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SIDNEY WEINHOUSE
1909—2001

A Biographical Memoir by

GLORIA M. HANSON AND RICHARD W. HANSON

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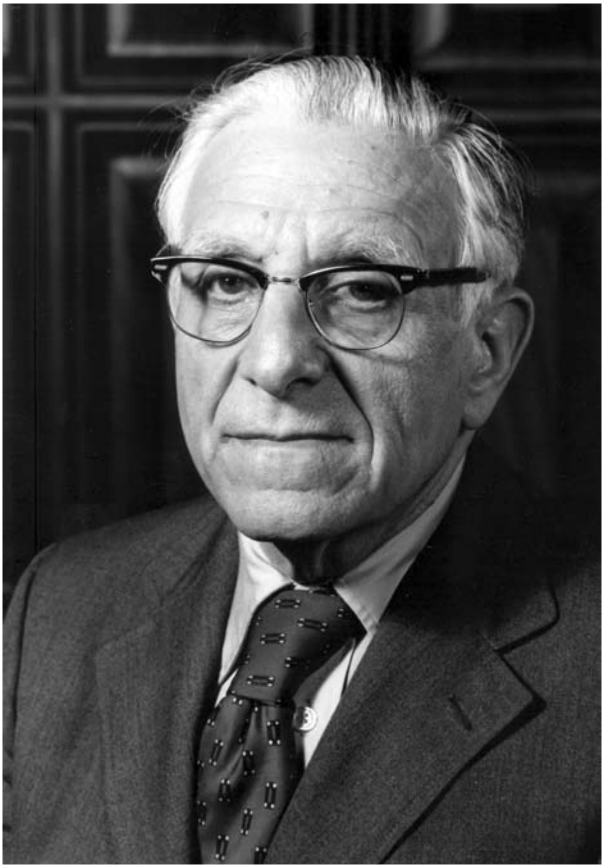

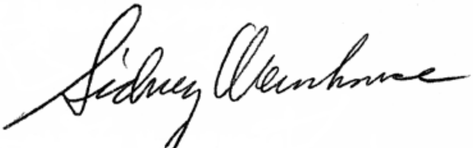

SIDNEY WEINHOUSE

May 21, 1909–February 9, 2001

BY GLORIA M. HANSON AND RICHARD W. HANSON

"Praising what is lost, makes the remembrance dear."
All's Well That Ends Well, William Shakespeare

HIS LIFE AND TIMES

SIDNEY WEINHOUSE WAS BORN on May 21, 1909, in Chicago, Illinois, to parents who had emigrated from Bessarabia. Bessarabia was a region of 17,600 square miles located in the current Ukraine and Moldova. The Dniester River in the north and east, the Prut in the west and the Danube and the Black Sea in the south bound the land. It was an area of hilly plains and flat steppes, perfect for agriculture, dairy cattle, and sheep herding. As a gateway to the Danube region Bessarabia became an invasion route from Asia to Europe, and had been part of the Ottoman Empire, Rumania, Moldova, and the Soviet Union.

The family was reticent to speak of their immigration from Bessarabia so there is not much history the children and grandchildren can access. Sidney's father was 18 when he immigrated to the United States; his parents came later. In April 1903 the Kishinev pogrom occurred in Chisinau, the capital. Anti-Semitic articles incited the public to act against Jews. One newspaper, *The Bessarabian*, insinuated that the local Jews had killed a Russian boy while another, *The Light*, elaborated on the story, writing that the Jews used the boy's blood to make matzos. This was the first media propaganda blitz against the Jews in the 20th century. The pogrom in Chisinau killed 47 Jews, wounded 92, and destroyed 700 homes. We can only speculate as to whether this anti-Semitic atmosphere spurred the Weinhouse family to flee.

Sidney's father worked as a newspaper distributor. In typical immigrant style he welcomed his parents to reside with his family. Although not religious himself, he did encourage his children to attend Hebrew School. Sidney's grandfather was the religious one and assisted the rabbi as a shahmus. Sidney remembered this gentle, patient man with a white beard who loved to read Yiddish and who would obtain books from the library through the efforts of his grandchildren.

Sidney, his sisters Pearl and Edith, and his brothers Myron and Norman lived with their family in the Bridgeport area of Chicago, a melting pot neighborhood of Irish, German, Lithuanian, Italians, and Jews. Despite the name calling, fights, and competition, the younger generation coexisted. Since they were all at similar socioeconomic levels, they possessed a community spirit that was evident in the sharing of the same milk, bread, and coal home-delivery men and the condolences and inquiries when a parent or relative would die. They all wanted to "fit in," assimilate and become Americans. Sidney was embarrassed when his grandmother would yell from the window in Yiddish so all the children could hear her. He would devour books about boys' lives and then try to emulate the American boys described in the stories.

Sidney was a precocious youth, learning to read by three years of age. He would sit at the kitchen table by his brother who brought homework from school. At age six he was in the second grade, at 12 he was in the eighth grade, and he graduated from high school at 16. The high school in his community was not academic, as most of the kids would go to apprenticeships or vocational, secretarial, or industrial work classes. Sidney, the eager student, would travel an hour by streetcar to a new high school in Lyndbloom and the only one in the city with a swimming pool and one of the few with a strict academic regimen. He would later praise his school where he would be required to take four years of mathematics and English in addition to two years of Latin and courses in general science, chemistry, and physics. There he developed a love of chemistry with books such as *The Wonders of Chemistry* and a beginning passion for research that was conducted in his home basement. He benefited greatly from these days of less parental oversight and regimentation where children could roam at home and outside in the pursuit of their interests.

