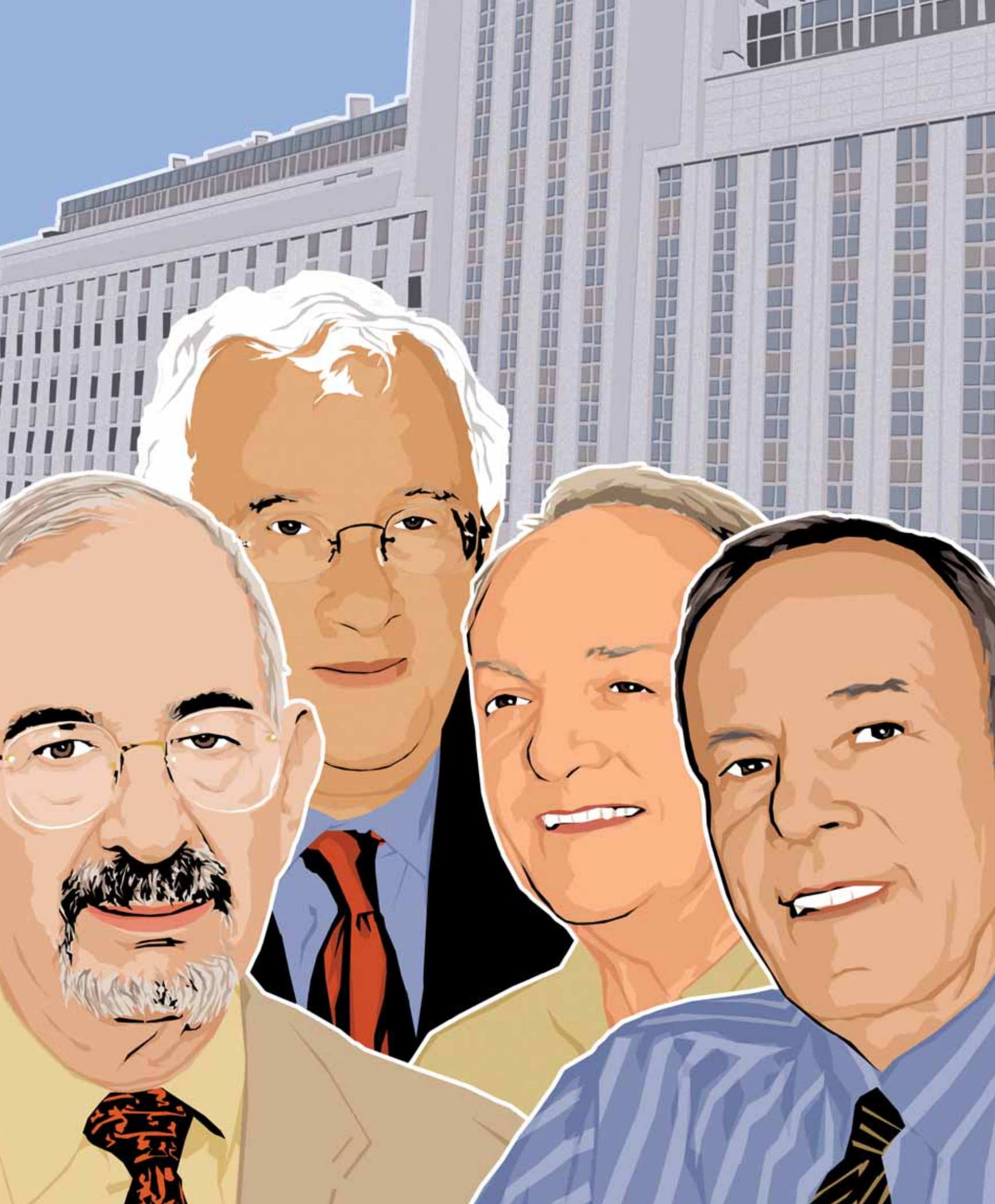

45 YEARS OF DISCOVERY LATER

INTERVIEW BY SHARON TREGASKIS

DEFINING MOMENTS

The University of Pittsburgh medical school's Class of '62 trained in the shadow of giants—biochemist Klaus Hofmann, pathologist Frank Dixon, internist Jack Myers, Jonas Salk and Julius Youngner of the killed-virus polio vaccine, surgeons Henry Bahnson and Albert Ferguson. Molecular biology was an emerging field, and even first-year students could contribute to the explosion of knowledge. Nearly half a century after they earned their degrees, four members of the Class of '62 recall moments that shaped their careers and reflect on the life of the physician-scientist, a profession some have called endangered.

