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BARRY BRENNER CHANGED THE WAY KIDNEY DISEASE IS TREATED AND UNDERSTOOD

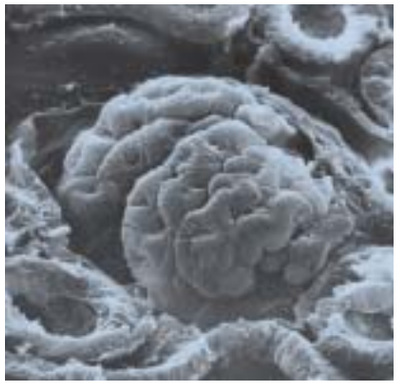
BY ERICA LLOYD

A BIG BANG

It was bound to happen. A renal fellow at Boston's Brigham and Women's Hospital—in all likelihood, someone new to the division—would give a presentation at the weekly research conference.

Let's say the analysis was not well thought through or the data were questionable. At the end of the presentation, Barry Brenner (MD '62), the Brigham's formidable renal division director, would rise and crumple the fellow's handout into a ball, saying, "You've just wasted 40 man-hours on this dreck."

Worse was when he didn't say anything—just stood, balled up the paper, and slam-dunked it into the wastebasket on his way out.



COURTESY BRENNER

Brenner showed that glomerular failure lies at the root of nearly every renal disease.

PHOTOGRAPH | JIM HARRISON

Tough audience. Brenner also required his fellows to rehearse their papers for upcoming conferences in front of the division. If you did okay at that high-voltage session, the "real" conference presentation was cake, recalls Mark Zeidel, who trained under Brenner and is now the chair of medicine at the University of Pittsburgh: "Barry was a much harsher critic than anyone you'd run into at the meeting, and some of them could be pretty harsh."

Brenner, the Samuel A. Levine Professor of Medicine at Harvard Medical School, is known for his uncanny ability to synthesize information and determine what's important. He gets impatient with mediocrity and sloth, whether he sees it in fellows, waiters, taxi drivers, or the Red Sox. Still, even trainees who've made his ears turn red with fury will tell you Brenner is a generous—and they always speak of him as generous—teacher and mentor. The word around Boston: *Once you're Barry Brenner's fellow, you're always Barry Brenner's fellow.* He's interested in making opportunities for people, helping them in their careers, notes more than one trainee and colleague. He didn't build what is considered to be *the* finishing school for nephrologists merely by being impatient or tough. And under Brenner, Brigham's division grew to be the largest in the world.

He trained "some of the really great renal physiologists," says Julian Seifter, associate professor of medicine at Harvard. Among the 200 or so former Brenner fellows: Tom Hostetter of the National Institutes of Health, Bryan Myers at Stanford University, Iekuni Ichikawa at Vanderbilt University, Zeidel at Pitt, and dozens of other heads or former heads of medicine and of renal centers around the world. Now, Brenner notes, since he stepped down as division director two years ago, he has one fellow: "Me. And I don't get any trouble," he says with a wry smile.

At renal conferences, it's not unusual to see people seeking out Brenner to ask him to autograph his textbook *The Kidney,* which he originally coedited with Floyd Rector. (Brenner is working on the seventh edition.) There are reports of fans having autographed pages laminated and of hanging framed photos of the renal celebrity in their offices. Besides *The Kidney,* Brenner has edited several other well-received books, journals, and served on almost 30 editorial boards. He's an author on 600 papers.

"Many of ... the commandments of renal physiology started with him," says David Mount, assistant professor of medicine at Harvard and an investigator at Brigham.

"Barry Brenner is probably the world's top nephrologist," notes longtime friend John Dirks, president of the Gairdner Foundation, chair of the International Society of Nephrology's commission for global advancement, and a professor emeritus at the University of Toronto.

"What he's done won't shut down dialysis centers but will slow them down."