Sidney would describe himself as an above average student with a strong intellectual curiosity and perseverance. He would brag about his grades of E's, G's, and S's with no F's. The demanding courses in high school with the grilling in grammar rules and Latin conjunctives would serve him well later when he would become a good writer and editor. Sidney was not very social in high school since he loved doing his thing—reading, chemistry experiments, and working in the school kitchen, and delivering newspapers in order to earn his spending money. His one very good friend, Fred Stand, would remain his lifelong buddy. Stand's daughter would marry one of Sidney's students, George Streiker.

Because father wanted Sidney to become a musician, he provided violin lessons and would accompany Sidney to instrumental concerts and plays. At home the family would listen to music on the RCA Victor phonograph or the radio; despite his parents' lack of formal education, the children were encouraged to learn and advance. This message was a common one among immigrant families, who saw education as a way out of the backbreaking work of the uneducated man.

Sidney was interested in sports, especially baseball, ice skating, and swimming. He recalls his early experiences with ice skating when community leaders would flood the baseball field. The children would fasten their skates to their shoes and glide well into evening dusk since they could warm up in a hut nearby. In summer he would swim at the city pool on “boys days” and shower in the public facilities once a week after paying two cents for soap and towel. Sidney, being too small for varsity school sports, enjoyed the games in his neighborhood with his friends.

Following his graduation from high school in 1925, Sidney worked at Western Electric making $26 per week. He knew that he wanted to go to college and enrolled in nearby Crane College, a two-year affordable school. He soon lost interest in studies and quit after one year. He worked for a chemical supply company and at a margarine company in the Chicago stockyards. At that time there were two kinds of margarine: one made from lard and beef fat and the other from vegetable oils. Federal laws governing margarine prohibited manufacturers from adding dye to the white margarine to make it look like butter. The company management decided to switch to vegetable oils. They imported yellow palm oil from Africa and treated it to remove the bad taste. Congress then rescinded the law and allowed coloring to be added to animal fat margarine. This left the company with enormous quantities of palm oil, and it eventually went bankrupt.

Sidney lost his job, but since he was living at home with his extended family he could afford to return to Crane, where he studied and worked as a laboratory assistant. Finishing his second year, he graduated, worked, and took courses at the prestigious University of Chicago in the evenings studying with the graduate students. He earned his bachelor of science degree and then worked with Professor M. S. Kharasch; his Ph.D. came two years later. He would later finish his postdoctoral work with this same mentor, studying the chemical composition of steroids.

At the time of his university studies and around the time his mother died of colon cancer, Sidney began dating his sister Pearl's best friend, Sylvia Krawitz, who worked as a financial reporter for Dun and Bradstreet. Sylvia came from a large family that had emigrated from Lithuania. She was not too happy with the prospect of marrying a Ph.D. student, but the young couple finally tied the knot in a schul in 1935. A party was held at Sylvia's parents' home. This was during the Great Depression, and there was not much money for an elaborate affair or a honeymoon, so both returned to work after the celebration. Their first apartment was on Kimbark Avenue near Midway where they lived for six years before starting a family.

Sidney became the first recipient of the Seymour Coman Fellowship, receiving $3,600 a year, and began working at St. Luke's Hospital at 14th Street and Michigan Avenue. There he collaborated with Edwin Hirsch, a pathologist who was interested in the etiology of arteriosclerosis. They would study autopsied arteries and analyze the plaques that contained lipid deposits similar to those found in blood. This research gave Sidney some recognition in science, and he and Hirsch remained friends and colleagues until 1941, when Sidney was called to serve in the Office of Scientific Research and Development at the University of Chicago.

At this laboratory Weinhouse and Hirsch worked on nitrogen mustard gases. On one occasion a fire broke out in the laboratory; Sidney jumped from a third-story window and broke his leg and several vertebras. The burns he sustained would keep him in the hospital for three weeks and imprint a memory on his daughter, Barbara, who still remembers the scars on his knuckles. While recovering at home, he learned of the attack on Pearl Harbor. Upon returning to work he was told that he would be required to get periodic blood analysis, and that if his white blood count was too low, he would be furloughed. Years later he discovered that scientists on the fourth floor of the Jones Laboratory Building were concentrating uranium. He and three other scientists developed a rash and were told that this skin eruption was from the compounds they were using to study gases, but Sidney believed the cause was from radiation spilling down the walls. He continued to work in this laboratory until 1944. By that time Sidney and Sylvia were the proud parents of Doris, born on March 31, 1941, and James, born on July 18, 1943.

The family moved to Chester, Pennsylvania, in 1945, following an invitation by A. G. Von Grosse to work on biochemical research at the Houdry Process Corporation. Von Grosse had worked briefly on the Manhattan Project, developing the atomic bomb. Many of the best scientific minds in the United States and Europe had been employed to work on the bomb, since the government suspected that Hitler was close to success in the development of his own nuclear bomb. Many scientists refused to work on this project, and Von Grosse was one of them.

The president of the company, J. Howard Pew, asked Sidney about his knowledge of isotopes; he was interested in extending the use of isotopes to study metabolism. Sidney was excited to enter this field and helped the engineers of the company build and equip a laboratory capable of producing carbon 13 for biochemical research. The results of these studies encouraged Sidney to learn more about biochemistry, and he undertook a self-study course to learn this specialty.

On December 14, 1948, Barbara Weinhouse joined the family. Despite Sidney's busy career, he was a supportive and involved father. His daughter Doris was the student in the family, earning her father's praise. James, interested in music, was encouraged by his father to practice one hour per day. If he didn't complete this daily task, he would have to play along with Sidney on the violin, a consequence no one in the family relished. James would take up the trombone in the fourth grade, and Sidney would accompany him to his auditions. Sylvia, an intelligent and talented woman, who although not formally educated, played the piano by ear and became the artsy parent who would be devoted to her family and to their activities. Sidney would play ball with his son and his friends in the back yard and entertain students and colleagues from all over the world. Sylvia would sometimes tire of the constant stream of visitors and guests as she tried to balance her role of wife of the famous scientist, mother, hostess, and scout leader. She realized that she and her children benefited from the exposure to people from different cultures.

