In Memoriam

The Celebration of a Leader

With the passing of Irvine H. Page from the scientific and world arenas, the curtain has descended on an exciting era of biomedicine. To us, with the death of Irvine Page on a June day in Hyannis Port, the 50-year “Golden Era” of American medicine from 1930 to 1980 was concluded. As we sat in the proper and small New England church on that sunny day, with the gentle breath of spring blowing across the chapel, this feeling became inescapable. Not that the excitement of science and medicine was over—surely, the search for new horizons still looms as exciting and promising as ever. Nevertheless, the era of the clinician, trained at the bedside, nurtured by the discipline of clinical investigation, and sustained by ample tangible support from the federal government, voluntary health agencies, and private sources, is but a fond memory.

We cannot emphasize enough that without this remarkable recent history, the framework of our existing biomedical structure would not be available to us. But with the retirement or passing of our immediate progenitors and “giants” such as Irvine Page, James Shannon, Donald Van Slyke, Julius Comroe, and Louis Katz, this chapter of our history is closed. Without these men our scientific and professional existence would be vastly different today. These were the visionary biomedical leaders, who along with Lister Hill and John Fogarty of the congress, transformed bedside descriptive clinical medicine to one of critical clinical and laboratory investigation. This transformation initiated the concept of the “triple threat” in academic medicine. These were the leaders who championed and fashioned with remarkable vision the present and indispensable role of the National Institutes of Health, the American Heart Association and its Scientific Councils (of which our Council for High Blood Pressure Research is but one), the Institute of Medicine, and the International Society of Hypertension. Prominent among these innovators and leaders was Irvine Heinly Page.

All of us who knew Irv Page will have vivid recollections of him. We remember him ever-present in the front row of our scientific meetings, always ready with a pertinent (or impertinent) commentary. This was the “spark” that provided excitement and motivation for free exchange and unfettered critical thinking and intellectual professional growth. And these present comments were what we expected from him in our daily work in the Research Division of the Cleveland Clinic—and what we have missed after his retirement.

Our contemporaries are well aware of Dr. Page’s contributions to the understanding of hypertension, but a summary should be given here because younger investigators need to know the wellsprings of modern hypertension research. Given the relative superficiality of electronic information retrieval systems, it is easy to remain ignorant of early accomplishments.

Irv Page’s contributions were many. Perhaps the most outstanding were 1) identification of the renin-angiotensin system, 2) identification of serotonin, 3) description of a neurogenic mechanism in renal hypertension, 4) baroreceptor resetting, and 5) the mosaic theory of hypertension.

It was Page and his colleagues at the Lilly Laboratory for Clinical Research in his boyhood hometown of Indianapolis who discovered that renin is an enzyme acting on a plasma substrate to release a vasoconstrictor compound. A similar discovery was made practically simultaneously by Braun-Menendez and colleagues in Buenos Aires. Page called the vasoconstrictor angiotonin, and Braun-Menendez termed it hypertensin. They later settled on angio-
tension. This was the true beginning of research into the renin-angiotensin system; although renin had been discovered by Tigerstedt and Bergman in 1898, nobody had an inkling of its enzymatic action before the work of Page and Braun-Menendez.

Page was also responsible for identifying serotonin and for the early work on its pharmacology. Although serotonin was isolated by Maurice Rapport and Arda Green, it was Page who started them on the search for a vasoconstrictor substance in clotted blood that had first been noted almost 80 years before. As part of that early work, Page and Twarog reported finding serotonin in brain tissue. We now know it is a neurotransmitter.

The nervous system's control of the circulation was an ongoing interest for Page. James McCubbin and he described the amphibaric action of serotonin that depended on the state of neurogenic vascular tone; when that tone was high, serotonin was sharply depressor, but when it was low, a pressor response resulted. McCubbin and Page showed how hypertension initiated by one factor (e.g., renal artery clamping) could be maintained by a neural mechanism. Continuing in that vein, they and John Green, a visitor from England, described baroreceptor resetting and considered it not only an important factor in the maintenance of chronic renal hypertension but also a likely factor in essential hypertension.

