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IRVINE HEINLY PAGE

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A Biographical Memoir by

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BY HARRIET P. DUSTAN

FOR OVER FIFTY YEARS, from his first scientific paper on hypertension (high blood pressure) in 1935 to the publication of a massive text (1,102 pages), *Hypertension Mechanisms*, in 1987, Irvine Page was a dominant figure in the field of hypertension research. In addition to his scientific contributions, which were many and seminal, his unflagging advocacy of hypertension as a major public health problem did much to focus the attention of patients, physicians, investigators, and politicians on the need for its control. Largely forgotten is the fact that Page initiated the negotiations that eventually led to the establishment of the Institute of Medicine of the National Academy of Sciences.

Irvine Heinly Page was born on January 7, 1901, in Indianapolis, Indiana. His father was Lafayette Page, a physician of considerable local repute. Irvine Page was one of three children; his brother was a lawyer, and his sister, Ruth Page, became a famous dancer. She died in 1991 and was eulogized by the *Chicago Tribune* as "a world renowned choreographer who reigned as the grand dame of dance of Chicago." Page's early schooling was in Indianapolis, and his summers were spent on Cape Cod at Hyannis Port. He attended Cornell University, majored in chemistry, and di-

rected a dance band that nicely supplemented his family's financial support. Page liked chemistry, so after graduating in 1921 he worked for a year on the recently discovered insulin with George Clowes and Elliott Joslin. Then he enrolled in Cornell Medical College, attracted by biochemist James Sumner who won a Nobel Prize for crystallizing urease. Page found he liked medicine also but not to the exclusion of chemistry, because after a two-year internship at Presbyterian Hospital he was recruited by Geheimrat Richard Wilstätter to establish a department of brain chemistry at the Kaiser Wilhelm Institute of Psychiatry in Munich, Germany. Page in his memoir, *Hypertension Research*, recounts that in the three years he spent there his accomplishments were to set up a laboratory of neurochemistry and conduct research that gave "fats and sterols a better name." During that time he also accomplished a marriage to Beatrice Allen, a dancer with the Denishawn Company. Page returned to the United States in 1931, having been warned by a German army officer of the likelihood of war. When he made the decision to return he had no position to go to; nobody wanted or needed a brain chemist. Then good fortune struck. Donald Van Slyke of the Rockefeller Institute happened to be in Munich with his family and needed a doctor for his daughter who had an infected finger. Page was the only American physician there, so he was consulted. Not only was Van Slyke one of Page's heroes but, as it turned out, he held the key to Page's immediate future. The results were that the finger infection was treated successfully and Page was offered a position at the Rockefeller Institute.

Before leaving Europe, Page went to Frankfurt for two months of study with Frans Volhard, a professor of medicine particularly interested in hypertension who was responsible for some of the early descriptions of its effect on the kidney. There Page met two of Volhard's assistants, who

played important roles in his future. One of them, Bohn, claimed that he could extract a blood pressure raising (pressor) substance from the blood of malignant hypertensives. (Malignant hypertension is a type of elevated blood pressure that is uniformly fatal if untreated. The term "malignant" refers to its clinical course and not to any specific causation.) The other Volhard associate was Hessel, who was working on renin, a pressor substance found in saline extracts of kidney that had been described forty years earlier by Tigerstedt and Bergman.

Page spent six years at the Rockefeller Institute as an associate member, and it was there that he began his work in hypertension. First, he tried to reproduce Bohn's finding of circulating pressor substances in malignant hypertension but to no avail; none was found. He also tried to purify renin and isolate it from blood; that was not successful either. He did make an important observation, however, when he lowered blood pressure with colloidal sulfur injections and found that kidney function was well maintained. Prior to that observation, conventional wisdom held that elevated blood pressure was essential for blood to circulate through narrowed renal arteries.

Toward the end of Page's stay at the Rockefeller Institute, Arthur Corcoran joined him, and in 1937 the two men moved their research activity to the Laboratory for Clinical Research at the Indianapolis City Hospital, which was supported in part by the Eli Lilly Company. Already there were Kenneth Kohlstaedt and Oscar Helmer. This team had great success, and in a 1940 publication they described renin as an enzyme that produces a pressor compound they called angiotonin. Braun-Menendez and his colleagues in Buenos Aires had similar success, and the two discoveries were published almost simultaneously. The Argentineans,

however, had a different name for the pressor compound; they called it hypertensin.

In another first, Page, in collaboration with a young clinician, Robert Taylor, was able to reduce blood pressure by kidney extracts and later by pyrogen therapy. Those were the only nonsurgical treatments available in the early 1940s; low-sodium diets were under study but at that time were not widely used.