The family moved near Fox Chase in Pennsylvania in 1950 when Sidney took a position as leader of the Department of Metabolic Chemistry at the Lankenau Hospital Research Institute and the Institute for Cancer Research, where he studied the synthesis of essential amino acids and the metabolism of cancer cells. This became his major research focus for three decades both here and at the Fels Research Institute at Temple University. In 1957 tragedy struck. Sylvia died of a brain tumor after a short illness when her cancer metastasized from her lungs. She was 45 and left Sidney as sole parent to three youngsters of 16, 14, and 8. His family from Chicago flew in to assist him during this terrible period of grief and adjustment. Sidney would consider moving to Chicago to take a position at Rush Medical School in order to provide some family support for his children, but he decided to remain with his professional family in Philadelphia. He hired a housekeeper to help with the running of his home and care of his children.

Sidney did not speak to his children regarding their mother's illness and death. This reticence was part of his personality, but it was also uncommon for a parent to show much emotional involvement with children. The 1950s were not years of daily I-love-you's, hugs, kisses, and over-involvement. In addition, cancer was not spoken of openly, since it was a feared and dreaded disease. Sidney, who had once been a two- to three-pack-a-day cigarette smoker, quit and turned to oranges as an antidote. His daughter Doris once asked her father whether he believed in life after death. "You are my life after death," he replied.

Sidney was not a particularly religious man, but he joined a temple in order to bring stability to his children's lives. In 1962 Sidney moved the children to a house on Lawton Street in Philadelphia. Here he could continue with his gardening and entertaining while being closer to work. The widower was a devoted father but expected the best from his children. If they were able, they were to excel and at least try their best. If they did not achieve, he would try to find out why and help them. If they misbehaved, he sought to solve the problems on his own since he was not a believer in seeking professional help. At that time the major focus in the mental health field was psychoanalytical, and he did not want to enter himself or family into long-term treatment.

The children struggled to cope with the death of their mother in their own individual ways. Doris would try to please dad by becoming a good student and helping to care for her siblings. She and Jim developed strong sibling rivalry, especially since Jim was a more rebellious adolescent than she. He wanted to be "cool" and become a musician. He needed a firm hand, and Sidney tried to be firm and fair. Of course, Jimmy didn't always see his father's behavior in that light, so there were many skirmishes during his teenage years. Barbara, being the youngest, was the happy child who would bring joy to her father, even when she struggled with math and being motherless.

As adults the children agree that their father was strict, reasonable, and an engaged parent despite his long days in the laboratory and travel for his scientific career; they did not feel deprived or unloved. When Sidney was with them, he was "there." The children developed their own interest over the years. Doris attended college, majoring in Spanish and French, and became a librarian. Jim attended West Chester State College, where he majored in the trombone. Barbara made a career in public school nursing.

Meanwhile, Sidney, an eligible bachelor for 12 years and dating many women, met a vivacious widow named Della Kannerstein Klein, who had been raised in the ethical culture philosophy and was the mother of three children, Susan, Robert, and Andy. Della was an ebullient woman with an elegant look, and the couple traveled and entertained colleagues, friends and his son, Jim and his fiancée, Barbara. Sidney had always been known to have an appreciation for good-looking women, and Della met that standard in addition to being gregarious and free-spirited.

Since the children had graduated and moved, Sidney was free to move from his family home into Della's apartment at 19th and Chestnut in Philadelphia following their marriage. Doris married Charles Angell and moved to Oak Park, Illinois, where her husband joined his family's baking business; the couple had two boys, Jim and Mike. Jim Weinhouse worked in New Jersey as a public school music teacher, retiring in 2004 to devote his time to playing with the Atlantic Brass and the Lansdowne Symphony, in addition to playing euphonium with various jazz groups. Barbara married Steve Hanan, a government employee, and moved to Chicago, where the couple raised three girls, Sandy, Diana, and Linda.

In 1990 Della suffered a stroke, leaving her with aphasia and damage to her judgment capabilities. Sidney cared for her in their apartment until his own physical problems necessitated outside help and more reliance on his son, Jim. Sidney had developed shingles and knee problems that necessitated surgical intervention, and he was diagnosed with leukemia that had been first labeled as "anemia requiring transfusions." Sidney wanted to care for Della, as he had done with his children once his wife died. He would hire outside help only when needed, but he did allow his son, Jim, and his fiancée, Barbara, to assist him. He struggled and persevered despite his pain until his death on February 9, 2001. He was in his home surrounded by his children. Surviving him were five grandchildren, one great-grandson, two stepchildren, two sisters and a brother, his son, and two daughters. Della, his wife of 32 years, died of lung cancer a few years later.

Sidney Weinhouse was an American success story. He lived in a time of expanding scientific advancement. Scientific research in all of the disciplines was a jewel in the crown of the United States. The government and the populace supported the outlay of money to encourage young scientists, and the field of biochemistry was exploding with groundbreaking research. Sidney was at the forefront of this movement, not only for his scientific contributions but also in his policy making and creative building of institutional alliances. He was a beloved mentor and teacher to the hundreds of students, postdoctoral fellows, and colleagues; he was thoughtful and available for advice or exploration of ideas, and his attitude was one of a patient, encouraging parent who would allow individuals to grow without control. He was not a selfish man seeking fame on the backs of others.