In his talks, Page liked to say that when he "started out" the scourges of tuberculosis, syphilis, typhoid fever, and typhus were a paramount concern and there was little awareness of hypertension and atherosclerosis. Page was also keenly concerned about mental illness and brain chemistry. Today, we are all convinced of the importance of neurotransmitters, brain peptides, and neurochemistry in unraveling the mysteries of psychiatric diseases and the integration of neural function with other systemic bodily functions. When Page accepted an invitation to establish a Department of Brain Chemistry at the Kaiser Wilhelm Institute in Munich in 1928, after only a 2 year internship at Presbyterian Hospital in New York, there were few who recognized that potential. There were far too few at the time who were aware of his tome on brain chemistry, as it went largely unappreciated for years. Now the numbers of scientific workers in brain chemistry and neurophysiology are far greater than those of us in the cardiovascular area. Page continued his interest in brain chemistry until his death; he continued to learn and as he put it "read through" Current Contents, even as he remained confined to his upstairs rooms.

Another of Page's great contributions was his mosaic of hypertension. This theory has been around so long (over 40 years) it is easy to forget, or never to have known, that in the 1940s and 1950s, investigators were searching for "the cause" of essential hypertension. Page's contribution was the recognition of the multifactorial nature of arterial pressure control and that hypertension represents a disregulation among these many factors. It has been said by some of this theory that "its weakness is that it can't be wrong."

These milestones were but one aspect of Page's existence. There was the hard-driving man, never satisfied with complacency in the present state, skeptical of conventional practice, always anticipating the future, and a deep concern for what lies ahead for us and our successors. Thus, we witnessed his efforts to strengthen the National Institutes of Health, to create a scientific base for the American Heart Association that was linked to the Council for High Blood Pressure Research, to broaden interest in world medicine by his participation in forming the International Society of Hypertension (of which he was the first president), and of course, to initiate a "full court press" on the pages of Modern Medicine for a National Academy of Medicine. Even the fruits of the National High Blood Pressure and National High Cholesterol Education Programs of today owe much to the efforts of Page. He also deserves credit for the development of effective antihypertensive drugs and for his pivotal role in the National Diet Heart Study that are on the front pages of our press today.

His retirement was not idle. Although he died at the age of 90, he published two books in the last 5 years. The first was a major single author "tour de force" on the mechanisms underlying hypertension (with 131 triple column pages of references, all read by him at his Hyannis Port home, a great distance from the medical libraries in Boston). The second was his memoirs, which by his design, only covered the period to 1965 since he did not wish to comment on those of us who were still "active on the hypertension scene."

In closing, we should like to refer to two personal anecdotes about Irv Page that we enjoyed. They are typical "Pagean." The first occurred only 2 years ago when he commented to one of us (E.D.F.) who had just finished serving a 2 year tenure as council Vice Chairman with the responsibility for developing the annual fall scientific meeting of the Council. After reviewing the council's proceedings for that year, Page commented on the increasing number of papers dealing with molecular biology and asked if E.D.F. could recommend one of two books on molecular biology recently reviewed. Knowing first hand of his proud penurious characteristic, E.D.F. suggested that no matter which of the two would be recommended, he would not think it worth the high price of these (or any other new) textbooks. Two months later in a telephone conversation Irv indicated that he had purchased one and volunteered that there wasn't much he had read that he hadn't already known. This was believable for he had been a member of the American Chemical Society since he was 14 years of age and had been a compulsive reader of "Chem Abstracts."

The second anecdote was described by his son Chris concerning his final visit with his father. Real-
izing that Irv was failing rapidly, Mrs. Page had called Chris to their home. Irv wanted to get up from his bed to sit in his chair across the room. With great difficulty, Irv moved slowly but unassisted to his favorite chair. He was too weak to sit down unassisted but when he was finally in his chair, Irv thanked Chris and his wife Bea and then passed on. To us, this was the true and vital Irv Page, determined not to finish his days in bed but sitting upright and proud. This was the Irvine Heinly Page whom we wish to remember. Whether we wish to accept it or not, we are all both his legacy and the beneficiaries of his lifetime of scientific quest.

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