Jerome W. Conn

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By William H. Daughaday

JERRY, AS HE WAS known to his contemporaries, was a member of a small group of clinical endocrinologists who applied the new knowledge in hormone structure that arose in the middle decades of this century to the definition of important clinical syndromes of hormone excess and deficiency. The contributions of these clinical scientists made this the golden age of clinical endocrinology. Almost single-handedly Jerry Conn defined the syndrome of aldosterone excess and contributed to the recognition of the renin, angiotensin, and aldosterone control mechanisms in hypertension.

Jerry was born in New York in 1907, the oldest of four children of Joseph and Dora Conn. His father operated a small shop that grew to a busy luncheonette, and his mother was a homemaker. The parents shared a common belief in the value of education and made great sacrifices to ensure that their children had the benefits of the best education possible. Jerry was an outstanding, inquisitive, and industrious student who skipped a grade in primary school. A family friend, a physician, probably influenced Jerry's choice of profession. After three successful years at Rutgers University Jerry entered the University of Michigan Medical School in Ann Arbor in 1928. The Great Depression, which began the following October, depleted the family resources, and his two sisters, both of whom were equally gifted, contributed materially to Jerry's education from their salaries as secretaries. Jerry never forgot this sacrifice, and when his brother Harold, who was twenty years his junior, came to the University of Michigan for his medical education, Jerry paid his tuition and expenses. Jerry had two precepts for Harold as he embarked on his own academic career: (1) Stay in one place because every move will cost him at least one year, and (2) find a good umbrella (by this he meant a supportive chairman) and stay under it--to which he added, do not be seduced into becoming an umbrella. Harold went on to a distinguished career in hepatology entirely at the Yale University School of Medicine.

In medical school Jerry met a classmate, Betty Stern, who shared his interests in clinical research. They were married after the first year. He graduated from the University of Michigan School of Medicine in 1932 with honors and as a member of the Alpha Omega Alpha Honor Society. He chose to take his internship in surgery at the university's hospital, but after one year he switched to internal medicine, which presented more of an intellectual challenge to him. After two years of medical residency he was attracted to the exciting research in the Division of Clinical Investigation in the areas of obesity, energy metabolism, and diabetes under the direction of Dr. Louis H. Newburgh. Betty joined the division at the same time. She collaborated with Jerry in

important studies of the relationship between obesity and noninsulin-dependent diabetes. Jerry entered the division as a fellow in 1935 and became an assistant professor of internal medicine in 1938.

Jerry's entire professional career was at the University of Michigan. In 1943 he became director of the Division of Endocrinology and Metabolism, a position he held until 1973. In 1968 he was named the L. H. Newburgh Distinguished University Professor. He retired from the university in 1974.

Jerry Conn and his associates made major contributions in four areas of clinical endocrinology and metabolism: (1) dietary modification of glucose tolerance, (2) aldosterone and the regulation of salt excretion (the syndrome of hyperaldosteronism), (3) the renin-angiotensin system in hypertension, and (4) the nutritional regulation of insulin secretion.

Dietary Modification of Glucose Tolerance. Conn began his research career in Newburgh's laboratory with a series of studies of the relationship between diet and glucose tolerance. He reported on the comparative glycemic effects of carbohydrate and protein on glucose tolerance. He was one of the first to advocate a high-protein diet in the treatment of hypoglycemia. An important contribution of this period was the carefully conducted metabolic studies of what is now known as type II diabetes mellitus. Those studies found that the oxidation of glucose in this condition is not reduced but achieved only at an elevated level of blood sugar. This explained the rarity of ketoacidosis in this condition. Conn's group was one of the first to clearly recognize the relationship between obesity and adult-onset diabetes by showing the resumption of normal carbohydrate tolerance after attainment of normal weight in twenty of twenty-one patients. This was quite an achievement in view of the difficulty of obese patients to reach normal weight by dietary restriction.