To his family Sidney was the same man. Familiarity did not breed contempt. He was generous, determined, ambitious, perseverant, independent, and sometimes stubborn. Generally, he was a gentle soul with a long fuse for anger. Reserved and ever the gentleman, he would shun you if he didn't like you or what you were doing, but loyalty to family, friends, colleagues, and to his science was bred into his bones. Although he kept his own counsel, he could enter into a lively conversation on any topic or enjoy a good laugh. His voice was smooth and inviting, and he always had something interesting to say when he decided to speak. As a humanist and teacher he led by example. As a husband he was attentive, loving, and steadfast. As a parent and doting grandparent he was supportive and kind. As a human being he was one of a kind.

HIS SCIENTIFIC CONTRIBUTIONS

Sidney Weinhouse began his scientific career as a biochemist in the period following World War II. This period witnessed an explosion of new information about the chemical basis of cellular function, and Weinhouse was for his entire career at the cutting edge of this field. His doctoral research was in organic chemistry; this training equipped him to approach biochemical problems with a firm understanding of the chemical principles upon which all life processes are based. There were two areas of research that especially interested Weinhouse throughout his career: metabolism and cancer. Early in his career his research focused on metabolism as a discipline. His major contributions to biochemistry came with the elucidation of key steps in metabolic pathways and later in the application of metabolism to an understanding of the mechanisms responsible for neoplasia. He worked mainly in the era that preceded molecular genetics, so that much of his research involved an analysis of the results of neoplasia rather than its cause. However, he was an early proponent of biochemical research aimed at a better understanding of cancer in all its stages; in this regard he was a true pioneer.

DEFINING METABOLIC PATHWAYS—THE EARLY YEARS

Weinhouse began the biochemical phase of his research career in the early 1940s in Chicago, where he was the Seymour Coman Fellow in the Department of Pathology at the University of Chicago. His two postdoctoral years were spent studying the synthesis of vitamin D from cholesterol (not a very productive exercise). During this period, he published several papers on the biochemistry of atherosclerosis that included an extensive review in the *Archives of Pathology* entitled "The Blood Cholesterol" (1943), based in part on research in this area Weinhouse published in 1940[1] on the role of fatty acids in the development of atherosclerosis. Weinhouse concluded that this disease develops from "disturbances in the metabolism of lipid infiltrating into the tissues of the intima." More than 65 years later this conclusion seems prophetic.

In 1945 Weinhouse moved to the Houdry Process Corporation (a subsidiary of Sun Oil Company) in Marcus Hook, Pennsylvania, as head of biochemical research. The president of the company, J. Howard Pew, had a keen interest in biomedical research and supported the use of company facilities for the generation of isotopes for use in studying metabolic pathways. Weinhouse had the good fortune of working with Aristide Von Grosse, a physical chemist who led a program to produce ^{13}C-labeled compounds. Interestingly, Harold C. Urey, the Columbia University physicist who first isolated deuterium, helped Von Grosse and Weinhouse extend the use of isotopes to biological research.

The company built a thermal diffusion plant, complete with columns that separated and concentrated ^{13}C from ^{12}C; the ^{13}C was used by Weinhouse and his collaborators to produce labeled compounds of biological interest, such as fatty acids and glucose. They decided to focus on lipid metabolism, and in 1944 he published, together with Grace Medes and Norman Floyd, what was to be a seminal paper on the mechanism of ketone body synthesis; this paper would help establish Weinhouse as a leader of a new group of biochemists that used isotopes to probe biochemical processes.

In the 1940s the specific reactions in the pathway of β-oxidation of fatty acids were not understood, and acetyl CoA, the active form of acetic acid (the product of β-oxidation) was yet to be described. Studies had established that the oxidation of a fatty acid in the liver occurs by cleavage between the α and β carbon atoms of the fatty acid, generating acetate. However, a question remained concerning the mode by which the four carbon ketone bodies, acetoacetate and β-hydroxybutyrate, are formed from the fatty acid. At the time there were three prevalent theories.

The β-oxidation theory postulated that fatty acids were oxidized to the last four carbon atoms, which formed ketone bodies. The multiple alternate oxidation theory presumed that oxidation occurred at alternate carbon atoms prior to splitting into four-carbon units. The third possibility, first suggested by Knoop, was the β-oxidation-condensation hypothesis, which predicted that ketone bodies arise from random condensation of two-carbon units formed through β-oxidation.

To test these three theories, Weinhouse and colleagues incubated liver slices from a fasted rat in a medium containing [1-^{13}C]octanoate, and isolated the ketone bodies. The distribution of ^{13}C in acetoacetate was determined by heating it to generate CO_2 and acetone; they then measured the content of isotope in each fraction, using a mass spectrometer. They noted an even distribution of isotope in each fraction, which supports the prediction of the β-oxidation-condensation hypothesis. Subsequent research found that fatty acids are oxidized by hepatic mitochondria to acetyl-CoA, which is then condensed into acetoacetate, a portion of which is reduced to β-hydroxybutyrate and released from the liver. These groundbreaking studies helped establish the usefulness of isotopic tracers in metabolic research. In 2005 the *Journal of Biological Chemistry* selected the 1944 paper by Weinhouse and his colleagues as part of its biochemical Classics series, an honor reserved for only the journal's most historically significant publications.

