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EDWARD C. KENDALL

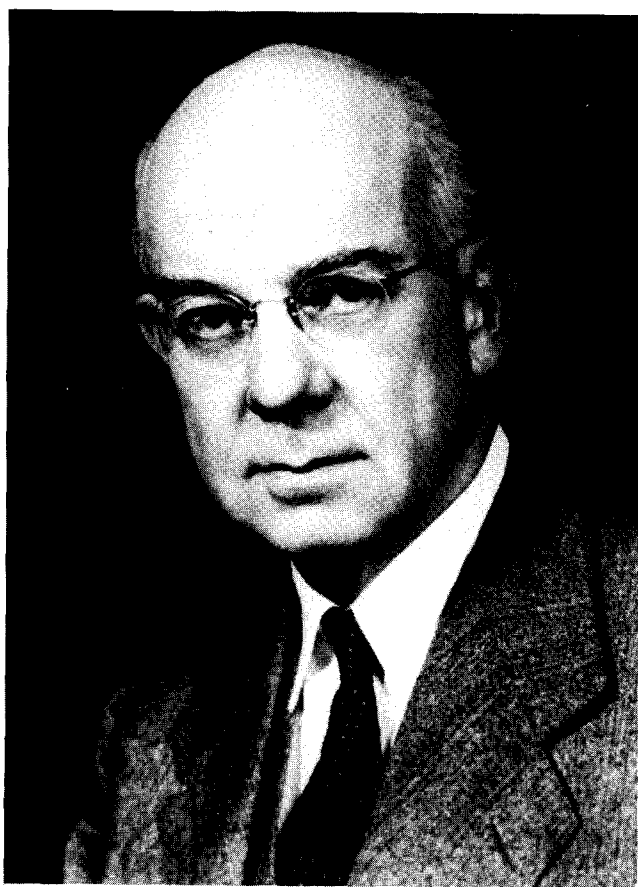
1886—1972

A Biographical Memoir by
DWIGHT INGLE

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Biographical Memoir

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Edward C. Kendall.

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March 8, 1886–May 4, 1972

BY DWIGHT J. INGLE

EDWARD CALVIN KENDALL isolated thyroxine from the thyroid gland; he and associates crystallized glutathione and established its chemical structure; and he and associates isolated a series of steroid compounds from the adrenal cortex and contributed importantly to the determination of the structure and synthesis of several of them. With Philip S. Hench, he conceived the idea that cortisone might be useful in treating rheumatoid arthritis, and they planned clinical studies that confirmed the hypothesis. Kendall also initiated and participated in a number of related studies.

During his professional life he was called "Nick" by close friends and by his wife. He was referred to as "The Chief" by some of his laboratory associates, but commonly he was addressed with deference, as "Doctor Kendall."

Edward C. Kendall, the third child of George S. and Eva F. Kendall, was born March 8, 1886, at South Norwalk, Connecticut. The home was a citadel for religious teachings. The father, a dentist by profession, took an active interest in community affairs. Edward attended the Franklin Elementary School and, for two years, South Norwalk High School. He spent a year at Stamford High School preparing for college. During these years he excelled in mathematics and became interested in the work of a foundry and a machine shop. In his

teens, he set up a shop in the attic of his home; there he built electrical apparatus and did machine work.

At Stamford High School Kendall developed an interest in chemistry. It was enhanced by his brother-in-law's stories of an amateur chemist who developed a secret process for making high-quality writing paper. This much admired brother-in-law graduated from Columbia University in 1900, and this influenced Edward to enter there four years later.

Edward concentrated his attention on chemistry and, as a college senior, he wrote a thesis under the guidance of Professor H. C. Sherman. During the summer of 1908, he served as a laboratory instructor in the department of biochemistry. He was awarded a scholarship for post-graduate work in biochemistry and received an M.S. degree in June 1909.

He then became the first recipient of the Goldschmidt Fellowship and began research on amylase, an enzyme of the pancreas. Kendall observed that the amount of reducing sugar produced by given amounts of amylase varied considerably, and he identified sodium chloride as the factor causing the variability; the presence of the salt enhanced the activity of amylase severalfold. His first paper reported this research in the *Journal of the American Chemical Society*; Professor Sherman was co-author. He received the Ph.D. from Columbia in June 1910. (Hereafter, I shall refer to my subject as Dr. Kendall, for I addressed him thus for forty years.)

In his memoirs, Dr. Kendall tells of departing from the sheltered, restricted life of his boyhood; but he cites specifically only that he played cards on Sundays and that he once tested the consequences of saying "God damn" out loud. As an adult, he was not overly religious, but he was more puritanical than many who practice religion loudly. These early years must have been important in the development of his quiet, scholarly demeanor and self-discipline. He continued to keep physically

fit throughout his adult life. He had participated in high school sports and, in college, he was a bow oar in a four-man shell.

On September 1, 1910, Dr. Kendall began working in the chemical laboratory of Parke Davis and Company; his assignment was to isolate the hormone of the thyroid gland. He stayed five months. He found that punching a time clock was annoying, and he was disappointed by the intellectual isolation. There were no seminars, and he found himself working in competition with another chemist who was assigned the same problem.

After returning to New York City, he accepted an invitation to occupy and equip a new laboratory in St. Luke's Hospital. In the beginning, he worked without salary but was given funds for supplies and equipment. Eventually a salary of \$1200 a year was provided, but it was never increased.

Dr. Kendall continued research on the thyroid gland. Near the end of the nineteenth century, Professor Eugen Baumann, a physiological chemist at the University of Freiburg, had prepared iodine-containing extracts of thyroid glands that were useful in treating clinical hypothyroidism. Baumann's partially purified principle was named iodothylin. The findings of Baumann served as a starting point for Dr. Kendall. By 1913 he had purified the active principle about a hundredfold. The method of bioassay was to measure changes in the urinary nitrogen of dogs. The biologic activity of the partially purified preparations was also demonstrated in hypothyroid patients. The research was not appreciated by the clinical staff of the hospital, whose attitude toward the partial purification of the iodine-containing compound seems to have been "So what?"

