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CECIL JAMES WATSON

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A Biographical Memoir by

RUDI SCHMID

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C J Watson

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SINE DOCTRINA VITA EST QUASI MORTIS IMAGO[1] (Life without teaching would be just an image of death).

Cecil James Watson was first and foremost a medical educator. His boundless enthusiasm and insatiable intellectual curiosity stimulated countless medical students to search for the why of clinical phenomena observed at the bedside. When neither clinical observation nor literature search were able to provide answers, the laboratory became the arena where solutions were sought. Cecil Watson was far ahead of his time in recognizing the indispensability of chemical and biochemical exploration for the understanding of disease. His pioneering scientific work on the metabolism of hemoglobin, porphyrins and bile pigments emanated largely from puzzling clinical observations for which his restless mind demanded explanations. But even when his scientific inquiries took him deep into the realm of chemical analysis, animal experiments, or tracer studies, he never lost sight of the original clinical observations which had stimulated his far-reaching investigations. Long after his retirement from academic responsibilities, he had the unique intellectual satisfaction of discovering a highly effective and often life-saving therapy for a disease which had preoccupied him for

over forty years—the successful treatment of acute porphyric attacks with the infusion of hematin.

Cecil James Watson was born in Minneapolis, Minnesota, the oldest of four children of James Alfred Watson, M.D., an eye, ear, nose, and throat specialist who practiced in Minneapolis. The senior Doctor Watson was born in Ireland and immigrated at the age of sixteen to Western Manitoba, where he taught school. He enrolled in the University of Manitoba and received his M.D. degree in 1895. After a few years in general practice in rural Woodlake Tours, Minnesota, he took special training in New York and Vienna before setting up his specialty practice in Minneapolis. In Wood Lake, he met his future wife, Lucia Coghlan, the daughter of Irish immigrants who homesteaded in western Minnesota shortly after the Civil War. Both parents were self-taught scholars in the classics who provided Cecil with ample intellectual nourishment and stimulation during the school years, and engendered in him a lifelong passion for literature and history and particularly for Greek and Roman mythology. He later somewhat ruefully acknowledged, "I spent a great deal of time reading in this general area and must say that I devoted relatively little time to mathematics and science which I now regret." But his classic education left him with an unusually broad range of knowledge in the liberal arts, and endowed him with a superb command of the English language which, during his professional life, was reflected in the brilliance of his lectures and the lucidity of his scientific publications.

In 1919 Cecil entered the University of Minnesota, where he concentrated primarily on English and French literature and writing. In fact, he seriously considered a literary career because at that time science had little attraction for him. Summer recesses were either spent working on farms in western or southern Minnesota or on a small island in

the Rainy Lake wilderness of Ontario, which Dr. Watson, Sr., had bought as a holiday retreat. This romantic island, accessible only by boat, became a lifelong second home to the extended Watson family, as both of his brothers and sister and their families built cabins of their own, located around a common dining and recreation area. In later years, Cecil was fond of inviting intimate friends or distinguished foreign colleagues to his island retreat, where they could relax in congenial informality, spoiled by Cecil's generous hospitality.

The turning point in Cecil's intellectual orientation came with an advanced course in comparative physiology taught by Professor Lund, who was one of the University of Minnesota's outstanding teachers. So stimulated was he by this magnificent intellectual experience that he carried out a number of experiments in heliotropism. His experiments, as he says, "contributed nothing new," but the seed had been planted and his interest in biology was further invigorated by Jacques Loeb's classic *The Physical-Chemical Basis of Life.* In 1921 he decided to enter medical school. Since he lacked qualification in organic chemistry and quantitative analysis, he had to satisfy these requirements in the summer of 1921, too late for admission to the University of Minnesota School of Medicine. Fortunately, the University of Michigan accepted him for the entering class of 1921 and he spent a highly rewarding year in Ann Arbor, enjoying particularly the stimulating contact with his anatomy teacher, Professor Carl Huber. In 1922, family reasons compelled him to return to Minneapolis to complete his medical curriculum at the University of Minnesota.