In January 1950 Weinhouse became a senior member and chair of metabolic chemistry at the Lankenau Hospital Research Institute. He was also appointed an adjunct professor of chemistry at Temple University, where he taught an evening course in biochemistry and attracted graduate students to his research program. At Lankenau he joined Grace Medes, a well-known biochemist who had discovered tyrosinosis in human subjects when she was at the University of Minnesota. At the Lankenau Hospital Research Institute Weinhouse was involved in delineating the metabolic pathways that produce inorganic sulfate from methionine and cysteine. Over the next decade he published a series of papers in the *Journal of Biological Chemistry* with Medes, Ruth Millington, and Norman Floyd that helped establish the basis for understanding the metabolism of fatty acids in mammalian tissues. This research employed isotopic tracers to determine the oxidation of fatty acids in liver, kidney, muscle, and brain and to trace the metabolic fate of the acetate formed from the fatty acids as it was being oxidized in the citric acid cycle. During the 1940s, it was not clear whether the breakdown product of glucose metabolism, pyruvate, was oxidized to CO_2 by the same mechanism as fatty acids. Weinhouse and his colleagues clearly demonstrated that the addition of citric acid cycle anions, such as oxalacetate or fumarate, to liver slices stimulated the oxidation of fatty acids to CO_2. In addition, isotope from ^{13}C-labeled fatty acids, which was metabolized in the liver, was found in citrate, indicating the entry of fatty acid carbon into the citric acid cycle.

Sidney Weinhouse's research interests were not confined to fatty acid metabolism. Throughout this early period in his career, he had used isotopic tracers to determine the rates of glucose utilization in mammalian tissues and to elucidate the pathways of amino acid metabolism. In 1954 he wrote an article for *Annual Review of Biochemistry*, entitled "Carbohydrate Metabolism," that reviewed the current literature in the field. With Murray Strassman he studied valine and leucine metabolism in yeast and the synthesis and degradation of glycine with Bernice Friedmann and Henry Nakada. Weinhouse was among the first to determine the hierarchy of fuel use in mammalian tissues. Together with Arthur Allen he demonstrated that fatty acid oxidation spares glucose utilization by a number of tissues in the rat.

By the mid-1950s Weinhouse began studies of the disorders of carbohydrate and lipid metabolism characteristic of diabetes. This work with his longtime collaborators George Reichard and Bernice Friedmann was one of the first detailed studies of glucose turnover in mammals. A number of students and fellows also contributed to these studies over the years, including Herman Levin, David DiPietro, Doris Dunn, and Norman Hochella. The use of isotopic tracers to quantify whole body metabolism in the intact animal was a relatively new approach in metabolic research at the time these studies were performed.

Biochemistry is largely a reductionist discipline in which tissues are removed for the analysis of metabolic pathways (liver slices were a favorite of many investigators interested in hepatic metabolism) and enzymes extracted for further study. Weinhouse understood that the interaction of metabolites in vivo is a key element in whole-body metabolic regulation and that studying isolated tissues destroys that interaction and thus provides only a portion of the overall picture. In this regard Weinhouse was a pioneer in obtaining quantitative measurement of metabolite flux rates in living animals, including humans.

In 1960 Weinhouse with a graduate student David DiPietro published the first of several papers on hepatic glucokinase. In this paper they described a method for separating the activity of glucokinase from glucose-6-phosphatase by centrifugation of the microsomal fraction of rat liver and demonstrated that fasting and diabetes dramatically decreased the activity of the enzyme. This was the first detailed study of hepatic glucokinase, and it was followed by a more complete analysis of the properties of glucokinase, in which the K_m glucose (10 to 40 mM) was first reported. Subsequent papers by Alberto Sols and coworkers in Madrid, Spain, and D. G. Walker in Birmingham, England, continued the characterization of the enzyme; their papers compared the kinetics properties of glucokinase with those of the more ubiquitous hexokinase and investigated other physiological aspects of the regulation and development of the enzyme; for example, Sols and colleagues made the important observation that unlike hexokinase, glucokinase is not inhibited by glucose-6-phosphate, and Walker first noted that glucokinase is absent in rat liver until after weaning. The discovery of glucokinase by DiPietro and Weinhouse remains to this day a key advance in our understanding of carbohydrate metabolism.

METABOLISM AND CANCER

In 1950 Weinhouse began a phase of his research that would be a major focus of the rest of his career as a scientist. Employing the same critical approach he had used to study lipid and carbohydrate metabolism in liver, muscle, and other normal tissues of the rat, he demonstrated that fatty acids were oxidized by tumors as readily as they were in normal tissues. He noted that the rates of CO_2 output from labeled palmitate and acetate by slices of hepatomas, mammary carcinoma and rhabdomyosarcoma were similar to the values found with liver and kidney (even higher in some cases). In addition, the enzymes of the citric acid cycle, citrate synthase and aconitase, were present at activities equal to those noted in the liver. These were among the first systematic studies of oxidative metabolism of tumor tissues and were to mark an important milestone in his career, since they would ultimately pit Weinhouse against Otto Warburg, one of the leaders in the field of metabolism.

Starting in the 1920s Otto Warburg proposed a general theory that cancer originates when a normal cell adopts anaerobic metabolism as a response to an alteration in respiration. Thus, a tumor is initiated by damaged respiration that persists and becomes a primary feature of the neoplastic state. Warburg used manometric procedures to quantify glucose metabolism by tissues slices, measuring lactate production and oxygen consumption. He noted that tumors had a far higher rate of anaerobic glycolysis than did normal tissues and that the presence of oxygen did not reduce the rate of anaerobic glycolysis (the Pasteur effect) in the tumor. In the preface to the English edition of a book on the subject[2], Warburg commented:

While normal cells die if they glycolyze aerobically, the glycolyzing tumor cell is able to grow to an unlimited extent turning to account the chemical energy of the glycolysis. Whether the respiration of the tumor is large or small, aerobic glycolysis is present in every case. The respiration is always disturbed, inasmuch as it is incapable of causing the disappearance of glycolysis.

