

FRANK DIXON DREAMS IMMUNOPATHOLOGY AND

WHITE SAND BEACHES | BY LEAH KAUFFMAN

CALIFORNIA DREAMING

During a lunchtime football game near Pennsylvania Hall, young Frank Dixon cut a swath through the opposition. His build was average, yet strong from daily workouts, and he played with the determination of an all-American. Dixon's aggressiveness led to an escalation of the hits against him, which he met without complaint. Not everyone was able to keep his cool as the competition became bruising. One flustered medical student grabbed Dixon by the sweatshirt and let him know he didn't like his playing style. Dixon turned his piercing, blue-eyed gaze on his opponent, then shook him and the incident off easily. The game broke up as the lunch hour ended. At 1 p.m., the term's first pathology class convened. To the shock of all assembled, including the student who had threatened him on the field, in walked Frank Dixon, the new chair of the University of Pittsburgh School of Medicine's Department of Pathology, to lead the course.

Dixon was not long out of his own student days when a search committee led by Jonas Salk in 1951 tapped him to start a new research-oriented pathology program at Pitt, one of the first of its kind. He had a new tool to contribute to pathology, a way to track proteins as they moved through an organism. Salk must also have sensed the intangibles that his recruit brought to Pitt. The confident 31-year-old would later be named the nation's leading medical researcher under the age of 35 by the American Association for the Advancement of Science.

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Frank Dixon started his career by changing the way people think about pathology. Then, while at Pitt, he showed the world how our bodies' defenses for keeping us healthy can actually make us sick. (He's shown here with his pup Dixie at a family ice-skating outing in Pittsburgh in the '50s.)



LEFT: Pitt became a center for immunopathology research. Shown here, faculty, fellows, and lab technicians in the Department of Pathology in the '50s. Dixon is in the second row, third from left. ABOVE: In 1975, Dixon surveys construction for a new building at Scripps on La Jolla's northern bluffs—not far from the Salk Institute.

As a teenager, a restless Dixon left his hometown of Mankato, Minnesota. His parents, whose days were consumed running the family restaurant, had high expectations for their only child. Dixon yearned to see life elsewhere and find “somewhere in the world that’s kinder to you than Minnesota.” He glimpsed then that a spirit of adventure could pay off. After hitchhiking west, he and a high school friend happened upon the southern California seaside town of La Jolla. The temperate sea air was benevolent and beckoning compared with Mankato’s extremes—its long months of short winter days and bitter cold, then stifling summertime heat and humidity. “La Jolla was about as good as you could do,” Dixon thought; but he soon found himself back home, packing his parka to enroll in the bachelor of science program at the University of Minnesota in Minneapolis.

He thought he would pursue math as an undergrad, but was dissuaded by his adviser, a mathematician himself who didn’t want Dixon to suffer the same poverty. Dixon chose medicine, then pathology, because he liked the idea of investigating a wide range of disease processes. After serving as a Navy lieutenant with the Marines (which lacked a medical corps of its own) during World War II, he went to Harvard University. There he worked with Shields Warren, a pathologist who would become the Atomic Energy Commission’s first chief of the division of biology and med-

icine and an authority on radiation-induced disease. Because of Warren’s connection to the AEC, Dixon had access to materials that were otherwise hard to get. Dixon applied a new technique for tagging proteins with radioactive iodine. He used this technique to follow proteins injected into lab animals, confirming their location and number with a Geiger counter, which reported the iodine’s decay with disinterested accuracy. Pathology—which had been a science limited to observations of the microscope-aided human eye—suddenly became molecular and quantifiable.

At his first faculty position at Washington University in St. Louis, and then at Pitt, Dixon applied this new tool to one of immunology’s oldest puzzles, serum sickness. Pathologists first came across serum sickness in the Preantibiotic Era, when the best hope for curing a nasty bacterial infection was to inject the patient with animal serum containing antibodies that targeted the bacteria. Those antibodies would lick the bacterial infection, but the serum exacted payment, typically in the form of fever, an enlarged spleen, joint pain, and rashes. Because these symptoms are so similar to human diseases like rheumatoid arthritis, rheumatic fever, and lupus, serum sickness induced in experimental animals is a good model of human immunologic disease. To the pathologist, the symptoms are most visible in lesions in the heart, blood vessels, joints, and kidneys.

It was already known that antibodies, see-

ing the proteins or antigens in serum as foreign, latched onto them to form so-called antigen-antibody complexes, but it was unclear what those complexes had to do with serum sickness. Dixon tagged the antigens with radioactive iodine and saw that they were circulating in the blood during serum sickness. Further work showed that antigen-antibody complexes were visible in the lesions as they developed. This was strong evidence that the antigen-antibody complexes themselves worked like a pathogen, not just sign-posting disease, but actually causing damage to the tissue. Dixon’s work at Pitt showed how our antibody response, which was thought to keep us healthy, could actually make us sick.

A new field, immunopathology, arose to describe what happens when our bodies’ own defenses turn on us. Dixon assembled a group of young researchers high atop the hill in Pennsylvania Hall, where, since it had been left by the rest of the medical school for the new Scaife building, he had unlimited space. Clinical duties were carried out by an arm of the department dedicated to that task, so his crew spent a lot of time in their labs. With Dixon’s radioactive iodine tracers and another new technique for making proteins glow under ultraviolet light (immunofluorescence), they had the quantitative and visual tools to start answering the flurry of questions raised by Dixon’s early serum sickness work: How many antigens does it take to cause disease? How long must they circulate in the blood to be harmful? Do all

antigen-antibody complexes cause disease? Why do they land in the kidneys?

