young adults do not like taking their medicine. They will stop taking it, or not take it every day, and then they have to go for re-transplantation. We also find that some patients develop mental health problems contributing to poor adherence to medication. If we know their needs, I think we will be in a much better position to assist them.

Q3 You qualified as a doctor in India, and have since worked in the USA and the UK. What are some of the main differences you have noticed in liver transplantation between the places you have worked?

When I left India, there were no transplants happening there, but the UK was doing very well. When I went to Nebraska, in the USA, I was exposed to a new culture, and different ways of practising medicine. However, in terms of surgical techniques, I would not say there is much difference. Healthcare professionals speak to each other formally and informally to deliver the best care possible.

The advantage in the USA is that they have a better donor pool, they have twice the number of paediatric donors compared to the UK per million population. The number of donors on every level overall is higher, and donation consent is twice the UK number. Unfortunately, paediatric deaths are also slightly higher than in the UK.

In India, as I said, there was no transplantation, but I can take some pride in the fact that I was part of the group that helped starting liver transplantation in India. Now, India's transplant programme is really one of the biggest in the world, and the results are very good too. The majority of liver transplant procedures are from living donors, but outcomes are no different than in the UK. I visit India regularly, I teach online, and I attend meetings. As part of continued education, I have hosted a lot of doctors, not only from India, but also from China, South America, the Middle East, and Africa, to provide training into new aspects of liver disease management and transplantation.

Q4 Tell us a little about the Dhawan Lab at King's College London, how it started, and the work that goes on there

My mentor, who helped me to establish my career, believed that we, as clinicians, need to be researchers and academicians, and we need to understand mechanisms of disease. When I came back from the USA, I had been exposed to a treatment that was just emerging in Nebraska: hepatocyte transplantation where you do not replace the whole liver, but you replace the cells of the liver, like a building is made of millions of bricks. A liver is made of billions of cells, so the functional unit of the liver is a little cell. It does all the work; it synthesises proteins and detoxifies toxins. The hypothesis was that, if we could

replace the cells, rather than the whole liver, we could get away with many problems of whole liver replacement.

We started the Dhawan Lab in 2000. We were awarded a grant by the National Lottery Charities Board and the Children's Liver Disease Foundation of UK, which allowed us to start research into hepatocyte isolation and transplantation. We succeeded in setting up the lab, and in treating certain metabolic conditions, but the problem we faced was that the treatment we were giving was not lasting long enough. It was lasting 16–18 months, likely because these cells were being destroyed by the immune system despite immune suppression, and these people would then opt for liver transplantation. We were not alone with this problem. Other centres in Pittsburgh, Pennsylvania, USA; Valencia, Spain; Hannover, Germany; and Brussels, Belgium, all realised that longevity of hepatocytes was the problem. We went back to the lab, where we looked at animal experiments, and found a protein we used called α-1 antitrypsin, which can improve the quality and engraftment of hepatocytes. Clinical trials will inform us if it will be of clinical benefit. Another life-threatening liver condition is acute liver failure, where only proven treatment is liver transplant. Our lab developed a novel treatment for the first time in the world to treat children with acute liver failure. The treatment involves embedding liver cells and coating them with alginate, an algae product that is available for medicinal use. We set all of that up in our lab, did all the work that we needed to, got the approvals, and then used it in patients. Essentially, the lab is looking at treating diseases, and at the same time looking at the mechanistic side of liver disease.

Q5 Could you briefly explain to our readers a little bit about the process of hepatocyte transplantation, and the benefits of using this method instead of liver transplantation?

As I mentioned earlier, the hepatocyte is a single functional unit of the liver, and there are billions of them. We are using hepatocyte transplantation for conditions that are single gene defects in the liver. Currently, the liver cells we are getting are from livers that are either not used, or are only partly used for liver transplant. Sometimes, even though the liver is not suitable, we can use the liver for cell isolation, and sometimes it is reduced to suit the patient's liver size, and some is left over. Unfortunately, some newborn babies pass away, and their livers are not suitable for transplantation because their vessels are very small. We evaluated these cells in the lab, which proved that the cells isolated from a newborn baby's liver are very effective in terms of quality and durability.

Essentially, hepatocyte transplantation can be used for conditions that currently require liver transplantation. Then, you indirectly expand the donor pool, as one liver used for cell isolation can be used in two or three patients, or more. Otherwise, one liver goes to one or two patients. That is definitely a benefit. Another benefit would be that it is less invasive. Additionally, hepatocyte transplantation is futuristic because, if the gene therapy were to become available tomorrow, then these patients could still have it. Otherwise, if you have a liver transplant, then you would not be able to have gene therapy for many liver based conditions. We are looking to the future, rather than only the immediate effects. I think that, once you have taken off the initial establishment costs, it will be a lot less expensive, as well as a lot less invasive.

Q6 What do you think are the most exciting developments happening in the world of hepatology at the moment?

Developments in hepatology can be divided into many subgroups: diagnostic hepatology, therapeutic hepatology, and surgical hepatology. In terms of diagnosis, we are moving away from liver biopsy, and going more towards liquid biopsies. Previously, we did biopsies for most patients, now, not so many. The second is small molecules. Previously, to improve quality of life, we gave patients liver transplantation for cholestatic disorders, but now we have medication that can help with itching so dramatically that we avoid liver transplantation. New antiviral medications have changed the outcomes of viral hepatitis C and B patients.

Moreover, robotic surgery has made a big difference. Now, you can perform a transplant without opening up the patient's abdomen and without leaving a big scar. Some centres are even looking at whether they can implant a liver with a robotic arm, and those who have undergone this surgery report less pain, shorter hospital stays, and a much smaller scar size. Things are moving and developing all the time. A lot of work is also being done in immunosuppression and the ways to avoid it.

Future understanding of AI will help early diagnosis and management of liver diseases, like all other health conditions.

And finally, as stated by Thomas Starzl: "History of medicine is such that what was inconceivable yesterday becomes a routine tomorrow."