Aldosterone and the Regulation of Salt Excretion. With the onset of World War II, medical research was redirected to problems of military relevance. Jerry's mentor, Louis Newburgh, left Ann Arbor for Washington to join the U.S. Naval Investigative Laboratories, and Jerry took over the Division of Endocrinology and Metabolism in 1943. Because acclimatization to tropical heat was a major military concern in the South Pacific, Jerry undertook a series of investigations of the regulation of salt loss in sweat in conscientious objectors exposed to elevated heat and humidity. It was possible to do detailed metabolic studies under controlled dietetic conditions with excellent clinical chemistry laboratory support. Measurements of mineral loss in body sweat, saliva, urine, and feces were made daily for long periods of heat exposure. Conn established that acclimatization involved a rapid curtailment of renal, sweat, and salivary sodium excretion. He suspected that this response was mediated by adrenal activation, but he observed that the negative nitrogen balance was transitory while the sodium retention persisted for the duration of the heat exposure. Conn suspected that the persistent sodium retention was due to increased adrenal "salt-active corticoid secretion." He postulated that "certain types of stimuli can provoke a preponderant secretion of one type of steroid depending upon the condition, type and duration of the stress imposed." This prompted his interest in the measurement of these salt-active corticosteroids even before the isolation of aldosterone by Simpson, Tait, and Bush in 1950.

Because of these studies in the hormonal regulation of salt excretion in acclimatization, Conn was well prepared for a thirty-four-year-old patient who entered the university hospital in 1954 complaining of seven years of episodic muscle weakness that often resulted in virtual paralysis of her lower legs. In addition, she noted muscle spasms and cramping of her hands. The initial laboratory studies established severe hypokalemia and alkalosis. There were no signs of cortisol excess. Selective excess of mineralocorticoid secretion was suspected, and the patient was transferred to the metabolic ward for intensive investigations, which occupied more than seven months. Repeated measurement of thermal sweat found the same low concentration of sodium previously found in heat-acclimatized volunteers. Balance studies established a continuing negative potassium balance despite low levels of serum potassium. A young associate in the laboratory, Dr. David Streeten, found that the patient's urine contained an excess of mineralocorticoid, as demonstrated in a bioassay using adrenalectomized rats. These and other studies convinced Conn that the patient was suffering from mineralocorticoid excess (hyperaldosteronism) and that surgical intervention was indicated.

Jerry took the occasion of his presidential address to the Central Society for Clinical Research on October 29, 1954, to present for the first time his extensive clinical investigations of this new syndrome, which he called primary aldo-steronism. The author of this memoir was in attendance that day and remembers the excitement with which this brilliant clinical study was received. The following December the patient had a surgical exploration of her adrenal glands and a 4-centimeter tumor was found, much to the delight of Jerry and his colleagues. In the years that followed, Conn's clinic became a world referral center for patients with hyperaldosteronism. Many subsequent publications expanded on the clinical description, and laboratory and radiologic diagnosis of this and related conditions.

The Renin-Angiotensin System in Hypertension. When the work of others established that the secretion of aldosterone was under the control of angiotensin renin secretion, Jerry's group published a series of studies of this system in hypertension and related conditions. A possible role of functional hyperaldosteronism in idiopathic benign edema and periodic paralysis was suggested. More importantly, he studied the renin-angiotensin system in secondary hyperaldo-steronism, which can be difficult to distinguish from primary hyperaldosteronism. Jerry reported that finding a suppressed serum renin activity was an important distinguishing laboratory finding in primary aldosteronism due to an adrenal tumor. Interest in the renin-angiotensin-aldosterone axis in hypertension allowed Conn to recognize one of the first cases of a renin-hypersecreting renal tumor and to contribute to our understanding of the pathophysiology of this rare tumor.

Nutritional Regulation of Insulin Secretion. With the advent of radioimmunoassay for insulin, members of Conn's division conducted extensive studies on the ability of certain amino acids, particularly leucine and arginine to promote insulin secretion. They speculated that leucine sensitivity might be responsible for certain cases of functional hypo-glycemia.

