

# A New Liver A New Hope

When there is no cure, transplantation is often the only hope for liver cancer patients.

BY IDELLE DAVIDSON

**T**HE MAN LYING ON THE OPERATING TABLE at Johns Hopkins School of Medicine was in a coma, brought on by a rare reaction to a prescribed drug. His liver had failed him. The next few hours would determine his fate. An attending surgeon stood by, scrubbed, ready, and more than a bit nervous. This was his first week on the job. The

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young doctor took a deep breath to steady his nerves and began what would be the first liver transplant of his career.

Now 19 years and more than 500 liver transplants later, Andrew Klein, MD, MBA, is director of the Comprehensive Transplant Center at Cedars-Sinai and the former chief of transplantation at Johns Hopkins. To this day he likes to joke about that rite of passage, claiming with a wink that the nurses talked him through his first transplant while reading from an instruction manual. In reality,

he finessed the procedure. Not only did the patient live, but he and Dr. Klein remain fast friends. They scuba dive together at least once a year. There is a beautiful symmetry in that, Klein says. “In 1988 his life was in my hands. But when we’re buddies at 100 feet under the ocean, my life is in his.”

Today, Dr. Klein and his team at Cedars-Sinai focus on all forms of liver disease. He is especially excited about novel treatments for primary liver cancer, or hepatocellular carcinoma (HCC). Cancer affecting the liver is more commonly metastatic cancer, which occurs when tumors from other parts of the body spread (metastasize) to the liver. For instance, cancers of the colon, lung, or breast, among others, can spread to the liver, but since they retain the same cellular characteristics of their origin, they are not treated as primary liver cancers.

Primary liver cancer begins in the cells of the liver itself. Most people don’t show signs and symptoms in the early stages of liver cancer. It is therefore rarely discovered early and generally doesn’t respond to



Dr. Andrew Klein stands behind a scan showing a cancerous liver. “Our one focus is this: to take individuals whose livers are failing and diseased and restore them to health.”

current treatments. The prognosis is often poor. “Not too long ago, liver cancer was a death sentence,” says Dr. Klein. “Now with transplantation, we are offering patients real chances at being cured.”

Liver cancer is the fourth most common cancer in the world. One million new cases are diagnosed each year. It will claim the lives of about 17,000 Americans

in 2008. That number is rising because of an epidemic of hepatitis C and B viruses in this country which predispose people to develop liver cancer. “We expect the viruses to reach their peak only 10 years from now, so we are unfortunately going to see a steady rise in these tumors as well,” says Dr. Klein.

The reason hepatitis and other

chronic diseases such as alcoholic liver disease can lead to cancer is that they cause cirrhosis, or scarring. The liver is constantly inflamed. “It is like cutting yourself in the same place every day for the rest of your life,” says Dr. Klein. “Eventually the cells involved in the healing process may go haywire.”

It is precisely because cirrhosis is present in most patients with liver cancer that surgery to remove tumors in these individuals is generally not an option. “You can’t safely cut out a tumor because scarring will reduce liver function,” says Dr. Klein. “Patients would bleed to death or go into liver failure.” But HCC patients with otherwise healthy livers often do undergo surgery. “It is a big operation, but that is the procedure of choice,” he says.

Yet even surgery does not always cure the cancer, says Fred Poordad, MD, chief of hepatology at the Cedars-Sinai Center for Liver Disease and Transplantation. “The recurrence rate is 70 percent by the five-year mark in liver resection of non-cirrhotic individuals,” he says. “So the sole truly curative procedure for liver cancer is transplantation.”

**U**NFORTUNATELY, NEARLY 17,000 people in the U.S. are currently on liver transplant waiting lists, but only about 5,000 organs from deceased donors become available each year. “Patients are dying while waiting,” says Dr. Klein. “Many thousands of others are experiencing a severe decline in their quality of life.”

This year, Dr. Klein—along with fellow Cedars-Sinai surgeons Steven Colquhoun, MD, director of Liver Transplantation and Surgical Oncology, and Nicholas Nissen, MD, assistant surgical



Dr. Steven Colquhoun holds one of his favorite photographs, in which he poses with his son on his shoulders and seven of his patients, who all have received lifesaving liver transplants.

director of the Multi-Organ Transplant Program—will perform about 70 liver transplants. About one-fourth of those patients will have liver cancer along with hepatitis C, hepatitis B, or another underlying disease. The largest group receiving a transplant will be patients with hepatitis C, but without cancer.

Because there are not enough livers for every patient who needs one, the United Network for Organ Sharing (UNOS)—the organization that administers the nation's policies on organ transplantation—now also reviews and designates institutions as live-donor-liver

transplant centers. In 1999, Cedars-Sinai was the first medical center to receive this UNOS designation. This allows family members or other volunteers to donate a part of their liver to save someone's life. Usually doctors take the right side, which is about 60 percent of the liver. Remarkably, the liver begins to regenerate within 24 hours. It is of normal size within three months postsurgery.