In his second year of medical school, Cecil came in contact with Elexious Thompson Bell, professor of pathology, a brilliant and exceptionally stimulating teacher and one of the era's great experimental pathologists. "Tomi" Bell be-

came, as Cecil said, "my great personal friend, advisor, and teacher, and one of the two most important influences on my professional life." (The other was Nobel laureate Hans Fischer, professor of chemistry at the Technische Hochschule Munich.) At the end of his senior year, he accepted a fellowship in pathology under Bell's direction. In his first experiments, he confirmed previously published observations that thrombocytopenic purpura could be reproduced with an antiplatelet serum, a finding which later turned out to be of seminal significance for the understanding of autoimmune diseases. Another study, which served as a thesis for a master in science degree earned with his M.D. degree in 1926, concerned periarteritis nodosa, then a little understood disease. In the same year, he happened to perform an autopsy on a patient who had died from a peculiar systemic disease which turned out to be the first case of disseminated histoplasmosis discovered in the continental United States. This logically led to a more expanded study of the origin and function of phagocytes in the spleen, an investigation which eventually formed the basis for a thesis for a Ph.D. degree in pathology.

In 1928, equipped with every academic degree which a medical school can confer, an independent professional position beckoned and Cecil and his young wife, the former Joyce Petterson, moved to the recently founded private clinic in Minot, North Dakota. In his new position he was the resident pathologist and director of laboratories, but also functioned as an internist and, most importantly, found time to continue laboratory studies which he had begun in Minneapolis. While in medical school, he had suffered a bout of catarrhal jaundice, recognized today as epidemic viral hepatitis. Notwithstanding the distressing discomfort associated with this illness, he made detailed observations about the course of his disease, including the curious finding that

urobilinogen (an intestinal reduction product of bilirubin) disappeared from his excreta at the height of his jaundice, but strikingly reappeared in his urine when the condition began to improve. This personal experience of ill health had a decisive influence on his professional career, stimulating his lifelong obsession with bile pigment metabolism and diseases of the liver. It was his nascent interest in basic aspects of bile pigments that led him back to an academic career of investigation and teaching.

In the summer of 1930, the Watsons returned to Minneapolis where Cecil took an advanced course in organic chemistry under his old teacher, Professor William Hunter. With the help of Dr. George Fahr, a pioneer cardiologist at the University of Minnesota, he was successful in obtaining a fellowship in the laboratory of Nobel laureate Hans Fischer in Munich, who was then the world's leading expert in the chemistry of hemoglobin, bile pigments, and porphyrins. The two years in the Bavarian capital were among the most stimulating and enjoyable periods of Cecil's life. He and Joyce fully partook of the exciting cultural offerings of this budding metropolis and made deep friendships with many German and foreign scientists working in Munich's famous academic institutions, including Ian Waldenstroem, Richard Duesberg, Irvine Page, and von Kress. On many outings to the Bavarian Alps, sometimes in the company of his younger sister Elinor, Cecil learned to ski, a sport which he continued with great enthusiasm and considerable ability for most of his life. He also learned to speak fluent German, which he spoke with an alluring American accent. Many years later when he was awarded an honorary doctor's degree from the University of Munich, he still was able to present his acceptance oration in nearly flawless German.

In Hans Fischer's laboratory under the master's personal supervision, Cecil succeeded in crystallizing stercobilin from

human feces, an accomplishment that had eluded even Hans Fischer. The crystalline material was used to provide definitive proof that stercobilinogen (the normal intestinal reduction product of bilirubin) was not identical with urobilinogen nor with mesobilirubinogen, as up to then had been believed. A violet by-product that fell out during the crystallization was identified as mesobiliviolin, which was the first time that occurrence of this pigment was demonstrated in nature. But apart from these remarkable research achievements, Cecil was enormously stimulated by the scientifically exciting atmosphere of the Fischer laboratory and the Technische Hochschule Munich, as well as Professor Friedrich von Mueller's medical clinic at the University of Munich, which he often visited.