Brooklyn's SUNY Downstate Medical Center professor of medicine **Albert Braverman**, a hematologist-oncologist, has investigated breast cancer treatment, thalassemia, and sickle-cell disease. Braverman's credits include medical publications as well as literary analyses of the works of Thomas Mann and Robert Frost. Director emeritus of the renal division at Brigham and Women's Hospital **Barry Brenner** is the Samuel A. Levine Professor of Medicine at Harvard University. He authored the textbook *The Kidney* and defined the role of the glomerulus in chronic

Four standout classmates talk about a life of discovery. FROM LEFT: Albert Braverman, Barry Brenner, James Kushner, and John Hibbs.

ILLUSTRATION | ROB KELLY

renal diseases. **John Hibbs** is Distinguished Professor of Internal Medicine and chief of the Division of Infectious Diseases at the University of Utah in Salt Lake City, where former classmate **James Kushner** is the M.M. Wintrobe Distinguished Professor of Internal Medicine and heads the Division of Hematology. Hibbs garnered a Nobel Prize nomination for teasing out the biochemistry of nitric oxide. Kushner serves as director of the University of Utah's Center of Excellence in Molecular Hematology; he delves into genetic disorders of iron metabolism.

These far-flung old friends gathered this winter through teleconferences. Here we share excerpts of two recent conversations.

PM: What do you remember of one another as students?

Kushner: My most striking memory of Albert Braverman involves incredible glassware breakage during biochemistry lab. He smoked Turkish cigarettes.

Braverman: Gauloise. My wife is Turkish, but I don't smoke anymore.

Brenner: Albert and I were in adjacent rooms on the eighth floor of Salk Hall. Having him as a next-door neighbor was one of the great enrichments of my young life. He carried an aura of goodwill that spread to everyone he met and touched.

Hibbs: We would often eat together in the cafeteria at Scaife Hall and have these wonderful, free-ranging discussions, always intellectual.

Brenner: On Friday nights, we'd go down to Cantor's in Oakland. It was $2.95 a dinner. Not much wine was poured, but they did have wonderful food. Those dinners were probably three hours.

Braverman: I came to medical school interested in psychiatry. Because of Barry, my interest turned to science. He was the first person I knew personally who had an intellectual interest in science and clinical medicine. John had intelligence, breadth, moral rectitude, seriousness, and good humor. It was a tremendously enriching time.

Brenner: John was tall, very handsome, casual in appearance. Never the type to interrupt, he'd just let you talk and then he'd respond. Jim was very smart, witty. Pitt was my first away-from-home experience. Right from the start, Jim, you were in an apartment.

Kushner: I lived on the second floor of a funeral parlor on Negley Avenue. In the evening, I and my roommate—Eduardo Delgado (MD '60)—would cruise through the salons and, instead of supper, eat all the chocolates that were set out for the mourners.

Brenner: But did you have any embalming responsibilities?

Kushner: Barry, I remember you were very funny, with round glasses and an ability to incorporate knowledge at a tremendous pace. Medical school seemed very easy for you.

Brenner: I spent that whole summer before medical school working in the post office. The foreman told me, "You better do well in medical school because you wouldn't have any future here." I was motivated, having been cut off from this other opportunity.

Braverman: I was a very successful message runner on Wall Street. That career was open to me.

Kushner: Barry, you were commenting that John was a casual guy. John is a hopeless romantic. He sees drama and romance everywhere, particularly in science. I remember when he was first discovering the pathway from L-arginine to L-citrulline and nitric oxide, and how macrophages got activated. It was like listening to the most wild-eyed guy in Union Square standing on a soapbox.

Braverman: I remember John's macrophage paper. I had my doubts about the immunotherapy of cancer, and here I saw this paper in *Science*—and from macrophages and cancer came an overwhelmingly important discovery [the mechanism for formation of nitric oxide in the human body] that was completely separate.

Brenner: John should have received the Nobel.

Kushner: He couldn't. He doesn't have a tie.