"This is a major operation and clearly there are risks involved. We have to evaluate the donor very carefully to make sure there are no health issues, not even little ones," says Dr. Klein, who

serves as the vice chair of the UNOS Living Donor Transplantation Committee. "The number one thing we are taught as doctors is, 'First, do no harm.'"

"Living-donor liver transplantation is not appropriate for all patients and it is not the answer to the organ shortage," says Dr. Colquhoun. To date, surgeons at Cedars-Sinai have performed about 40 of these procedures and just five for patients with HCC.

Patients are generally categorized into three groups, says Dr. Colquhoun. First are those who are very ill and at the top of the waiting list. They will

likely receive a deceased donor organ. At the other end are those who are not especially ill and can safely wait. "It is the middle group that is really suffering," Colquhoun says. "Unfortunately they will need to become much worse before they are likely to get an organ offer." It is these patients who are generally considered good candidates for living-donor liver transplants.

**A**s Dr. Colquhoun sits at his desk, the afternoon sun streams across the credenza, landing like shimmering particles on a black-and-white photo. The image shows Colquhoun with his young son perched on his shoulders. They are posed with a group of men and one woman, each flashing a bit of skin. "All those people have received liver transplants. We were lining up to take the picture and at the very last second, unbeknownst to me, they lifted their shirts to show off their scars," he says, laughing. Most are grinning like goofy kids pleased with their antics, in what is clearly an affectionate tribute to their surgeon.

"The thing that is as dramatic for me today as the day I started is seeing the recovery in these patients," he says. "At first you see they are sick in more ways than you can believe. They are yellow, they look like skeletons wasting away, they have lost their hair, their kidneys might be failing, they are not thinking clearly," says Dr. Colquhoun. Then within weeks after transplant, they have put on weight. Their faces are rosy. They are healthy. "It is an unbelievable transformation," he says. "They are back at work. They have normal lives. I see that daily, whether the transplant is for liver cancer or for anything else. It feels really good."

Although Drs. Klein, Colquhoun, and Nissen specialize in liver transplants, other teams at Cedars-Sinai perform liver-kidney, heart-kidney, liver-double lung, and heart valve-liver transplants. In 1998, Cedars-Sinai conducted the first heart-liver transplant in the Western states. The surgery is so rare that only about 40 have been performed in the U.S. "That combined transplant is something that distinguishes us from most other places on the

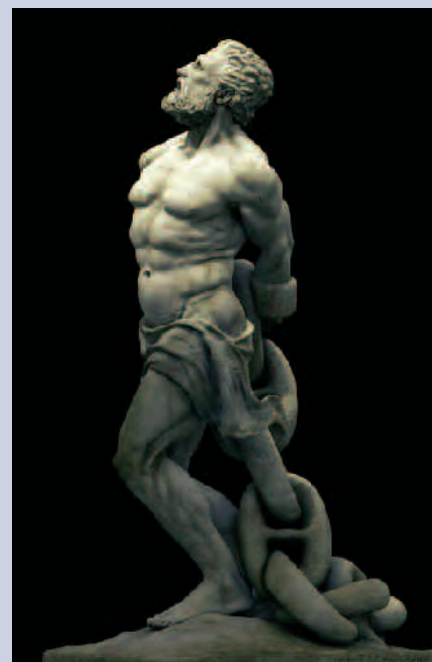
planet," says Dr. Colquhoun. In fact, just months ago, two organ transplant teams performed Cedars-Sinai's second such procedure. Dr. Colquhoun, the lead liver surgeon, and Dr. Alfredo Trento, lead heart surgeon, took on this very high-risk procedure to save the life of 22-year-old Kelli J., who is now home and recovering well.

"Traditionally, the type of treatment someone receives for liver cancer depends on where their primary doctor

**T**HE LIVER IS AN AMAZING ORGAN, THE LARGEST IN THE HUMAN BODY.

Located on the right side of the upper abdomen, its complexity is rivaled only by the brain and affects every other organ system. It plays a major role in metabolism. It breaks down almost everything we ingest, including medications. It controls our levels of cholesterol and regulates sugars. Unlike the vital heart and kidney, the boomerang-shaped liver does not wear out. "You can take a liver from a 70-year-old person and transplant it into a 30-year-old patient," says Dr. Klein. It also self-adjusts. A liver that is transplanted, but is too small for the person who receives it, will grow bigger; if too big, it will shrink.

Scholars speculate that even ancient civilizations may have known of the liver's regenerative properties. In Greek mythology, the gods chained Prometheus to a rock for revealing fire to humans. A predatory bird, perhaps a vulture, attacked Prometheus and pecked out his liver. Each day the liver regrew, and the bird returned in eternal punishment.