In 1945 Page was invited to set up a hypertension research program at Cleveland Clinic. Corcoran and Taylor went with him. Page was director of the Research Division at Cleveland Clinic from 1945 until his retirement in 1966. Much was accomplished by him and his co-workers: serotonin was isolated and its pharmacology carefully detailed, the mosaic theory of hypertension was introduced and refined, the importance of the autonomic nervous system as the controlling mechanism in hypertension was firmly established, angiotensin was crystallized, treatment of hypertension was a constant and successful focus, the National Foundation for High Blood Pressure was begun, and the Institute of Medicine had its origins there.

Retirement for Irvine Page did not mean a retirement from hypertension activities; he only changed his venue by moving to Hyannis Port. Separated from a laboratory and research administration he did the next best thing; he wrote. From that period came four important scientific texts: *Renal Hypertension* in 1968, edited with J. W. McCubbin; *Serotonin* in 1968; *Angiotensin* in 1973, edited with F. M. Bumpus; and *Hypertension Mechanisms* in 1987. Equally informative but in a different vein was his last book, *Hypertension Research, A Memoir, 1920-1960*, published in 1988.

For almost three decades Page was associated with *Modern Medicine*, and for at least half that time he was the editor. The journal was published biweekly, and this meant

writing two editorials a month for practicing physicians, a task in which Page was aided immeasurably by his wife, who is herself a writer and was his justifiably trusted critic and copy editor. Although Page was not a practitioner in the usual sense, nor had he ever been, he used his editorial position to inform, cajole, teach, and exhort the country's practitioners, who were the readers of that journal. In the 1992 presidential campaign lexicon, it was a bully pulpit for him and it worked; thousands of physicians came to know more science, politics, and sociology through those editorials than they would have otherwise. In 1972 a selection of them was published under the title of "Speaking to the Doctor."

Page was injured in an auto accident in March 1990 and was in poor health from then until his sudden and unexpected death on June 10, 1991. He is survived by his wife and two sons, Christopher and Nicholas, and their wives and children.

The honor of election to the National Academy of Sciences came to Page in 1971, some time after his major scientific contributions. Having known him as I did through an association of forty-three years I can hear him say "about time." Of course, he was immensely pleased but being a bit of a curmudgeon was a necessary part of his public persona.

This brief biographical sketch in no way details the quality of Page's contributions and their impact on biology and medicine as we understand them today. One of Page's major scientific contributions was his description of the enzymatic nature of renin and its production of a potent pressor compound, angiotonin, from a plasma protein substrate. Although his first efforts at isolating renin while at the Rockefeller Institute were unsuccessful, he hit pay dirt when he resumed his studies upon moving to Indianapolis. There

he had the manpower needed for the task. Oscar Helmer prepared protein fractions of kidneys, which were tested for their ability to raise blood pressure in the dog by Page; to cause vasoconstriction in isolated vascular beds by Kohlstaedt; and to decrease blood flow to the dog kidney by Corcoran. They found that, as purification proceeded, activity decreased but could be returned if plasma was added to the injectate. They called that plasma substance *renin activator* and the pressor compound that it produced *angiotonin*. A little later they realized the nature of the activator and called it *renin substrate*.

At about the same time, a group in Argentina headed by Eduardo Braun-Menendez also found a pressor substance of kidney origin. It too was the product of the enzymatic action of renin, but they called the pressor substance so produced *hypertensin* and the substrate *hypertensinogen*. Some years later Page and Braun-Menendez agreed on the names *angiotensin* and *angiotensinogen*.

That was only the beginning of the story. Page was set on crystallizing renin, and after moving to Cleveland he enlisted the collaboration of Arda Green, a protein chemist, but years of effort, many kilos of kidneys, and tons of ammonium sulfate produced nothing. However, work on the renin-angiotensin system was proceeding. First, it was learned that angiotensin was more complex than first thought when Skeggs and colleagues (1954) showed that the product of renin's action on its substrate is a peptide that is without effect on blood vessels and must be converted to an active form by what they called *converting enzyme*. These angiotensins came to be known as angiotensin I and II. Very soon (1956) Peart described the amino acid composition of angiotensin I, and within a year Bumpus, Schwarz, and Page reported the synthesis of angiotensin II, the active compound, and confirmed that it is an octapeptide. Almost

simultaneously Schwyzer and colleagues reported the synthesis of L-arginine angiotensin II. Some years later renin was finally isolated and characterized in the laboratories of Corval and Menard, of Inagami, and of Haber.

The renin-angiotensin system is widely distributed and has been identified in blood vessels, brain, salivary glands, uterus, placenta, adrenal, and, of course, the kidney, where it was originally found. It is one of the most important systems of the body: it regulates blood pressure by directly affecting the smooth muscle of arteries, it is the primary factor in aldosterone release, it has an independent effect on salt excretion by the kidney, and it influences brain function. It plays a major role in hypertension and heart failure, as witnessed by the beneficial effects of angiotensin-converting enzyme inhibitors. Page's description of the renin-angiotensin system was a major contribution.