At about this time the hospital administrator sent Dr. Kendall a box of cereal with a letter directing him to analyze the contents. The letter and the cereal were thrown summarily into the wastebasket. Not then or ever would the young chemist

take orders of this sort or accept distraction from his own goals. This and similar incidents formed the basis of his determination to move to a research-oriented institution.

It was Professor Clarence M. Jackson, soon to become a great teacher of anatomy at the University of Minnesota, who told Dr. Kendall of developments at the Mayo Clinic and suggested that he apply to Dr. Louis B. Wilson, Director of Laboratories, for a position. Dr. Henry S. Plummer, a many-sided genius, was involved in the treatment of diseases of the thyroid and in studies of its pathologic physiology. Drs. Will and Charlie Mayo were interested in diseases of the thyroid. Dr. Kendall was invited to join the staff of the Mayo Clinic and he began his research there on February 1, 1914. He was concerned with two projects: first, the isolation of the hormone of the thyroid gland, and second, the determination of the amount of the acid-insoluble fraction of thyroid glands removed surgically from patients so these data could be correlated with other clinical and laboratory findings.

Baumann had prepared iodothyryn by boiling thyroid tissue with 10 percent sulfuric acid to hydrolyze the proteins; Dr. Kendall came to use repeated treatment with hot dilute sodium and barium hydroxides followed by separation of the acid-insoluble material. Near the end of 1914, an acid-insoluble fraction that contained 47 percent iodine had been prepared. At this point, ethanol was used as a solvent. On December 23, a sample was dissolved in a small amount of ethanol and evaporation started. The young chemist was tired and fell asleep. When he awakened, the ethanol had evaporated, leaving on the bottom of the beaker a white crust surrounded by a ring of yellow waxy material. When more ethanol was added, the latter material dissolved but the white crust did not. When the residue was analyzed the following morning, it was found to contain 60 percent iodine. During the day, more of the crust was prepared. On Christmas morn-

ing, some of the white crust was dissolved in ethanol that contained a small amount of sodium hydroxide. The addition of a few drops of acetic acid precipitated crystals. This pure compound was later named "thyroxin" and, still later, when it was found to be an amino acid with an amine group, an "e" was added to make the name "thyroxine" (The ending "ine" indicates the chemical class to which the compound belongs.) Some hypothyroid patients were treated with the crystalline hormone; it was fully active in relieving the symptoms of thyroid deficiency.

A year later, Edward C. Kendall married Rebecca Kennedy of Buffalo, New York. To Dr. Kendall and "Becky," four children were born—Hugh, Roy, Norman, and Elizabeth.

Before coming to the Mayo Clinic, Dr. Kendall had applied for a position at the Rockefeller Institute and was bluntly turned down by its director, Dr. Simon Flexner. This rankled the younger man and, in 1916, he took special satisfaction in reading a paper, "Isolation in Crystalline Form of the Iodine-Containing Compound of the Thyroid Gland," at a session of the Federation of American Societies for Experimental Biology, chaired by Dr. Flexner.

Efforts to identify the structure of thyroxine and to synthesize the compound extended over the next ten years; they resulted in failure. Dr. Kendall described thyroxine incorrectly as triiodo-hexahydro-oxindolepropionic acid. In 1926, Dr. C. R. Harington of University College, London, identified the nucleus of thyroxine as the tetra-iodo derivative of thyronine and he synthesized thyroxine. At that point, the Mayo Clinic closed its research on the chemistry of the thyroid hormone.

Dr. Kendall was already an important scientist and was to accomplish goals more significant than the isolation of thyroxine; but he was not then, nor was he to become, a great chemist. His formal training in chemistry had been brief, and from the time he had received his Ph.D., he no longer worked

with a master. A stubborn man, throughout his life he held that his intuitive beliefs were valid until the evidence against them became overwhelming. Other chemists had advised him over and over that his proposed structural formula for thyroxine was incorrect. Usually, when confronted with proof that a belief was incorrect, he would accept it with good grace; but undue faith in his own ideas and resistance to the suggestions of others characterized his whole life as a scientist. Yet, in another sense, these foibles may have been necessary for his noble aims, his tenacity, and, hence, his great achievements. As Albert Szent-Györgyi said, "Discovery consists of seeing what everybody has seen, and thinking what nobody has thought."

The research interests of Dr. Kendall shifted to studying the specific compounds involved in the effect of thyroxine on oxidation in the body. Attention was focused on cysteine and glutathione. Since the latter compound could not be purchased, the Mayo group became involved in a program to crystallize it and prepare it by synthesis. The compound was first isolated, analyzed, and named by Professor F. Gowland Hopkins of Cambridge University in 1921. Bernard F. McKenzie and Dr. Harold L. Mason were collaborators of Dr. Kendall in isolating glutathione in crystalline form and in identifying it as a tripeptide of glutamic acid, cysteine, and glycine. This was accomplished independently of the isolation of crystals of glutathione and determination of structure by Professor Hopkins. The two groups agreed that the compound is glutamyl-cysteinyl-glycine. It was first synthesized by Dr. C. R. Harington.

The Section of Biochemistry at the Mayo Clinic was involved in basic research, graduate education, and performing clinical biochemistry. The last-named function was directed by Dr. Arnold E. Osterberg, first research associate of Dr. Kendall at the Mayo Clinic. It was Osterberg who suggested the name "thyroxin." Although Dr. Kendall participated in graduate

education to a small extent—he held the rank of professor since 1921—he would permit few distractions to his research. He was never to become a sitting scientist; he was almost always at the bench.