“You didn’t have to be a rocket scientist to think of a problem,” Dixon says. “They were all there.” He was likely to pose physical challenges to his faculty, too. Because he didn’t like to sit for long, he was often encouraging the others to join him in a lunchtime run or a game of squash.

Dixon’s energetic group was the first to realize that the immune response can result in two types of kidney disease. In one, the antigen-antibody complexes get stuck in the glomeruli of the kidney and attract disease-fighting white blood cells that cause inflammation, as in lupus; in another, antibodies attack the kidney directly, as in antiglomerular basement membrane (anti-GBM) disease.

Also among their firsts: They figured out how to transfer anti-GBM disease antibodies from a human to a monkey, which made the monkey sick and definitively proved that the antibodies were the cause.

Each week, Dixon gathered the faculty and fellows together to discuss their work. Sometimes they grilled each other ruthlessly. If a scientific meeting was coming up, they practiced their talks. Even if the topic in

the fraternizing revolved around Dixon, who could revel as intensely as he worked. The stories he told could make a longshoreman blush. He was likely to get on a table and lead a Marine corps charge. At a meeting in Switzerland, where it is customary to leave one’s shoes in the hotel hallway overnight to be cleaned, he secretly moved the second-floor guests’ shoes to the third floor and the third-floor guests’ shoes to the second floor.

Still, he didn’t stay away from the lab for as long as planned, not even on family trips. Each summer the Dixons would get away, usually to Cape Cod, Massachusetts, where he and his wife, Marion, would go for long ocean swims, often as far as a mile. (They once returned to the house itching from small critters in their suits. Dixon took a few down to the lab at Woods Hole for analysis: They were baby lobsters.) Though the Dixons usually planned to be away for a set month, they always seemed to come home to Pittsburgh a day or two early. That was the only sign Dixon showed of the weight of running a department. He never came home from work beleaguered; instead he was likely to reenergize himself with his oft-repeated maxim, “When the going gets tough, the tough get going.”

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question wasn’t his area, Dixon always had a cogent question that cut to the heart of a subject, revealing where more detail was needed. When the phrase “Don’t you think?” rang out in Dixon’s clear voice, they knew he was about to home in. These rigors prepared his faculty not only for presenting at scientific meetings but also for running their own organizations: A half-dozen of Dixon’s fellows from Pitt went on to become department heads elsewhere—at the University of Colorado, at Washington University, and at what’s now the Medical College of Pennsylvania-Hahnemann, to name a few.

Immunopathology was so new it spawned just one or two national meetings each year, and everyone seemed to know everyone else in attendance. During the meetings of the Federation of American Societies for Experimental Biology, a lot of science was discussed on the Atlantic City boardwalk or in the hotel bar. Such association meetings were as social as they were scientific, and much of

By 1960, Dixon’s work in Pittsburgh had come to the attention of Edmund Keeney, the allergist running the Scripps Clinic in, of all places, La Jolla, California, who wanted to start a research program. Scripps was unknown then; it was just a small-town hospital with an allergy clinic. This was a risky career move. But La Jolla offered Dixon the possibility of fulfilling his professional and teenage dreams: There would be no teaching duties, no medical school administering, just pure, autonomous research, along with miles of beach and endless summer. He and Marion chose a sprawling stucco house with ocean views and decorated it in cool gray tones. During long walks on the beach with their dad, Dixon’s three children collected pebbles; he polished the rocks in a tumbler in the garage, then gave them a special place in the living room.

As the chair of the Department of Experimental Pathology for the Scripps Clinic and Research Foundation, Dixon

lured six postdocs, a half-dozen support staff, and four faculty members with him from Pitt to La Jolla, where many remained for the rest of their careers. Scripps had only space and good will; Dixon and his team needed grants to cover their salaries and operating expenses. Fortunately, Dixon already knew the formula: Spend lots of time in the lab, do great science, write good papers, give the best talks, submit sound proposals, get the money He’d already taught it to the faculty he brought with him from Pitt, and everyone he recruited thereafter was expected to do the same. While at Scripps, Dixon attended scores of scientific meetings to get out the word about the institute and his faculty’s research. One year he spent 200 days away from home. As the institute grew, he became chair of the biomedical research departments, then director of the Research Institute of Scripps Clinic.

He was, nevertheless, in the lab as much as possible. Dixon further elucidated the kidney diseases he had discovered at Pitt. Another project, a collaboration with Thomas Starzl, showed the world that a transplanted kidney can fall prey to the same antibody-inflicted disease that damaged the patient’s original kidneys, even if the new kidney came from an identical twin. Later, in a few otherwise understudied mouse strains that spontaneously develop lupus, he found an ideal animal model for exploring the immunopathology of the disease. His associates at Scripps are now close to describing the cause of lupus, which looks to be a series of genes that are benign in isolation but, when inherited as a suite and triggered by environmental factors, make the immune system attack the body’s DNA.

Dixon stepped down as director in 1986, though he continued his research for several more years. Now he enjoys having no vacation. Friends work with him on his bonsai garden. He and Marion walk the poodles on the beach. He has just stepped down from editing *Advances in Immunology*, which he’d overseen for 35 years. Still, talking science animates him. He’ll punctuate sentences with “Okay?” or “Right?” to make sure he is understood. When asked if, in building institutions, he followed the tenets of any particular management school, he scoffs.

“I have no idea what you’re talking about,” he says.

“You work like hell. First of all you raise the money, and then you work like hell, and everything works out.” ■