In a paper, published in *Science*[3], titled "On the Origin of Cancer Cells" Warburg expanded on this thesis using recent studies that employed ascites tumor cells. His major thesis was that the study of the metabolism of pure cancer cells is superior to the use of tumor tissues that contain a mixed population of normal cells and cells at various stages of transformation to malignancy. This paper induced an often cited and critical reply from Weinhouse, subsequently published in *Science* (1956), which outlines the basis for his objection to the Warburg theory of the metabolic origins of cancer. It is important to remember that Warburg was a Nobel laureate and a leading figure in biochemistry, so that his theory of the origins of cancer held great weight in the scientific community; to take him on in such a direct manner took considerable courage and confidence in one's own data. In his rebuttal letter Weinhouse pointed out that "it has been recognized by all, including Warburg, that despite their high glycolysis, oxygen consumption is not quantitatively diminished; by and large, a representative group of tumors absorb oxygen about as rapidly as a comparable group of non-neoplastic tissues." He cited as an example an extensive set of tables on the subject published by one of Warburg's collaborators Dean Burk (of Lineweaver-Burk fame).

Weinhouse sums up his views by asserting, "I believe it would be more accurate to state that anaerobic glycolysis is so high in tumors that a normal respiration and a normal Pasteur effect (a decrease in glucose utilization by cells exposed to oxygen) are incapable of eliminating it." Later in the same letter he noted, "It is evident that all tumors produce large amounts of lactic acid, but so do many non-cancer tissues; and just as non-cancer tissues display a wide diversity in oxygen uptake, so do tumors." Read with today's understanding of the factors that induce malignancy in cells, the arguments that fuel this debate seem somewhat arcane in nature, however the amount of emotional energy generated at the time was considerable.

To illustrate the acrimony raised by the Weinhouse challenge to the Warburg hypothesis, one has only to read the exchange of letters in the same issue of *Science*. In his letter Burk supports the hypothesis and attacks Weinhouse as follows: "Respiratory impairment in living cancer cells, first discovered by Otto Warburg in 1923, is an experimental fact, and not, as described by Weinhouse a hypothesis based on 'an essentially fallacious reasoning.' Statements of Weinhouse indicating that the author of 'Burk's extensive tables' has at any time ever denied the factual existence of an impaired respiration in cancer cells are categorically untrue." Burk also accuses Weinhouse of extensive errors in his statistical approach to analysis of the tumor data and of mixing tumor types together in the analysis of his biochemical data, which he admitted had "superior quantitative finesse." It is of interest that despite the apparent heat generated by this exchange of letters, in the mid-1970s Burk, who was also quite a good amateur artist, sent a portrait he painted of Weinhouse, on the back of which he had made the inscription "to Sidney Weinhouse from Warburg's angel," which he signed "Dean Burk.

Warburg himself weighed in against Weinhouse in a letter aimed directly at his rebuttal[4]. In it he commented that Weinhouse was "not appreciative of this progress (i.e., of the importance of studying the metabolism of pure cancer cells) and of the many important discoveries made in this area since 1925." He also noted, "Obviously, nothing could be less enlightened than the opinion of Weinhouse that the respiration of cancer cells is as high or even higher, than the respiration of normally growing cells." Warburg ends his letter as follows: "Imagine two engines, the one being driven by complete and the other by incomplete combustion of coal. A man who knows nothing at all about engines, their structure, and their purpose, may discover the difference. He may, for example, smell it." Clearly, Otto Warburg did not take scientific criticism lightly.

Weinhouse's arguments against the Warburg hypothesis were based primarily on his extensive studies of lipid and carbohydrate metabolism by tumor tissues, in which he employed labeled substrates to determine rates of oxidation by mitochondrial process, as well as balance studies of the flux of intermediates in and out of the citric acid cycle. In this regard he was well prepared to debate Warburg from the strong experimental base of a decade or more of state-of-the art research on the subject. The major argument raised by Weinhouse in opposition to the Warburg hypothesis was that tumors and non-neoplastic tissues show no difference in their ability to convert glucose and fatty acids to carbon dioxide, a process that requires respiration and functional mitochondria. In his view the increased glycolysis noted in all tumors was not the cause of the malignancy but a result of alterations in genetic function that affect specific genes that regulate the expression of the enzymes and other factors that control a complex metabolic pathway.

Weinhouse noted that a cancer cell cannot be precisely defined and wrote, "An awareness that a cancer cell is continually changing its biochemical make-up should be a restraining influence on all of us to refrain from the all-too prevalent tendency to regard each newly discovered enzyme deletion as an explanation for the neoplastic process." Here he spoke from long years of research into the switch in isozymes for key enzymes such as glucose-ATP phosphotransferases, aldolase, lactate dehydrogenase, glycogen phosphorylase, creatine kinase, pyrophosphorylase, and pyruvate kinase that are noted in tumors. The list is impressive and demonstrates the breadth of his interest in the factors responsible for the metabolic alterations noted in cellular malignant transformation.

Perhaps because he was almost a generation younger than Warburg and far less dogmatic, Weinhouse's view is more in tune with current thinking on the etiology of malignancy. Despite the various arguments against it over the years, the Warburg hypothesis remains an enigma. It is true that glycolysis is greatly increased in malignant cells but the mechanism is still not fully understood. At this distance from the debate it appears that both Weinhouse and Warburg made valuable contributions to our understanding of metabolic alterations that occur in cancer. However, both lived in too early an era to be able to do the definitive experiments required to understand the underlying biochemistry of the effects that they were studying in such detail. As early as 1970 Weinhouse was aware of the importance of genetics in this process when we wrote[5] in reference to alterations in isozyme patterns that occur in cancer cells: "Underlying the differentiation of hepatic tumors there appears to be a switch in genome readout involving the suppression of enzymes involved in hepatic function and the unmasking of other enzymes normally suppressed in the tissue of origin."