Having gained a comprehensive understanding of tetrapyrrole chemistry, he began to recognize the immense potential of this new knowledge for the study of human disease. Upon his return to Minneapolis in 1932, he was firmly resolved to pursue an academic career of basic and clinical investigation in the bile pigment/porphyrin field, hoping eventually to become professor of medicine. The first two years at the University of Minnesota were spent on the medical house staff of the Minneapolis General Hospital and the university hospitals, gaining broad experience in clinical medicine, including riding the ambulance which, at that time, was a duty assigned to assistant residents. Part of the afternoons and some evenings and weekends were available for research in a small laboratory equipped with the essential tools paid for with personal funds. When he was still an assistant resident, he was assigned the medical school's course in clinical chemistry and microscopy, including all the lectures and supervision of the students' laboratory work. He was a brilliant teacher whose stimulating discussions of the application of laboratory methods to

the solution of clinical problems profoundly influenced many of his students. The medical school's administration quickly recognized his exceptional talents as teacher, investigator, and clinician. In 1934 he was appointed assistant professor of medicine, and in 1936, associate professor and director of the Division of Internal Medicine, which was a component of a larger department of medicine including neuropsychiatry and dermatology. In 1942 internal medicine was made an independent full department and Cecil was appointed its first full-time head.

The newly established Department of Internal Medicine was quite small; it consisted of only two other full-time faculty members, two interns, and two residents. Although much of the clinical teaching was assigned to part-time clinical faculty, Cecil and his two full-time colleagues carried a heavy load of lectures and courses. Administrative duties were relatively undemanding, leaving a reasonable amount of time for his research in which he was soon joined by Samuel Schwartz. Unfortunately, these busy and happy days were soon interrupted by his war-related assignment to the Manhattan Project. In 1943 Cecil was appointed associate director of the Health Division of the so-called Metallurgical Laboratory, a top secret position which for the next two years required him to divide his time between departmental responsibilities in Minneapolis and supervision of novel toxicity studies of uranium and related radioactive substances in Chicago. It wasn't until 1946 that he was able to return full-time to his department and to resume his personal research activities.

During the early postwar years when the federal government began its progressively expanding support of biomedical research, the Department of Medicine at the University of Minnesota rapidly grew in size, both in breadth and in depth. Under Cecil's strong and visionary leadership, it soon ac-

quired a national reputation as one of the country's outstanding departments, combining academic excellence with sound teaching of clinical medicine. He was a tower of intellectual strength and inspiration and contributed in a major way to make the University of Minnesota one of the nation's outstanding institutions of teaching and research. As his pioneering scientific achievements gained national and international recognition, Cecil was increasingly asked to serve on national committees or boards and to chair scientific conferences or research meetings. He had a major impact on the policy of the newly established National Institutes of Health, serving in sequence as a member of the Advisory Council and chairman of the Board of Scientific Counselors of the National Institute of Arthritis and Metabolic Diseases. As consultant to the Surgeon General of the U.S. Army and director of the Commission on Liver Disease of the Armed Forces Epidemiological Board, he guided the early studies on the transmission of viral hepatitis. At the level of the National Research Council, he was a member of the Committee on Medicine, the Medical Fellowship Board, and the Executive Committee of the Division of Medical Sciences. He also was president of three of the country's most prestigious academic research organizations, the Central Society of Clinical Research, the American Society for Clinical Investigation, and the Association of American Physicians. As a member of the Executive Committee of the American Board of Internal Medicine, he was instrumental in revising its examination system and introducing objective types of testing. But despite his many responsibilities on the national level, he never neglected his own research, continuously carrying out experiments in his personal laboratory and guiding and stimulating his students and research fellows. Everybody in his department was expected to be doing research, and Cecil took an active interest in all

of these projects, personally reviewing the data and helping with the writing of the manuscripts.

Cecil Watson's major scientific contributions centered on broadly defined aspects of the formation and degradation of the heme group (iron-protoporphyrin) of hemoglobin. The knowledge and insight into tetrapyrrole chemistry which he had acquired in Hans Fischer's laboratory served as the essential experimental tools. He used them with great originality and skill to gain an understanding of the nature and physiological significance of the many biosynthetic intermediates and degradation products of heme which are eliminated in human excreta. He was particularly fascinated by a series of hereditary defects in heme synthesis—the porphyrias—in which relatively large amounts of porphyrins and porphyrin precursors are excreted in urine and feces. Another area of great interest to him was the formation and structure of the various heme derivatives which are formed in the intestine from bilirubin and are in part reabsorbed and re-excreted in urine or bile. His studies supplied the essential experimental proof that excreted porphyrins represent intermediates formed in the course of heme synthesis, whereas the tetrapyrroles of the urobilin group are degradation products of heme formed by stepwise microbial reduction of bilirubin in the intestine. Clarification of this crucial difference of origin set the stage for a better understanding of the pathophysiologic and diagnostic significance of increases in the excretion of these compounds which occur in a variety of inherited or acquired diseases of the liver or the erythropoietic system.