In the fall of 1929, Albert Szent-Györgyi, who, throughout his life made discoveries and stimulated the research of others, became a visiting scientist in Biochemistry at the Mayo Clinic. Szent-Györgyi had isolated small amounts of a substance that he first named "hexuronic acid." It is widely distributed in plants and animals and relatively large amounts are in the adrenal cortex. Fresh beef adrenal glands were made available to Dr. Szent-Györgyi, and he isolated substantial amounts of the compound during the eight months he spent in Dr. Kendall's laboratories. Hexuronic acid was later identified as vitamin C and given the name "ascorbic acid."

The initiation of research on adrenal glands in Dr. Kendall's laboratories coincided with the publication of convincing evidence that an extract of beef adrenal glands would sustain life in adrenalectomized animals and would reverse the symptoms of Addison's disease in human patients. Several investigators claimed to have achieved this during the 1920s, but the first to publish statistically reliable evidence (1927) for the prolongation of life in adrenalectomized animals was Professor Frank A. Hartman at the University of Buffalo. In 1930, Hartman and Katherine A. Brownell at Buffalo and J. J. Pfiffner and W. W. Swingle at Princeton University prepared extracts of the adrenal cortex that would sustain adrenalectomized animals indefinitely, would revive them from a state of adrenal crisis, and would relieve the symptoms of patients with Addison's disease. The efficacy of the Pfiffner-Swingle extract was demonstrated on patients with Addison's disease by Dr. Leonard G. Rowntree of the Mayo Clinic. Dr. Rowntree came to Dr. Kendall with a plea to prepare adrenal cortical extract. The challenge was accepted, but Dr. Kendall looked beyond the

immediate clinical need toward the isolation and chemical identification of the hormone of the adrenal cortex.

During the early 1930s, Dr. Giles A. Koelsche, a Fellow in Biochemistry, carried out an important study of the effects of thyroxine and of adrenal cortical hormones on nitrogen balance in dogs. It is generally believed that the hormones of each gland are catabolic. This is true when they are given in excess, but Koelsche demonstrated experimental conditions in which physiological doses of adrenal cortical hormones favor a positive nitrogen balance and anabolism. Dr. Joseph L. Svirbely came to the Mayo Clinic for one year, did sophisticated biological studies, then returned for several summers. Svirbely had contributed importantly to the identification of hexuronic acid as vitamin C during his association with Dr. Szent-Györgyi at Szeged, Hungary.

Dr. Frank C. Mann supported the research of Dr. Kendall in two important respects. First, he was director of the Institute of Experimental Medicine of the Mayo Clinic, which carried out all animal experimentation. Dr. Mann performed all of the adrenalectomies on dogs used by the Kendall group in bioassay procedures and research. Second, Dr. Mann was a member of Mayo's Board of Governors for a number of years. He was one of the effective spokesmen for the Clinic's laboratory investigations. He was a great experimental surgeon and physiologist, and a pathologist of broad interests, who had important insights into the complexities of life and disease. Dr. Kendall and Dr. Mann were, in unique ways, strong personalities. Each had a warm personal regard for the other, but Dr. Mann was well aware of Dr. Kendall's foibles as a scientist. Dr. Kendall's knowledge of physiology was shallow; he did not appreciate the complexity of cause-and-effect relationships, and he did not fully appreciate the extent of biological variability. He was also given to making premature announcements of laboratory results. All of this exasperated Dr. Mann. On one

occasion, a brash young biochemist who came to the Institute to do research and bioassays on adrenalectomized dogs was questioned by Dr. Mann about his knowledge of physiology. The new Fellow replied that, since he was trained in biochemistry, he had good basic knowledge of physiological processes. Dr. Mann replied, "I know more than two hundred biochemists and not a damn one of them knows any physiology." When the remark was repeated to Dr. Kendall, he said, "I know more than two hundred physiologists and not one of them knows any biochemistry."

Some members of the Clinic staff and some members of the Board of Governors questioned the wisdom of supporting basic research in the Section of Biochemistry. So long as Drs. Will and Charlie Mayo ran the clinic, they supported Dr. Kendall's programs. Dr. Charlie especially would come frequently to Dr. Kendall's laboratory bench to chat and keep in touch with progress. When the Mayo brothers began to turn over more and more administrative responsibilities to committees, the research program of Dr. Kendall was in some danger. He had to appear before the Board each year and resell the program. These were depression days and the Mayo Clinic did not accept any outside support for any of its functions. Dr. Kendall could plead a cause with quiet optimism, always promising early progress. But there were years in which there was little progress to report. Dr. Mann was in a position to scuttle Dr. Kendall's program but did not. He would express misgivings, then support the continuation of the research. There was no true inconsistency in this, for Dr. Mann understood better than most physicians the necessity for basic research, that it is errant, and that years of effort may go by without discovery.

In 1928, when I was an undergraduate student, a physician friend gave me a publication containing "before and after" pictures of a ten-year-old girl in whom treatment with thyroxine at the Mayo Clinic had corrected cretinism within a few

months. There was a remarkable spurt in growth. I wrote a letter to Dr. Kendall. I received a reply to each of my questions about this patient. In 1932, I heard him speak on thyroxine at the University of Minnesota School of Medicine. After the lecture I wrote to him and was again treated with kind consideration. I was told that he now aimed to isolate the hormone of the adrenal cortex. I was studying the work performance of adrenalectomized rats: The general technique was to anesthetize the rat with sodium phenobarbital, weight the gastrocnemius muscle with 100 grams, and stimulate it electrically to lift the weight three times per second. Normal rats could continue work of the stimulated muscle for more than fourteen days. When the adrenal glands were removed, the amount of work accomplished began to fall below that of sham-operated animals within two hours, and muscular responsiveness was lost within a day. I had shown that ability to work was lost because of circulatory failure and that the state of shock was due to absence of the adrenal cortex rather than of the adrenal medulla.