The Brenners of Brooklyn were taken aback when their son said he wanted to go into medicine. No one in the family had ever gone to a four-year college. Now their boy, who'd graduated early from a commuter college, Long Island University, was being invited around the country for med school interviews. Brenner remembers his first time on a plane, a puddle jumper that took him to an interview in South Carolina. It was the same day Sputnik was launched; he peered out the window, wondering if he might catch a glimpse.

Eventually he landed at Pitt's School of Medicine. Shortly after his arrival, he spotted a "super genius" from his high school. Panic washed over him: *My God, how am I going to compete if everyone is at this level?* (The genius from home eventually dropped out of the program.) Brenner moved into a room in Salk Hall. Other medical students stayed there, as did the football team. Day and night the teammates called out plays to each other. More interesting was listening to Brenner's next-door neighbor, classmate Albert Braverman (MD '62)—"a really superior intellect. Whatever he said, you learned something. Albert would be in his room listening to all this great music and smoking French cigarettes and not being able to put down his Thomas Mann or Immanuel Kant. All I liked to do was memorize *Gray's Anatomy.*"

That's an odd thing to hear from a man known today as an aficionado of fine wine, gourmet cuisine, Schubert, and Klee, who delights in sharing such pleasures with friends and family. But Brenner the freshman had promised his parents he would get a scholarship; and after all he was there to learn medicine. So despite the distractions of the Panther playbook and great philosophy, Brenner stayed the course. He ended up doing so well on his first two anatomy exams, Professor Rosenthal thought he might be cheating. *What is it, son, that you're trying to do?*

Brenner realized he could ease up a bit. But letting-up Brenner style translated to volunteering in Harold Segal's and Abraham Braude's labs; starting a program for a group of sophomores to work in the pathology lab of Joseph Feldman (where they duplicated famous Frank Dixon experiments); moonlighting at small local hospitals; and signing up for the most rigorous rotations, which meant having Jack Myers and Thaddeus Danowski in medicine as attendings.

"Myers was scary. In those days, when you presented to the attending, everybody stood at the bedside. And you didn't use notes; you stayed up all night until you were ready," says Brenner, adding that Myers taught him "a standard"—"He was precise in a way that I'd never encountered before."

Likewise, Brenner must have impressed his attendings. When he graduated, he was handed the George Heard Memorial Prize in Medicine.

As an intern at the Albert Einstein College of Medicine, he became engrossed with Strauss and Welt's *Diseases of the Kidney.* Anyone hoping to really understand this organ needed to tackle ion transport, biophysics, biochemistry, thermodynamics, and then some. During Einstein's famous daily conferences (known as "morning prayers"), where residents were expected to give presentations on scholarly subjects rather than on cases they saw the night before, Brenner talked about the kidney. One morning when Brenner was presenting, someone had invited Robert Berliner, of the National Institutes of Health's famed renal and electrolyte lab, to sit in. Afterward, the distinguished guest asked Brenner: "What are you doing with the rest of your career?"

After his ascension at morning prayers, Brenner ended up spending a few fruitful years with Berliner at NIH. In 1969, he was recruited by the University of

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California, San Francisco, where he started a renal program for the VA hospital. That's where he heard about a curious strain of rats in the Munich lab of Klaus Thurau. For some reason, these animals had cherry red spots on their kidneys. Thurau was stumped. He couldn't figure out what the spots meant. Brenner asked if he could have a look.

Thurau sent a dozen rats to San Francisco. (Only 11 arrived, leading Brenner to wonder what essential 747 cables the escapee might have gnawed away.) It didn't take long for Brenner to realize that the mysterious spots were glomeruli, popping up on the cortical surface of the kidney. Here was a terrific opportunity: Each kidney is filled with a million microscopic nephrons that filter blood. Each nephron is made up of a narrow tubule, on one end of which is a roughly cauliflower-shaped pack of capillaries, the glomerulus. "The wisdom of the kidney," as Brenner puts it, is in how it interprets signals from your body to figure out, no matter what you have for lunch, which ions, toxins, and the like should end up in your urine and which your body needs to reclaim. In the nephron, this process begins in the glomerulus. And until Brenner came across these peculiar rats, most investigators focused on the role of the tubule, paying little attention to the nephron's other end. Scientists didn't know much about the glomerulus because they couldn't get at it; in mammals, glomeruli are usually buried in the kidney. They don't appear on the surface.