Cecil's approach to the study of these conditions was both logical and methodical. For example, he and his associates first developed the technology to identify and quantitate the prophyrins and their precursors excreted under normal conditions. The information gained was then used

for a study of over one hundred patients with porphyria from which gradually emerged data indicating that each of the various forms of the disease exhibited a characteristic pattern of increased porphyrin excretion. A demanding project in which the porphyrin content of the liver, bone marrow, and circulating erythrocytes was compared in thirty patients with porphyria, revealed that in most instances the excreted porphyrins were derived from the liver, suggesting a defect in heme synthesis expressed only in this organ. On the other hand, the very rare congenital erythropoietic porphyria was shown to be due to a recessively inherited defect of hemoglobin synthesis in maturing normoblasts of the bone marrow.

With his coworker Samuel Schwartz, Cecil in 1941 developed the classic Watson-Schwartz test for the qualitative detection of porphobilinogen in urine, a diagnostic test which is used to this day for identifying patients who carry the genetic traits of hepatic porphyrias associated with neurologic lesions. The discovery made in Watson's laboratory that allylisopropyl-acetyl-carbamide (Sedormid) induces an experimental hepatic porphyria in rodents laid the groundwork for the subsequent elucidation of the mechanism and regulation of heme synthesis in the liver. Crucial contributions to this problem were also made by many other laboratories in this country and in Great Britain. But it was Cecil who eventually put it all together when he recognized that acute porphyric attacks are associated with severe heme depletion in the liver. Although it is still unclear how hepatic heme deficiency produces acute paralysis or psychosis, he and his associates demonstrated that heme replacement by intravenous infusion of hematin strikingly reduces the greatly increased excretion of delta-aminolevulinic acid and porphobilinogen, which is the hallmark of the porphyric attack. This chemical improvement was associated with rapid

reversal of the neurologic lesions, thereby terminating the acute attack which in the past had often progressed to fatal respiratory paralysis.

Among other important contributions was the finding that in addition to protoporphyrin, circulating erythrocytes contain small amounts of coproporphyrin, the level of which is related to the rate of hemoglobin synthesis. In pellagra, the pink urinary pigment which had been assumed to be a porphyrin, was identified as urorosein, a derivative of indole acetic acid. A simple and practical bedside method was developed for the separate identification of porphobilinogen and urobilinogen in urine. But it was his comprehensive work on the hereditary porphyrias which made Cecil Watson the leader in the field and brought him national and international recognition, including election to membership in the National Academy of Sciences in 1959 and two honorary doctor degrees from the Universities of Mainz and Munich.

Cecil's other great passion was the bile pigment bilirubin and its derivatives. Recall that he had originally been attracted to bile pigment metabolism as a medical student after contracting viral hepatitis. The methods he developed for distinguishing and quantitating different bilirubin fractions in the serum are still in use today for the differential diagnosis of jaundice. But it was the metabolic fate of the bilirubin excreted with the bile into the intestine which had a particular fascination for him. A large number of his early investigations and most of his work in Munich were devoted to this puzzling problem which captivated him throughout his professional life. One of his early findings showed that when bilirubin has reached the intestine, it is almost quantitatively converted to colorless derivatives by the intestinal microflora. On oxidation, these chromogens turn into bright orange pigments, several of which Cecil

succeeded in crystallizing. He was enamored by the physical beauty of these colorful crystals, undoubtedly a legacy of Hans Fischer, of whom Cecil said, *"Er spuckt in die Hand und es krystallisiert sofort aus"* (he spits in his hand and it immediately crystallizes). Painstaking analytical work carried out with modern spectroscopic and chemical methods demonstrated three major types of bile pigment derivatives in feces: the levorotatory stercobilin, d-urobilin, and optically inactive urobilin, which he succeeded in producing by reduction of bilirubin in vitro. Much of what is known today about the chemical structure, formation and quantitative excretion of these tetrapyrrole compounds originated from Cecil's laboratory, and he was the undisputed master of the field.