When I asked Dr. Kendall for a sample of adrenal cortical extract, he suggested that I first test lactyl epinephrine. He had an intuitive guess that since the adrenal glands contain both lactic acid and epinephrine, the two compounds might be linked together to form the hormone of the adrenal cortex. He believed that he had extracted this compound from adrenal glands, but the evidence was tenuous. A final ether extract contained lactic acid and gave a positive test for the catechol grouping. He believed that synthetic lactyl epinephrine was prepared in his laboratory, again basing this conclusion on the finding that an ether-soluble product contained lactic acid and gave a positive test for the catechol grouping. There was no proof that lactic acid and epinephrine were chemically bonded. Dr. Kendall had injected this latter product into dying adrenalectomized dogs and had observed temporary improvement in some of them; I found the product to have an epinephrine-like

effect on my "fatigued" adrenalectomized rats and to cause a small temporary recovery in muscle work. The benefit to both the dogs and rats was due to the presence of free catecholamine and represented only a pharmacologic effect.

When I treated "fatigued" adrenalectomized rats with adrenal cortical extract supplied by Dr. Kendall, there was an almost complete recovery of work output. It was simpler to treat the animals with extract from the time of adrenalectomy and the beginning of muscle stimulation. I developed a twenty-four-hour assay test of adrenal cortical extract that was sensitive, fast, and reliable. Bioassays done on adrenalectomized cats and dogs required several days and large amounts of extract, and were not very sensitive. I was invited by Dr. Kendall to join his group as a Mayo Foundation Fellow, and I did so in September of 1934.

In December, 1933, a crystalline organic substance was isolated from adrenal cortical extract. Dr. Kendall announced the isolation in crystalline form of the hormone of the adrenal cortex. It was then assumed that the adrenal cortex secretes but one hormone and that any crystals formed during fractionation of the extract were likely to represent that hormone. The crystalline material was tested in adrenalectomized dogs, and it was concluded that it sustained the lives of these animals. After I established the muscle-work test at the Mayo Institute, my first assignment was to test this crystalline material. It did not have demonstrable activity. It was then retested in adrenalectomized dogs with negative results. During the first series of tests on adrenalectomized dogs, a high dietary intake of sodium chloride was used; this prevented symptoms of adrenal cortical insufficiency. It is possible that the crystalline material contained some biologically active compounds, but the data did not prove the presence of a hormone, nor were the crystals shown to be a single compound. Dr. Kendall never fully explained these facts in any subsequent publication, so his claim to have

isolated the hormone of the adrenal cortex in 1933 has been regarded by some reviewers as a report of the first isolation of cortisone.

At about the same time, Dr. Arthur Grollman at Johns Hopkins Medical School reported the isolation of crystalline material from adrenal cortical extracts and that the crystals sustained the life of adrenalectomized rats. These claims were not independently confirmed and the chemical nature of his crystalline material was not fully determined.

Dr. Mann was deeply concerned, first, when Dr. Kendall reported verbally on the apparent activity of lactyl epinephrine—he did not publish a claim for activity—and, again, when his published claim (1934) to have isolated the hormone of the adrenal cortex was not confirmed. At this time, Dr. Kendall was asked by the Board of Governors to give Dr. Harold L. Mason increased responsibility for the purification of crystalline material and chemical characterization. Mason was well trained in organic chemistry and had learned the then new methods of microanalysis. He was a perfectionist, who did elegant work at the bench. Dr. Kendall was not a master of the principles of research nor of all the methods needed in this program; his intuitive judgments as to what should be done were a source of frustration to his young colleagues. He did not follow the advice of Dr. Mann to give Mason greater responsibility. About this time, Mason and Charlie Myers went to Dr. Kendall to air their complaints. At their suggestion, a weekly conference was set up and this proved an important means of advancing the project.

Happily, the muscle-work test was of use in following biological activity during fractionation and purification. By the fall of 1935, Dr. Hugo W. Nilson and Mr. Donald Krockow joined the group to conduct bioassays and research on adrenalectomized dogs. Each did his work superbly.

The Kendall group was at this time processing large quantities of beef adrenal glands supplied by Parke Davis and Com-

pany. Dr. Kendall was at his best as an extractionist. In exchange for the glands, epinephrine was separated, purified, and returned to Parke Davis. The Wilson Laboratories also supplied beef adrenal glands in exchange for bioassays on the adrenal cortical extract prepared for clinical use by this company. For at least five years, the laboratory processed 900 pounds of beef adrenal glands every week. Bernard McKenzie had an important part in the success of this program.

Dr. Kendall supplied adrenal cortical extract to Mayo Clinic physicians to treat patients with Addison's disease. It was now generally available from commercial sources, but large amounts were required to restore a patient with Addison's disease to normal vigor; no patient could afford to purchase all of the cortical extract needed. Dr. Robert F. Loeb of Columbia University demonstrated that animals and patients with insufficient amounts of adrenal cortical hormones will survive for a long time under nonstress conditions if given a high sodium chloride diet or saline to drink. Dr. George Harrop of Johns Hopkins Hospital called attention to the elevated blood serum potassium of animals and patients during adrenal cortical insufficiency. Under the direction of Dr. Kendall, William D. Allers, a Mayo Foundation Fellow, prepared high sodium-low potassium diets and demonstrated that adrenalectomized dogs could survive nonstress conditions for indefinite periods and could even reproduce—but did not lactate—when fed these diets. These findings were promptly applied in the treatment of patients with Addison's disease at the Mayo Clinic; some patients were stabilized for months on the high sodium-low potassium diet. Adrenal cortical extract was used only if the patient got into trouble when subjected to some form of stress or if he failed to continue the special diet. Dr. Hugo Nilson continued and advanced the studies on adrenalectomized dogs.