We now understand better that a major part of malignant transformation of cells involves a re-patterning of specific transcription factors that regulate expression of a number of genes for metabolic processes. The processes that control the interaction of the transcription factors themselves require a battery of corepressors and coregulators. The fundamental mechanisms that are responsible for the development of cancer in hitherto normal cells are still not well understood. Over the years research in this area has focused not on changes in metabolism but on alterations in gene function that control the expression of proteins involved in controlling cell division. As Weinhouse noted in 1982 in his Presidential Address to the American Association for Cancer Research (Cancer Research, 42:3471) "The answer to the cancer problem, in my judgment, will not come from large planned programs, designed by committees, but will come from the laboratory. It rests on the young generation of brilliant cellular and molecular biologists. It is they and their successors in the next generation whom we depend on to find the answers" (1982). It seems safe to say that both Weinhouse and Warburg would be excited by the current advances in cancer research.

LEADERSHIP QUALITIES

Academic Leadership

In 1961 Sidney Weinhouse accepted a position as associate director of the Fels Research Institute and professor of biochemistry at Temple University School of Medicine. The Fels Research Institute was established by Temple University with funds from the Samuel B. Fels Fund and was located on two floors of a new research building at the corner of Broad and Ontario Streets in Philadelphia. In addition to the Fels fund, the institute enjoyed financial support from the National Institutes of Health, the American Cancer Society, and the National Science Foundation. Weinhouse was recruited to the Fels Research Institute by Harry Shay, a gastroenterologist with an interest in cancer research. Upon Shay's untimely death a year later, Weinhouse became director of the institute.

Weinhouse began hiring faculty members for the institute, all of whom had joint academic appointments in basic science departments at Temple University School of Medicine. This arrangement allowed him to recruit excellent faculty from both inside and outside the university. The Fels Research Institute under Weinhouse's direction attracted a number of outstanding graduate students and postdoctoral fellows, many of whom have held leadership positions at institutions throughout the world. As director he had a low-key approach to management and gave his faculty great leeway in their academic activities. However, as anyone who has worked with him at the Fels Research Institute will attest, he was always ready to help in the career development of his faculty and to provide financial support for promising research. He had an open-door policy for his staff and students and was always generous with his time and advice.

A major part of Sidney Weinhouse's professional success was his ability to attract a cadre of loyal associates who worked closely with him over the years. Among his closest colleagues were Grace Medes, Murray Strassman, Irene Dunn, Charles Wenner, Bernice Friedmann, Jennie B. Shatton, Edward H. Goodman, Mel Paden, Howard Schurr, Marge Foti, and George A. Reichard; these together with students and fellows framed his career. Weinhouse was generous in giving credit to others and was supportive of students and fellows as they developed their careers under his mentorship. The atmosphere he encouraged at the Fels Research Institute was one of interaction and collaboration. Weinhouse became Professor Emeritus at Temple University in 1978 and then joined the Thomas Jefferson University as Professor Emeritus in 1991, a position he held until his death in 2001. His long-time colleague Renato Baserga commented in a tribute to Weinhouse[6]: "Sidney Weinhouse was one of the most beloved scientists in the scientific community. Universally respected for his integrity, he was an example to his colleagues and students alike for his altruism and his devotion to science."

Cancer Policy

Sidney Weinhouse was actively involved in shaping cancer policy in the United States. A major accomplishment in his life and one of which he was very proud was his important contribution to cancer research in all of its aspects. He served on advisory boards for the National Institutes of Health, National Advisory Council on Environmental Health Sciences, American Association for Cancer Research, American Cancer Society, and the Damon Runyon-Walter Winchell Memorial Fund for Cancer Research. In 1969 Weinhouse became the editor of *Cancer Research,* a position that he held until 1980; from 1986 to 1999 he was the cover editor of that journal. To recognize his commitment and many contributions to cancer, *Cancer Research* featured Weinhouse on its cover on four occasions. During his 21-year tenure as editor of *Cancer Research,* he worked tirelessly to increase the quality of the basic research on cancer that was published in that journal and to encourage what we now refer to as translational research. It was his view that as the major journal in the cancer field *Cancer Research* should be a forum for all aspects of investigation into the causes and treatment of this disease. As editor he doubled the size of the Editorial Board in order to permit a more thorough review of submitted manuscripts, and saw the number of papers published increase from 2,500 to 5,300.

Weinhouse was president of the American Association for Cancer Research and served two terms on its Board of Directors. In his presidential address delivered at the annual meeting of the association in 1982, he presented his sentiments on the importance of the association and cancer research in his professional life.

In sharing these reflections, I have to express a feeling of great satisfaction in being not only part of a crusade, if you will, against one of mankind's scourges, but being also part of a tradition that goes back to the turn of the century. As a member for over 30 years, as a participant at many of our scientific sessions, as an editor and an author of papers in the Journal, as a Board member and officer, I feel that the Association has been a large part of my life. To have served in these ways has been one of my life's great privileges (1982).

Sidney Weinhouse had the great good fortune of having lived a long life, full of accomplishment, that was recognized by numerous honors, all of which he bore lightly. He was a member of the National Academy of Sciences (elected 1979), the Japanese Association of Cancer Research, and the Accademia Nazionale dei Lincei (Rome). He received the G. H. A. Clowes Award from the American Association for Cancer Research, the Papanicolaou Award, the Lucy Wortham James Award from the Society of Surgical Oncology, and the National Achievement Award from the American Cancer Society. Weinhouse was awarded honorary doctoral degrees from the Medical College of Pennsylvania, Temple University, University of Chieti (Italy), and Thomas Jefferson University.

At his death at the age of 91 he was among the most respected scientists of his generation, a man who influenced events and contributed significantly to the science he loved. Perhaps the most fitting tribute to Sidney Weinhouse is to say he was a good man who lived a good life, one that greatly influenced all who knew him—in the words of William Wadsworth, "The best part of a good man's life are the little, nameless, unremembered acts of kindness and love."