Brenner: I would not have guessed, from the four years we were in medical school, that John Hibbs was destined for a career in basic science. John, tell me why I missed it.

Hibbs: When I was in medical school, I didn't do any science other than our laboratories—biochemistry, physiology, etc.—the smells and the activity seemed far removed from clinical medicine and what we were learning from the textbooks and professors.

Braverman: When did it change for you?

Hibbs: Jim and I were both drafted when we were interns. There was a hemorrhagic fever epidemic that began in eastern Bolivia, and I volunteered to go down and work with some scientists from the NIH. It was physical adventure, but the research turned out to be intellectual adventure.

There's nothing more stimulating than working in a basic research laboratory, once you learn how to use the scientific method. It's so powerful, so basic, and it's the rigorous testing of knowledge that separates science from superstition, from ideology, theology. It doesn't produce absolute truth, but it gets us closer. There's so much excitement in seeing things for the first time.

Kushner: See what I mean about him being a romantic? I found my transforming event in the pathology laboratory experience with Frank Dixon [the pathologist who showed that the immune response could cause disease].

Brenner: One of my interviewers was [molecular biochemist] Harold Segal. Not only did he set in motion my acceptance letter, but with it came an invitation to start work in his laboratory on the day I started medical school. I sent off a manuscript in January of my first year. It has my name as B. Morton Brenner. I went through this affectation that lasted only as long as that paper. Someone said to me, "Oh my god. I've been calling you Barry. I should call you Morton." I said, "Never mind, I'll change my name back."

PM: What was Pitt like then?

Braverman: This was the decade in which molecular biology came into being. The microbiology course was where we heard about tRNA and mRNA and all the things that were coming out then, where we got the foundation.

Brenner: I think it was the virology component, Al. Julius Youngner was giving these lectures where it was as if he would read a paper and the following week, the material was incorporated into the lecture. There was almost no dwell time.

We got to do that serum sickness experiment under [pathologist] Joseph Feldman's guidance.

Braverman: Low titer, medium titer, high titer. Medium titer did it.

Hibbs: The School of Medicine had gathered together a unique group of human beings both in basic science and the clinical years. It was like Athens during its heyday or Florence during the Renaissance.

Braverman: One person was more unique than the others. [Department of Medicine chair] Jack Myers was a force in Jim Kushner, I can attest to that.

Kushner: As a physician, a clinician, everything about me—my whole personality—was transformed by him. He knew his own mind. He had the courage to think through a clinical situation. And he really believed that doctors had to take responsibility to do things that were difficult.

Brenner: I remember presenting to Jack at the bedside, at 10 o'clock in the morning. You worked up the patient the night before, finished around midnight, stayed in that little Presbyterian Hospital library, read everything you could about the diagnosis you were entertaining. This year, on my first day of general medicine, I had a kid

"It was like Athens during its heyday or Florence during the Renaissance."

tell me about one of his 22 admissions the night before, but he had a clipboard in front of him. He's reading to me the age, the name, the history of the present illness. I said after 12 seconds, "Put your notes down. Just tell me about the case." He couldn't. I said, "We will have no more rounds today. Tomorrow, whoever presents better know the case, not the notes. Show me that you've thought about this, that there's been some integration of the information." I was brought before the department chairman as being out of line.

Kushner: That was Jack Myers speaking through Barry Brenner.

PM: What else stood out?

Brenner: The attendings we had were chiefs of service. Today the attendings—I only know it from where I work—are people who are out of their training a year or two, or they're hospitalists.

Braverman: I had [as attendings] Gerry Rodnan, head of rheumatology; Abe Braude, head of infectious disease; Ted Danowski, one of the world's premier diabetologists. And that was the rule; it wasn't that I drew the lucky three. Today you would see no equivalent people—almost none—in a similar role.

PM: What is your personal process of discovery?

Kushner: The idea-development process that leads to the experiments, the manuscripts, and the grants comes from interaction with the people in your lab, your colleagues, your mentor. The inspiration for discovery comes from constant reading, constant observing, and constant interaction.

Hibbs: Science is a very communal activity, and we interact on many dimensions. We're exposed to the ideas and the work of many different scientists, of many different nationalities. All of these go into the mix.