All phases of the program were significantly advanced during 1935-1936. The research led to the isolation of five crystalline compounds. It was an uneasy time, for two rival groups

were in the field. Dr. J. J. Pfiffner had moved from the Princeton University laboratories of Professor W. W. Swingle to collaborate with Dr. Oskar Wintersteiner at Columbia University. Wintersteiner was a superb organic chemist, who had mastered the methods of microanalysis: The Wintersteiner group began to isolate crystalline compounds at about the same time as the Kendall group. In Switzerland, Professor Tadeus Reichstein and his students were progressing rapidly toward the same objective.

Compound E of the Kendall group was found to be active in the muscle-work test in late 1935. Wintersteiner and Pfiffner were the first to report the isolation of a few milligrams of this compound, but they did not recognize it as being biologically active. The same substance, later to be called cortisone, was isolated by the Reichstein group; they too failed to recognize it as biologically active. The Kendall group converted their Compound E (cortisone) into a diketone, which had androgenic activity, as demonstrated by Professor F. C. Koch of the University of Chicago. It was correctly deduced from this finding that Compound E is a steroid. Independently, the competing groups recognized that the compounds isolated from the adrenal cortex are steroids.

Prior to the chemical identification of compounds, each of the three competing groups referred to a compound by letter, as A, B, C, or the like. Each group happened to assign a different letter to its compound. This led to some confusion among those who read the original research reports and among interested persons who had only secondhand information about the researches.

Noncrystalline preparations from the adrenal cortex were far more potent than was Kendall's Compound E in sustaining the life of adrenalectomized animals. This was first shown by Wintersteiner and Pfiffner. The search for the hormone of the adrenal cortex continued. In 1936 we heard a rumor that

Reichstein had isolated the life maintenance hormone and had named it corticosterone. There was some dismay in the Mayo group; but, when Reichstein published (1937) the chemical characteristics of the new compound, it was recognized as being identical with Kendall's Compound B, which had been isolated earlier. It, too, was much less potent than noncrystalline fractions in sustaining life in adrenalectomized animals.

As the structure of these compounds was worked out, it became possible to name them. In the Kendall series, Compound B was corticosterone, Compound A was 11-dehydrocorticosterone, Compound E was 17-hydroxy-11-dehydrocorticosterone (cortisone), and the soon-to-be-isolated Compound F was 17-hydroxy-corticosterone (cortisol or hydrocortisone). Each of these compounds was active in the muscle-work test, cortisol being the most potent. By 1938 Professor C. N. H. Long and his students at Yale Medical School had shown that each of these compounds affects carbohydrate metabolism and can be bioassayed by measuring the level of liver glycogen in fasting young adrenalectomized rats or mice.

In 1937 M. Steiger and T. Reichstein prepared 11-desoxycorticosterone by partial synthesis. Dr. George W. Thorn of Johns Hopkins Hospital found this steroid to be highly potent in sustaining the life of adrenalectomized animals and of patients with Addison's disease. Only minute amounts were found in adrenal cortical extracts. It seemed unlikely that this steroid was the naturally occurring life-maintaining hormone of the adrenal cortex, but the urgency to isolate an adrenal cortical hormone of clinical importance seemed to be over.

I interrupt the account of research to describe more of Dr. Kendall's personal life. He was a quiet man but did not conceal his enthusiasms. His treatment of others was usually kind, but he would sometimes become sharply impatient and sarcastic. I once caused him to lose his temper. I refused to do an experi-

ment according to his research plan and proceeded to tell him of his weaknesses in biologic research. This was well intentioned, but unwise, and I soon regretted it. He did not raise his voice but his face flushed, then paled, and his lips and hands trembled. I lost the argument and did the experiment as he directed, but I added controls. When my data showed the controls to be necessary, he accepted the findings in good humor. I learned to do my own experiments first and to bring the data to Dr. Kendall after the studies were completed. To be more precise, I reported results only if they seemed significant. Dr. Kendall neither tested ideas in private nor concealed his mistakes, as many of us do. He would announce what he expected to find "just around the corner."

During the holidays Dr. and Mrs. Kendall hosted members of the laboratory group. Mrs. Kendall was an unassuming, gracious, and generous lady. Summers, the whole family lived at their cottage on Lake Zumbro where each child became a fine swimmer. On weekends, a nap after lunch was routine. Dr. Kendall would plan research strategy then and some nights. One of his few diversions was playing chess, and he kept a few games going by mail. Each Fourth of July, the members of his laboratory group would gather at the Kendall cottage for a picnic. For years, Dr. Kendall offered a prize to any guest who could cross Lake Zumbro in a tub. There were some who made the attempt, but I am not aware that anyone won the prize. Several summers, Dr. Kendall took his three sons on long canoe trips.

Dr. Kendall was a man of scholarly demeanor, yet he was not a scholar. He excluded from his life many activities that others enjoy. He focused attention on long-range research objectives and relaxed his attention and effort only to the extent needed to maintain physical and mental fitness.

I have mentioned that Dr. Arnold E. Osterberg directed the laboratories of clinical biochemistry. Dr. Marschelle H. Power

was an important member of this group and was to become head of the section when Dr. Kendall retired.

In 1936 Dr. Willard Hoehn, a well-trained organic chemist, came to Mayo's to replace Dr. Charles S. Myers. Warren F. McGuckin and Bernard F. McKenzie were productive members of the team doing research on steroids. Miss Eva Hartzler joined the group to work with Dr. Hugo Nilson in studies of changes in electrolyte metabolism caused by adrenal cortical insufficiency in dogs.