So now Brenner had these bizarre animal models plus a novel micropuncture instrument he'd brought with him from NIH that he planned to use to measure pressures in tubules. He changed his plans. Time to concentrate on the glomerulus. No one knew, for instance, at what pressures the arterial tree pumped fluid across the walls of the glomerulus. Brenner's team (including physician Terrance Daugharty and chief technician Julia Troy, who retired from his lab only recently) found the pressures were much lower than everyone thought.

There was one thing Jane Brenner had to resign herself to: Usually around 3 a.m., her husband would wake up with a revelation, maybe a better title to his latest paper, maybe a new way of looking at physiology. Trusting nothing to memory, he would write it all down on a stack of index cards he kept on his nightstand. Those index cards brought forth a storm of breakthroughs—from mathematical models of glomerular pressure to defining the exact process of urine formation. They also helped crystallize for Brenner an understanding that would change the way kidney disease was approached, promising to better the lives of millions.

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As it turned out, problems with tubules were not the primary cause of kidney disease, glomerular failure was. Brenner's team found that when the kidney is injured, some glomeruli are damaged, and the others take up the slack. Their pressure level goes up, so they form more filtrate. That higher pressure damages the glomeruli that are helping out. "It leads to a vicious circle of progressive injury," notes Brenner. "This second wave of injury is not caused by the original disease; it's caused by the adaptation—which is common to every kidney disease." It became clear: To allow the kidney to survive longer, one needed to lower glomerular pressures. The best way to do that, Brenner found, was with antihypertensive drugs like angiotensin-converting enzyme inhibitors (ACE inhibitors). Low protein diets also helped slow renal deterioration. (Several scientists, including Brenner, suspected protein injured tubules.)

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He recently completed definitive clinical trials on antihypertensive therapies: "Now I can close my lab," he says, satisfied.

Today this eye-opening explanation of the vicious cycle inherent to chronic renal diseases is widely known as the glomerular hypertension theory, or Brenner's theory. Brenner refers to it as his "big bang."

"What he has done eventually will help millions," says Dirks. "If you just take diabetes, 200 million people have it worldwide. Probably one-third of them will get kidney disease."

"There certainly are people who did a lot of work in the glomeruli," says Zeidel. "But Barry basically defined how the glomerulus works, how it is destroyed, how it is damaged in various kinds of disease, and developed the only effective means we have to slow the damage that happens in the glomeruli. The scope of his contribution is almost unheard of in physiology."

ABOVE: China, 1998. Brenner traveled extensively on behalf of the International Society of Nephrology.

COURTESY BRENNER

One Brenner family joke (there seem to be a lot of them) goes like this: An old man falls from the curb onto the street, hitting his head. Onlookers rush over to help; one asks: "Mister, are you comfortable?" The man says, shrugging and raising his hands, "I make a living."

Robert Brenner and his sister, Jennifer Ash, have heard their dad tell that one umpteen times. There was a time, about a decade ago, when they didn't feel so much like joking: Barry Brenner was in post-op from bypass surgery. The family was concerned. Dad had made it through the operation, but bypass patients sometimes experienced decreased mental acuity. Robert Brenner, who's also a nephrologist, wondered, would his dad have the same razor-sharp wit? Would he be the man he'd always known?

When the family went to visit him after the procedure, they saw their patriarch on a ventilator with tubes pumping fluid into him and draining it out. A nurse was in his room, attending to him. As she wiped his brow with a cloth, she asked, "Dr. Brenner, are you comfortable?"

The perfect setup line.

The patient slowly shrugged his shoulders, then raised his hands.

He was fine. ■