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Several of the former associates of Sidney Weinhouse supplied important background information on aspects of his research career and the atmosphere in the Weinhouse laboratory, including George A. Reichard, Jenny Shatton, Ruth Millington, Herman Levin, F. John Ballard, Oliver Owen, and Sid Walkenstein. We are also indebted to Paula and Oliver Owen for hosting a meeting of the associates of Sidney Weinhouse, which allowed us to gather some of the information included in this biography. We apologize in advance for not being able to include the names and contributions of all the many colleagues who worked with Sidney Weinhouse over his long career in science.

REFERENCES

1. Weinhouse, S. and E. F. Hirsch 1940. Atherosclerosis. II. The lipids of the serum and tissues in experimental athrosclerosis of rabbits. *Arch. Pathology* 30:856.
2. Warburg, Otto. 1930. *Metabolism of Tumors.* London: Constable.
3. Warburg, Otto. 1956. On the Origin of Cancer Cells. *Science* 123:309-314.
4. Weinhouse, Sidney, Otto Warburg, Dean Burk, And Arthur L. Schade. 1956. On Respiratory Impairment in Cancer Cells. *Science* 124: 267-269.
5. Weinhouse, Sidney. 1970. Respiration, Glycolysis, and Enzyme Alterations in Liver Neoplasms. *Miami Winter Symposium, Vol 2:,* pp 462-480. Amsterdam: North-Holland Publishing Company.
6. Baserga, Renato. 2001. In Memoriam: Sidney Weinhouse. *Cancer Res.* 61:8930-8931.

SELECTED BIBLIOGRAPHY

1943

The blood cholesterol. *Arch. Pathol.* 35:617.

1944

With G. Medes and N. F. Floyd. Fatty acid metabolism: The mechanism of ketone body synthesis from fatty acids, with isotopic carbon as tracer. *J. Biol. Chem.* 155:143.

1946

With G. Medes and N. F. Floyd. Fatty acid metabolism. V. The conversion of fatty acid intermediates to citrate, studied with the aid of isotopic carbon. *J. Biol. Chem.* 166:691.

1947

With E. C. Anderson, W. F. Libby, A. F. Reid, A. D. Kirshenbaum, and A. V. Grosse. Radiocarbon from cosmic radiation. *Science* 105:576.

1949

With R. H. Millington and B. Friedmann. The effect of carbohydrate on the oxidation of fatty acids by liver slices. *J. Biol. Chem.* 181:489.

1950

With C. E. Wenner and M. A. Spirtes. Enzymes of the citric acid cycle in tumors. *J. Am. Chem. Soc.* 72:4333.

1951

With R. H. Millington and C. E. Wenner. Metabolism of neoplastic tissue. I. The oxidation of carbohydrate and fatty acids in transplanted tumors. *Cancer Res.* 11:845.

1952

With C. E. Wenner and M. A. Spirtes. Metabolism of neoplastic tissue. II. A survey of enzymes of the citric acid cycle in transplanted tumors. *Cancer Res.* 12:44.

1954

Carbohydrate metabolism. *Annu. Rev. Biochem.* 23:125.

1955

With A. Allen and B. Friedmann. Tissue preferences for fatty acid and glucose oxidation. *J. Biol. Chem.* 212:921.

1956

On respiratory impairment in cancer cells. *Science* 124:267.

1957

With G. Medes and G. Paden. Metabolism of neoplastic tissues. XI. Absorption and oxidation of dietary fatty acids by implanted tumors. *Cancer Res.* 17:127.

1958

With G. A. Reichard, B. Friedmann, and A. R. Maass. Turnover rates of blood glucose in normal dogs during hyperglycemia induced by glucose or glucagon. *J. Biol. Chem.* 230:387.

1960

With D. L. DiPietro. Hepatic glucokinase in the fed, fasted and alloxan-diabetic rat. *J. Biol. Chem.* 235:2543.

1962

With D. L. DiPietro and C. Sharma. Studies of glucose phosphorylation in rat liver. *Biochemistry* 1:455.

1963

With G. A. Reichard, N. F. Moury, N. J. Hochella, and A. L. Patterson. Quantitative estimation of the Cori cycle in the human. *J. Biol. Chem.* 238(2):495.

1966

With R. C. Adelman and P. D. Spolter. Dietary and hormonal regulation of enzymes of fructose metabolism in rat liver. *J. Biol. Chem.* 241:5467-5472.

1967

With R. C. Adelman and F. J. Ballard. Purification and properties of rat liver fructokinase. *J. Biol. Chem.* 242:3360-3365.

1971

With B. Friedmann, E. H. Goodman, H. L. Saunders, and V. Kostos. Estimation of pyruvate recycling during gluconeogenesis in perfused rat liver. *Arch. Biochem. Biophys.* 143:566-578.

1972

With K. Sato and H. P. Morris. Phosphorylase: A new isozyme in rat hepatic tumors and fetal liver. *Science* 178:879-881.

1974

With F. Farina, J. B. Stratton, and H. P. Morris. Isozymes of pyruvate kinase in liver and hepatomas of the rat. *Cancer Res.* 34:1439-1446.

1975

With D. Lawson, W. K. Paik, and H. P. Morris. Carbamyl phosphate synthetase in rat liver neoplasms. *Cancer Res.* 35:156-163.

1976

The Warburg hypothesis fifty years later. Guest editorial. *Z. Krebsforsch.* 87:115-126.

1979

With J. B. Shatton and H. P. Morris. Creatine kinase activity and isozyme composition in normal tissues and neoplasms of rats and mice. *Cancer Res.* 29:492-501.

1982

Prometheus and Pandora: Cancer research on our diamond anniversary. Presidential address. *Cancer Res.* 42:3471-3474.