Before the end of the decade, Drs. Piffner and Wintersteiner dropped research on the adrenal hormones. Both Hugo Nilson and I left the Kendall group. Harold Mason and Willard Hoehn were soon to drop out of the program. Dr. Frank Stodola came to work with Dr. Kendall for a time. Before shifting his interests to other problems, Mason prepared a non-crystalline residue of adrenal cortical extract that was far more potent than 11-desoxycorticosterone in sustaining the life of adrenalectomized animals. There was something important in the adrenal cortex that remained to be isolated in pure form and chemically identified.

In 1934 Dr. Kendall had suggested that the adrenal cortex may secrete more than one hormone; other investigators advanced the same hypothesis, but I believe that Dr. Kendall was the first. He then dropped the idea for several years. By 1939 Dr. George W. Thorn and I, working with steroids supplied by the Mayo group, demonstrated a qualitative dissociation of the biological properties of 11-desoxycorticosterone and 17-hydroxy-11-dehydrocorticosterone (cortisone). Our findings were supported by the studies of Professor C. N. H. Long and his associates at Yale, with whom we regularly exchanged data. Our general conclusions were confirmed independently by Dr. Benjamin B. Wells and Dr. Kendall. Dr. Roger Reinecke joined the Kendall group and did important studies of the glycogenic effects of the adrenal steroids. It became clear that Kendall's compounds A, B, E, and F, each of which is oxygenated at posi-

tion 11 of the steroid nucleus, affect organic metabolism and that 11-desoxycorticosterone, and an as yet unidentified principle in the amorphous residue, affected the metabolism of electrolytes and water. Professor Hans Selye called the 11-oxy compounds "glucocorticoids" and the latter "mineralcorticoids." These characterizations were too simple and not entirely accurate, but nevertheless useful. Animal experimentation by the Mayo group ended in 1942.

Meanwhile, events in other parts of the world had begun to affect the lives of all of us: Europe was at war. Prior to the direct involvement of the United States, our armed services and the National Research Council began to organize and set priorities for research to support military medicine. Attention focused on a rumor that Germany was buying beef adrenal glands in South America for the purpose of making adrenal cortical extract. It was said that the extract was being used to counteract the hypoxia of Luftwaffe pilots to permit them to fly at higher altitudes. It was being claimed, especially by American pharmaceutical houses, that adrenal cortical extract would counteract traumatic shock and surgical shock. There were other claims that it would raise resistance of laboratory animals to hypoxia. It was well established that adrenally insufficient animals and patients are abnormally sensitive to all forms of stress. It seemed reasonable to expect that the cortical steroids would raise the resistance of combatants to the kinds of stressors encountered in war. The medical research division of the Office of Scientific Research and Development gave top priority to the synthesis of Kendall's Compound A. In late 1941 a committee of outstanding chemists, most of them experienced in steroid chemistry, was appointed to plan and direct the research. Dr. Kendall was one of them.

The committee decided to first prepare Kendall's Compound A as a step toward the more difficult job of preparing Compound E. Research toward this objective was carried out in a

number of laboratories including those of Merck and Company. In the fall of 1943, Compound A was synthesized in very small yields by Professor T. Reichstein.

Research continued, especially in Dr. Kendall's laboratories. To this laboratory came a series of brilliant young chemists, several of them from Merck and Company, including Lewis H. Sarett. Dr. Vernon Mattox joined the Kendall group to stay; he has played an important role in the Section of Biochemistry since that time. The steps toward the synthesis of Compound A were improved. A small amount of the substance was prepared in Dr. Kendall's laboratories.

By the middle of 1944 all members of the collaborating groups, except those of Mayo's and Merck, stopped research on the synthesis of Compound A. By then the biological studies on the usefulness of adrenal cortical extract and adrenal steroids in raising resistance to hypoxia, surgical and traumatic shock, and other stressors had yielded largely negative results.

Collaboration between the Mayo group and the Merck group—the exchange of scientists was continued—plus information from Professor Reichstein, made it possible for Merck and Company to prepare nearly 100 grams of Compound A by the end of 1945.

Tests of Compound A were begun with high hopes by several groups of clinical scientists. All the results were in agreement: The compound had little therapeutic value in patients with Addison's disease.

Most of the once interested chemists dropped research on the synthesis of Compound E; Dr. Kendall wanted to keep at the original objective and the Merck group agreed to continue the collaboration. The officers and scientists of this company deserve great credit for farsighted policies of research in this and other areas.

The early years of the 1940s brought personal sadness to Dr. Kendall. Near the beginning of the decade, Mrs. Kendall

experienced the first of a series of periodic mental illnesses. Also, their son, Roy, developed a malignancy during his medical internship, and he died after about eighteen months. Hugo Nilson and I were with Dr. Kendall in Atlantic City when this happened. I had just left the two of them when Dr. Kendall received word that his son was dead. Hugo was stunned and unable to find words to express his feelings; Dr. Kendall was a father figure to each of us, and we had affection for each member of the family. It was the older man who placed his hand on Hugo's shoulder and spoke quietly of the cruelty of disease and that man must work toward the reduction of it. Nothing short of his own death would prevent his striving toward that goal. Dr. Kendall's son, Norman, took his own life soon after he was discharged from military service, adding to the tragedies of these years.

In December of 1944, Dr. Lewis H. Sarett of Merck and Company prepared a few milligrams of Compound E. During the collaboration aimed to improve the yields, several important contributions came from the Kendall group, most of them from the young men. Dr. Kendall had learned a great deal of steroid chemistry by this time and was the source of some fruitful ideas. Still, his major role was to keep the program going and to focus the efforts of a number of gifted collaborators on the problem.