With his associates, he conducted a large series of physiological studies which revealed that small fractions of the colorless chromogens are absorbed from the large intestine and either excreted in the urine or recycled to the liver for re-excretion in the bile. In many forms of liver damage this hepatic pathway is impaired, causing excessive excretion of chromogens and their oxidation products, the urobilins, in the urine. On the other hand, in more advanced liver disease which interferes with the excretion of bile into the intestine and produces deep jaundice, urobilin-type pigments almost completely disappear from the excreta. This finding had mystified him when he had a period of severe jaundice during his illness with viral hepatitis. In his later work, Cecil and his chemist associates proceeded to characterize a number of minor bile pigment derivatives and on several occasions attempted to isolate dipyrrolic compounds which were thought to represent further intestinal breakdown of bilirubin. Because of their insolubility and tendency to polymerize, these so-called fuscin pigments proved difficult to iso-

late, and their role in bile pigment metabolism, if any, has remained obscure.

Another of Cecil's interests was the broad area of chronic liver disease. Although the number of published papers was relatively small, several were of unusual significance because they introduced novel concepts in this poorly understood field. One was the discovery in 1947 that patients with evolving cirrhosis of the liver often had an antecedent transient episode of jaundice. This observation anticipated the modern concept that some cases of acute viral hepatitis develop a chronic smoldering form of the disease which eventually progresses to cirrhosis. Another was a critical evaluation of the usefulness and limitations of liver function tests, which at that time were being introduced as a means of differential diagnosis of liver ailments. A third important contribution was the description of so-called cholangiolitic cirrhosis, which in contrast to Laennec's cirrhosis, consists primarily of hyperplasia of bile duct elements, a condition which today is known as primary biliary cirrhosis. An additional series of papers unrelated to liver disease, but worth mentioning because of their uniqueness, reported the discovery with A. B. Lerner of cold-precipitable globulins in the sera of some patients with purpura. These so-called cryoglobulins, reversibly precipitated by cooling the serum to 5 C, were later recognized as part of a new form of dysproteinemias. These studies brought Cecil Watson international renown as an expert in liver disease, and his intellectual leadership had a major impact on the directions of research in hepatology in the postwar years. From 1942 to 1948 he served as chairman of the prestigious Liver Injury Conference, a series of annual meetings sponsored by the Josiah Macy, Jr. Foundation, which brought together many international experts in this emerging field. The published proceedings of

this conference set the scientific tone for contemporary research in hepatology.

In 1966, after twenty-four years at the helm of his department, Cecil resigned the chairmanship, and with the university's encouragement, moved the base of his operation to the Northwestern Hospital, one of Minneapolis's leading private hospitals affiliated with the medical school. Here he was given the opportunity to set up a new University of Minnesota Professorial Unit for Teaching and Research in Internal Medicine, which soon became an attractive center for undergraduate and graduate medical education. Freed from administrative responsibilities, he was able to devote much of his time and energy to research and his scientific productivity remarkably increased. During the subsequent fourteen years, he published a total of seventy-seven papers, eleven of them in the *Proceedings of the National Academy of Sciences*, the last of which appeared when he was seventy-eight years old. This was the time when he and his coworkers discovered the beneficial effect of hematin infusion for aborting acute porphyric attacks, but he also returned to his first love, the structural characterization of bile pigments excreted in the feces.

To Cecil, research was the fun of discovery and the personal satisfaction of contributing new knowledge. True to his credo that "the clinical investigator, though he may be actively involved in patient care, is under no obligation to slant his research toward treatment, or even toward mechanisms of disease, and may, if he wishes, devote himself to basic problems which may or may not have ultimate application to human disease," he searched for solutions wherever he saw a challenging problem. He was one of his generation's few leaders of academic medicine who was able to successfully combine excellence in clinical teaching and patient care with creative and original basic research, and

thereby was an outstanding and admired role model and inspiration to countless students and colleagues.

NOTE

1. "Life without teaching would be just an image of death," a quotation found in one of Cecil Watson's laboratory notebooks.

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