Brenner: For me, everything came at the end of the long day, in the quiet of the night, by replaying the tape that I went through in my waking hours. I have not spent a night since I was 25 years old without index cards on my night table. I go to work in the morning and just follow the leads of that digestion or reanalysis from the night before, thinking through how I should change [a study], do it differently. The data drive the steps day in and day out. Nothing else matters.

Braverman: Young people have one great advantage: Instead of index cards, there's a database program. If I have 10,000 notes and 700 to 800 patients on a program, I can ruminate over the data, look at it from different perspectives. It makes it so much easier, so much more convenient.

PM: How would you advise people aspiring to careers like yours?

Brenner: The name of my game was to amass an enormous number of experimental models, to make measurements repeatedly, to the point where I could pretty much fashion the discipline. I didn't have to look over my shoulder very much and didn't have the stress of competition. After 25 years, I could rely to a large extent on younger colleagues I had trained. And that gave me time and the freedom to extend myself into other areas.

Kushner: Pick the right mentor. The key to beginning a career as an academic person is to get a career development award. It assures you protected research time. It takes a mentor to tell you how to write the grant, how to organize your thoughts.

Hibbs: I still approach basic biology like a child, with this almost naïve enthusiasm.

Brenner: If you've really excelled in your clinical training, then go into a basic laboratory and find that you know nothing—that the technicians are dominant, and you're just learning how to mix solutions. When you go through that year depressed because nothing works, you're breaking glassware, that's when the mentor has to help you work on something where you can be successful.

PM: What are the prospects for the physician-scientist?

Brenner: The personal reward of a career in investigative medicine is second to none.

Braverman: My wife understood how important my work was to me, and we decided that despite the financial opportunities of private practice, we were going to stick with what I was doing in academic medicine. I've never regretted it.

Kushner: People who choose this path really have to have a terrific desire, a burning interest. And nothing will satisfy them other than testing their ideas and learning how to do the tests. I don't know how our partners put up with us. I don't go home very often.

Hibbs: If you're really doing something that's true investigation—and the more basic it is, the more risky it is in terms of really succeeding in uncovering new knowledge—there is this inherent risk that makes it very uncomfortable, but true adventure. Balancing this with clinical work can be tough.

Kushner: John, I remember a time when Françoise was urging you to spend more time at home. I came to your house, and you had moved part of your laboratory to the house. You had a microscope set up next to the living room; you had plates; and you were working from home.

Brenner: That's not what she had in mind.

Hibbs: I realized early on that I had to give up something, and what I gave up is academic travel. That way I could be a presence in my home as a husband and as a father.

Braverman: I used to take the kids to the lab and on rounds when they were young. They knew I wanted to be with them, and they had some notion as to what was going on. That was important.

PM: How do you feel about the prospect of retirement?

Brenner: I hate to confront it, which is why I tend not to. I spent 30 years doing mostly animal-oriented research. Then some very large clinical trials. Now I find myself in epidemiology, which I never would have guessed 20 years ago would have engaged me. I see my career just continuing to evolve. I pay less attention to the clock, with the hope that if my health stays good and my head stays reasonably good, this could continue for many years to come.

Hibbs: In a year or so, good lord willing, there will be time to do some other things—read philosophy and literature, spend time in France where my wife is from, walk in the Wasatch Mountains. We recently solved a major conceptual barrier in our research. Finishing this may open a new area for people to investigate, and I'll be able to stop with a success.

Kushner: I've got some tasks to finish, to ensure the future of the people who depend on me and on whom I depend to be productive. It's very hard to stop doing something you really like to do. We finally figured out the mechanism causing a type of porphyria. We have a lovely manuscript in *PNAS* [*Proceedings of the National Academy of Sciences*] now describing what goes on in the liver cell. And I've become a crystallographer in my old age.

Braverman: There are so many things I can do, that I want to do. But the one existential reality—I think we can all say—I strongly believe: We've had damn good lives. We've enjoyed our lives. They've been fulfilling, productive. That's why I don't really worry about the onset of age. I feel I can't stop because I'll end up depressed if I lose the things I love so much. It is a young man's job. I'm getting up at 5 in the morning to hear night-phone admissions in Brooklyn, and it's getting to be a little hard. But I just can't stop.

Brenner: We're the four horsemen—hopefully not of the apocalypse. ■