The first large-scale synthesis of Compound E was completed at Merck and Company in 1948. Most clinical endocrinologists had lost interest in the possible clinical usefulness of this and other glucocorticoids. Another phase of research on the hormones of the adrenal cortex seemed to be over.

Dr. Philip S. Hench of the Mayo Clinic had observed that patients with rheumatoid arthritis sometimes go into remission when they become jaundiced and that some women have relief from arthritis when they become pregnant. He postulated that some humoral substance formed during jaundice and during

pregnancy is responsible for the remission. I heard him talk about this theory and the relevant evidence in the middle 1930s. One of the young physicians working with him came to me to learn how to ligate the common bile duct of the rat so as to induce jaundice; he then studied the joints of the jaundiced animals, but there were no significant changes. Drs. Hench and Kendall discussed the problem on a number of occasions. It was decided in 1941 to test Compound E for a possible effect on rheumatoid arthritis, when a sufficient amount became available for clinical investigation.

In September of 1948 some synthetic Compound E was injected into a female patient. It came from a supply that had been prepared at the Mayo Clinic by Vernon Mattox from a precursor (4,5- β -dihydrocortisone acetate) supplied by Merck and Co. There was dramatic improvement in the patient. The clinical study was continued and expanded by the use of Compound E supplied by Merck; almost all arthritic patients treated with the steroid went into a remission that lasted as long as the hormone was given. There was great excitement at the Mayo Clinic, but it was tempered with caution against making a premature announcement. The results were kept confidential for several months.

At that time I was a research scientist at the Upjohn Company. In February of 1949, Dr. Gifford Upjohn told me of a rumor that a great medical discovery had been made at the Mayo Clinic. I made a trip to the Mayo Clinic and was taken by Dr. Hench to see arthritic patients in remission; I was shown the recently completed film of the effects of treatment. This was quite exciting, and I was especially pleased to hear the story from Dr. Kendall. He had never lost faith that Compound E would be of use in clinical medicine.

Dr. Randall G. Sprague talked with me about the possible overdosage effects of Compound E; doses required to suppress the symptoms of rheumatoid arthritis are large. Was it not

likely that continued high dosage would induce Cushing's syndrome in the patients? I knew that normal animals could be brought to death by overdosage with Compound E; it seemed plausible that unwanted effects would occur in humans as well. Would the adrenal cortices of these patients undergo compensatory atrophy? It seemed probable. Would continued high dosage of the steroid damage the capacity of the anterior pituitary to again secrete corticotropin when the administration of steroid was stopped? I was almost certain this would not occur, but I was wrong. When Dr. Sprague and I met in Atlantic City in April of the same year, he told me that Cushing's syndrome had begun to appear in some arthritic patients treated with Compound E.

Did Dr. Kendall have some special foresight that Compound E and related steroids would suppress inflammation and therefore the symptoms of arthritis? He never claimed to have. Dr. Kendall had suggested the testing of Compound E in mental diseases, in cancer, and in other diseases. It is my belief that he and Dr. Hench were playing a hunch without much evidence or logic to support it. In 1941 a strange, brilliant man named Valey Menkin demonstrated that adrenal cortical extract and Compound E would suppress inflammation in laboratory animals. Most of us ignored the research of Menkin. There is no evidence that Dr. Kendall attached special significance to it, although he supplied the Compound E for the studies.

Compound E could have been tested in arthritic patients years before it actually was, for several grams that had been isolated from natural sources were at hand, and more could have been extracted and purified at any time. The first test came about as follows: In the latter half of 1948, Dr. Hench had a female arthritic patient who had not responded to treatment; she begged him to try any possible sort of new therapy. Dr. Hench came to Dr. Vernon Mattox—Dr. Kendall was on a trip—and inquired into the possibility of obtaining some Com-

pound E to test. Dr. Mattox replied that he could not supply the steroid unless instructed to do so by Dr. Kendall. When Dr. Kendall returned, Dr. Hench raised the question with him and the two agreed to the clinical trial.

In May of 1949 Drs. Kendall and Hench discussed the naming of Compound E; they coined the word "cortisone."

In the days, weeks, and months that followed announcement of the therapeutic value of cortisone in inflammatory diseases, there was wide acclaim, which surely brought satisfaction to each of the two men. On October 25, 1950, a newspaper correspondent with an inkling that Dr. Kendall would receive the Nobel Prize called the scientist's daughter, Elizabeth, in New York State, and she passed the news on to her father. In the early afternoon on the following day, it was officially announced that Edward C. Kendall, Philip S. Hench, and Tadeus Reichstein would receive the Nobel Prize in Medicine and Physiology for their investigations of the adrenal cortex. Replying to my telegram of congratulations, Dr. Kendall thanked me and added, "That was the day!"

Dr. Kendall shared his financial award with several of his associates who had contributed importantly to the isolation, identification, and synthesis of cortisone; Harold Mason and Vernon Mattox were among them.

Other honors and awards followed, including election to the National Academy of Sciences in 1950. Dr. Kendall retired from the Mayo Clinic in 1951, but he did not retire from the bench. He moved to Princeton, New Jersey, became a visiting professor of chemistry at the university, and set up a research program at the James Forrestal Research Center just north of the city.

By then it had become apparent that cortisone does not cure rheumatoid arthritis or other inflammatory diseases. These diseases are not caused by a deficiency of adrenal cortical hormones and prolonged treatment with the amounts of corticoids

required to suppress inflammation causes unwanted side effects in a significant number of patients. A better form of treatment was needed and Dr. Kendall set out to find it. He postulated, first in 1945, that an unidentified steroid is secreted by the adrenal cortex and that this steroid is linked with ascorbic acid. His quest included the extracting of adrenal glands and the attempted synthesis of postulated formulae. He worked toward this general objective for almost all of his remaining life. He focused on the aim to synthesize a ketal representing a conjugate of ascorbic acid and hydrocortisone. As a step in this direction, he prepared furandiones—somewhat simplified analogs of ascorbic acid. He published two communications to the editor of the *Journal of the American Chemical Society*, concerning the preparation and properties of tetrahydro-3,4-furandione and its dioxolane and dioxane derivatives. He did not achieve his objective of creating a new therapeutic agent, although each letter and each Christmas message implied that success was near.