Dr. Mark Friedman (background) performs chemoembolization on a patient with liver cancer. The screen in the foreground shows a catheter being inserted into the hepatic artery.

sends them, says Dr. Klein. “The old saw is, if you go to a barbershop, don’t be surprised if you get a haircut,” he says. “We are unique in that we emphasize a multidisciplinary team approach to this disease.”

**A** **AT CEDARS-SINAI, SURGEONS, ENDO-**crinologists, oncologists, nuclear medicine doctors, hepatologists, and radiologists work collaboratively to come up with a treatment plan for each patient. “We look at the size of the tumor and the comorbidities of the patient,” says Dr. Klein. “For example, does the patient have diabetes or hypertension? We determine the risk of surgery versus transplantation. We are completely patient focused.”

It all starts with diagnosis. “In my opinion, we have the best and most sophisticated imaging center around,” says Dr. Colquhoun, who is particularly proud of the quality of Cedars-Sinai’s magnetic resonance scans (MRIs), which provide computer generated images of the liver. “You can see all the blood vessels and the bile ducts with such clarity. It just takes your breath away.” Doctors also use illuminated optic scopes to check for tumors in other areas of the body. One is a little camera, called a wireless capsule endoscope. Patients swallow the device, which travels through the small intestine and transmits images to a receiver. It is then safely excreted. “It is like something from *The Jetsons*,” says Dr. Colquhoun.

Often, while liver cancer patients are waiting for a transplant, they will undergo surgery to remove the tumor, along with regional chemotherapy. “Theoretically, we extend their life span in hopes that they will make it to a point where they can receive a liver,” says Marc Friedman, MD, chief of Vascular and Interventional Radiology

at Cedars-Sinai. One form of therapy is called chemoembolization. Under X-ray guidance, the interventional radiologist inserts a tiny catheter or tube into the hepatic arteries that supply the liver and delivers high-dose chemotherapy

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directly into these blood vessels. The doctor then injects tiny sponges into the blood vessel, cutting off the blood supply feeding the cancer. In effect, the tumor starves to death. Radioembolization is another technique.

It delivers tiny radioactive glass beads directly into the blood supply of the liver tumor. They lodge in the tumor and kill it locally, perhaps with fewer side effects than with regional chemotherapy.

Unfortunately, regional cancer therapy is considered palliative. It does not cure the cancer, but reduces the amount of disease and lessens symptoms. “Chemoembolization can be really effective at killing the

tumor,” says Dr. Colquhoun. “So why is it not a cure? Because you still have the underlying disease that created the tumor. The liver is fertile soil. Where there is one tumor, others may grow.”

Ultimately, says Dr. Klein, the goal is to rejuvenate liver function. “Today that might be through transplantation. Three years from now, you may see artificial livers. Ten years from now, transplanted cells may grow a whole new liver,” he says. “Our one focus is this: to take individuals whose livers are failing and diseased and restore them to health.” ●●

## CLOSING IN ON ARTIFICIAL LIVERS

**SINCE THE 1940s, WHEN THE FIRST** functioning artificial kidney was invented, dialysis has saved the lives of tens of thousands of patients with kidney failure. The machines remove waste products from the body and maintain safe levels of chemicals in the blood. But for patients in liver failure, this technology is still in its infancy.

A bioartificial liver developed by researchers at Cedars-Sinai Medical Center reduced mortality significantly among patients suffering from acute liver failure, according to a clinical trial conducted five years ago at 20 centers in the United States and Europe. With a complex filtering system that incorporates liver cells from pigs, the bioartificial liver cleanses and nourishes the blood to prolong life while an injured liver recuperates or a donor organ becomes available for transplantation.

Another device, called the SEPET™ Liver Assist Device, developed by Arbios Systems, Inc. of Waltham, Massachusetts, is currently undergoing clinical investigation at Cedars-Sinai Medical Center in patients with advanced chronic liver disease.

“I am very hopeful that this will have broad applications, not necessarily to cure people with liver disease but to serve as a bridge until they can undergo liver transplantation,” says Fred Poordad, MD, chief of Hepatology and Liver Transplantation at Cedars-Sinai and principal investigator of the trial. This form of liver support may also allow the liver to heal and regenerate in cases of acute liver injury or in which patients may not be eligible for transplantation.

During liver failure impurities accumulate in the bloodstream, which affects almost every other organ system and can culminate in overwhelming infection

and death. SEPET comprises a sterile, disposable cartridge that works with a standard blood dialysis machine. It contains tiny hollow fibers and synthetic membranes that remove harmful impurities such as ammonia from the bloodstream. Blood passes into the machine and returns to the patient, cleansed of toxins. Results from the clinical trial are thus far encouraging. Many patients experienced an improvement in overall liver function. In particular, doctors noted less encephalopathy, a condition that causes behavioral changes and confusion because of the buildup of toxins. “It is still too early to provide definitive results since we are just in phase I of the trial,” says Dr. Poordad. “But so far the device appears safe and effective.”

— I.D.