Conn had a deep interest in recognizing individuals with normal glucose tolerance who are at risk of subsequently developing adult-onset diabetes. In his Banting Memorial Lecture presented in 1958 to the American Diabetes Association, Conn summarized the findings obtained by Stefan Fajans and other members of his division with a glucose tolerance test that

followed cortisone administration. This stress to insulin secretory capacity proved quite effective in predicting which members of a diabetic family were most likely to come down with the clinical disease. Fajans, an early member of Conn's division, succeeded Jerry as head of the Division of Endocrinology and Metabolism at the University of Michigan.

During his career at Michigan, Jerry was highly productive. He authored 284 scientific papers and book chapters; but the most impressive product of his long direction of the Division of Endocrinology and Metabolism Research Unit at Michigan was the large number of bright young fellows that began their research career in his division. He tirelessly supported their development as independent investigators and promoted their research careers. His personal concern for those beginning their academic careers was well expressed in his 1954 presidential address to the Central Society. Before presenting his brilliant clinical studies of the patient with primary aldosteronism, Conn exhorted the members to avoid destructive criticism of young presenters. As he said:

> I am not old enough to have forgotten completely the perspective of younger colleagues. Their aspirations are pointed in your direction. They wish eventually to reach the standing and respect in clinical research which they believe you have achieved, and many of them will, and perhaps to a greater degree! Let us set for them a proper example of kindness, friendliness, and common decency.

Jerry then gave his philosophy of scientific communication:

> We speak glibly these days of "fundamental research" and extol the discovery of a fact, however disjointed from all other facts, as an addition to the sum total of knowledge acquired by mankind. Reason tells us that we must acquiesce in a vague kind of way to the statement that every fact has a potential usefulness. In the meanwhile it is regarded as background, available to all who choose to use it. Are there any of us capable of evaluating which fact, when eventually correlated with others, will have the greatest impact upon the lives of men? The answer is "No."
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> Let us remember that we are all painting background. Regardless of how important or unimportant your contribution of today may seem, no sooner has it been expounded than it has become background. There is some solace in the fact that your brain child is not dead! The entire background is seething with life and motion, but acceptance of the idea of painting background is sufficient to remove the undesirable gusts of wind from many sails. Let us rejoice in the knowledge that to us has come the opportunity to paint background.

Jerry received many honors, including the Claude Bernard Medal of the Institute of Experimental Medicine and Surgery of the University of Montreal (1957); the Banting Medal of the American Diabetes Association (1958); the Henry Russel Award of the University of Michigan; the Gordon Wilson Medal of the American Clinical and Climatological Association (1961) the Banting Memorial Award of the American Diabetes Association (1963); the John Phillips Memorial Award of the American College of Physicians (1965); the Elliott Proctor Joslin Award of the New Eng-land Diabetes Association (1965); the Howard Taylor Ricketts Award of the University of Chicago (1967); the Heath Memorial Award of the University of Texas, Houston (1971); and the Distinguished Achievement Award of the American College of Nutrition (1973).

He received an honorary doctor of science from Rutgers University (1964) and an honorary doctor of medicine from the University of Turin, Italy (1975).

Jerry was a member of twelve national professional societies and served as president of the American Diabetes Association (1962-63) and the Central Society for Clinical Research (1954). He was elected to the National Academy of Sciences in 1969 and was a founding member of the Institute of Medicine. He served on four committees of the National Research Council and was the chairman of its Committee for Evaluation of the National Pituitary Agency. He was also an honorary fellow of the American College of Surgeons and an honorary member of thirteen foreign medical societies. He was an invited lecturer at thirty-nine international meetings and gave more than fifty invited lectures at various institutions in the United States.

Jerry and Betty had a long and happy marriage. They had a son, William, and a daughter, Phyllis. Their Ann Arbor home was a mecca for family, students, fellows, and colleagues. Sunday evening barbecues with Jerry manning the grill were common and much-remembered occasions. Tennis was one of Jerry's favorite forms of relaxation and exercise. He approached tennis games with young members of his laboratory with the same intense competitive spirit as he did his medical research.

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