Another major contribution was the isolation and characterization of serotonin. It had been known for eighty years that when blood clots, the serum contains a vasoconstrictor that, as later work showed, is absent when sodium citrate is used to prevent clotting. Also, the appearance of this vasoconstrictor was found to have a quantitative relationship to the platelet count, and other work found a vasoconstrictor in platelet extracts. The isolation of this substance Page assigned in 1946 to a young postdoctoral research fellow, Maurice Rapport. This Page considered a necessary step before undertaking a search for substances in the blood of hypertensives that could be responsible for raised arterial pressure. Success came shortly, and in 1948 Rapport, Green, and Page reported the isolation, identification, and crystallization of that vasoconstrictor. It is 5-hydroxytryptamine that they called serotonin because it was isolated from serum and had a tonic effect on arteries. In 1953 Twarog and Page showed that the brain contains serotonin, and now it

is recognized as a neurotransmitter. Subsequently, Page and his colleague McCubbin carried out an extensive investigation of the cardiovascular pharmacology of serotonin, and they showed, among many other effects, that the blood pressure response is strongly influenced by the activity of the sympathetic nervous system. Now, almost fifty years later, we still do not know the true scope of serotonin's activity in human biology.

Page influenced the conceptualization of hypertension in a unique fashion. In the 1940s and early 1950s *the* cause of essential hypertension was searched for. By 1950 Page had concluded, however, that hypertension results from an interaction of many mechanisms. This he called the mosaic theory. It was first suggested as a combination of five mechanisms and subsequently refined, so that by 1960 it was made up of eight factors, all interrelated. Because this theory (as he called it, although it was actually a schema) presaged a large volume of evidence for the interlocking of multiple mechanisms of hypertension control, the mosaic "theory" is now the dominant concept and no longer are investigators looking for a single cause of hypertension.

Although Page was not a practicing physician, he had a keen appreciation of the public health importance of hypertension and what could be achieved by blood pressure control. From 1951, when antihypertensive drugs of long-term effectiveness were first introduced, until his retirement in 1966, Page was actively concerned with the treatment of hypertension: he tested every new drug in dogs, so that he and those of us involved in the care of patients knew the pharmacology and what we were dealing with. He was insistent on the importance of treating hypertension, and we were among the first to demonstrate a causal relationship between high blood pressure and the lethal conse-

quences of malignant hypertension by showing the life-saving effects of antihypertensive drug therapy.

In addition to his advocacy for the treatment of hypertension, Page was a strong, fervent, and vocal supporter of research and specifically research on hypertension. Early on he maintained that industry and business should contribute directly to that support because hypertension and other cardiovascular diseases ravaged middle-aged men, causing businesses to suffer accordingly. Thus, in 1945 he organized the National Foundation for High Blood Pressure, whose members were businessmen from Cleveland and hypertension researchers from across the country. The businessmen raised money for research support, which was competed for by all scientists involved in hypertension research, not just those who were members of the foundation. Page hoped that other cities would follow the lead of these Cleveland businessmen, so that a network of support for hypertension research could be established in this country. But other events overtook these aspirations; the network never materialized, the National Institutes of Health became the major funding source of biomedical research in this country, and the foundation gave up its independent status and joined the American Heart Association as the Council for High Blood Pressure Research. The annual meetings of the council represent the best of contemporary hypertension research and are a continuing tribute to Page's advocacy of research.

In the early 1960s Page became convinced that establishment of a National Academy of Medicine would benefit by bridging "the wide gaps among government, the American Medical Association, specialty societies, academia and industry—an ecumenical movement." He used his *Modern Medicine* editorials to test the waters. Finding considerable support for this idea he approached the president of the

National Academy of Sciences, who also was interested. Page then obtained a planning grant from the Cleveland Foundation, and in January 1967 the first organizational meeting was held at Cleveland Clinic. The deliberations took a long time, and in the end a National Academy of Medicine was not established. In its place was the Institute of Medicine, which came into being in 1971.

This then is a brief look at the life of a man who made significant scientific contributions; altered the course of the investigation and treatment of high blood pressure; and, in a more general sense, influenced medicine in the United States.

MATERIALS USED IN WRITING this memoir came from my forty-three-year friendship with Irvine Page, twenty-four years of which I worked closely with him; from his book *Hypertension Research, A Memoir, 1920-1960*; and from a rereading of his major scientific papers.

HONORS

In addition to his election to the National Academy of Sciences, Page received many other honors. He was president of the American Heart Association (1956-57); he received ten honorary degrees and a number of prestigious awards—the Ida B. Gould Memorial Award of the American Association for the Advancement of Science (1957); Albert Lasker Award (1958); Gairdner Foundation Award (1963); Distinguished Award of the American Medical Association (1964); Oscar B. Hunter Award (1966); Passano Foundation Award (1967); and the Stouffer Prize for Hypertension Research (1970).

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