On one occasion when I visited Dr. Kendall at his Princeton laboratories, he talked with me about a fable that I had written for reading at a dinner meeting of the Endocrine Society. It was about a great scientist who was destroyed by administrative duties. Dr. Kendall guessed correctly that I was frustrated by distractions from research; he proposed that we take a walk. Within the woods adjoining his laboratory was an abandoned circular building almost hidden by vines, brush, and untrimmed trees. Dr. Kendall called it "The Witches Nest." "I need a biologist with me," said The Chief. "If you want isolation, I will find salary money, research funds, and fix up 'The Witches Nest' for you. And you can have it with no telephone." (I dated the beginning of my troubles from the day I first acquired a telephone.) It was a high compliment from Dr. Kendall: He wanted me to work with him again. But I could not.

Dr. Kendall called our home a few weeks before he died.

I was away and he talked with my wife, Geneva. She said that he seemed tired and lonely and she was sad because this was completely unlike him. But he kept working. While having lunch with several scientists on a consulting trip to the Merck Company, May 1, 1972, he went to the blackboard to write a formula. He was suddenly taken ill, was hospitalized, and died from a coronary failure three days later. Mrs. Kendall died February 14, 1973.

I have argued that a man should be remembered for his best personal qualities and his achievements rather than for his foibles and failures, but I cannot write of Dr. Kendall without describing his weaknesses as well as his strengths. To do so would create an image of a person who never existed. His greatness lay in his ability to select important goals that were achievable, to persevere toward them during periods of adversity and disappointment, and to select gifted associates. Once when a younger associate asked permission to spend some time at another problem, Dr. Kendall replied, "I want to grow a great big oak tree; I am not interested in a bunch of black-berry bushes."

In his autobiography he writes of the driving force that keeps a scientist at an important goal, and he adds, "But two components of the drive can be understood and are appreciated by almost everyone. These are a love of whatever things are true and a desire to create something."

There was, I think, another quality of the man, which is suggested in this closing quotation by the French anthropologist C. Levi-Strauss:

A grain of slightly mad recklessness,
Might, in this domain as in others,
Be the price you have to pay for great
and noble findings.

HONORS AND AWARDS

AWARDS

- 1921 John Scott Prize, City of Philadelphia
1925 Chandler Medal, Columbia University
1945 Squibb Award, Endocrine Society
1949 Lasker Award (with P. S. Hench), Lasker Foundation
1949 Research Corporation Award, Research Corporation of New York
1950 Page One Award (with P. S. Hench), New York Newspaper Guild
1950 John Phillips Memorial Award, American College of Physicians
1950 Remsen Award, American Chemical Society, Maryland Section
1950 Edgar F. Smith Award, American Chemical Society, Philadelphia Section
1950 Research Award, American Pharmaceutical Manufacturers Association
1950 Passano Award (with P. S. Hench), Passano Foundation
1950 Medal of Honour, Canadian Pharmaceutical Manufacturers Association
1950 Nobel Prize (with P. S. Hench and T. Reichstein), Nobel Foundation
1951 Dr. C. C. Criss Award (with P. S. Hench), Omaha Mutual Insurance Association
1951 Award of Merit (with P. S. Hench), Masonic Foundation
1951 Cameron Award (with T. Reichstein), University of Edinburgh
1951 Heberden Award, Heberden Society of London
1952 Kober Award, Association of American Physicians
1961 Alexander Hamilton Medal, Alumni of Columbia College
1965 Scientific Achievement Award, American Medical Association

HONORARY DEGREES (DOCTOR OF SCIENCE)

- 1922 University of Cincinnati
1950 Western Reserve University
1950 Williams College
1950 Yale University
1951 Columbia University

1951 National University of Ireland

1964 Gustavus Adolphus College

MEMBER

American Academy of Arts and Sciences

American Chemical Society

American Philosophical Society

American Physiological Society

American Society of Biological Chemists (President, 1925–1926)

American Society of Experimental Biology and Medicine

American Society of Experimental Pathology

Association of American Physicians

Endocrine Society (President, 1930–1931)

National Academy of Sciences

Sigma Xi

HONORARY MEMBER

Columbian Society of Endocrinology

Heberden Society, London

Royal Society of Medicine of England

Swedish Society of Endocrinology

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KEY TO ABBREVIATIONS

- Am. J. Physiol. = American Journal of Physiology
Arch. Intern. Med. = Archives of Internal Medicine
Biochem. J. = Biochemical Journal
Collect. Pap. Mayo Clin. = Collected Papers of the Mayo Clinic and the Mayo Foundation
Fed. Proc. = Federation Proceedings
J. Am. Chem. Soc. = Journal of the American Chemical Society
J. Am. Med. Assoc. = Journal of the American Medical Association
J. Biol. Chem. = Journal of Biological Chemistry
J.-Lancet = Journal-Lancet
J. Org. Chem. = Journal of Organic Chemistry
Med. Clin. North Am. = Medical Clinics of North America
Minn. Med. = Minnesota Medicine
Proc. Soc. Exp. Biol. Med. = Proceedings of the Society for Experimental Biology and Medicine
Proc. Staff Meet. Mayo Clin. = Proceedings of the Staff Meetings of the Mayo Clinic
Trans. Assoc. Am. Physicians = Transactions of the Association of American Physicians

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