



Rudi Schmid

1922–2007

BIOGRAPHICAL

Memoirs

*A Biographical Memoir by
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RUDI SCHMID

May 2, 1922–October 20, 2007

Elected to the NAS, 1974

Rudi Schmid was born in the small Swiss Alpine town of Glarus on May 2, 1922. He died in Kentfield, California, on October 20, 2007. The personal and professional life that spanned those two events was remarkable for its vigor, enthusiasm, personal warmth, and excellence in diverse pursuits. Rudi made lasting contributions to mountain athletics, biomedical research, teaching, and leadership. Most would consider their lives to have been fulfilled by just one of these accomplishments. For Rudi, the absence of any of them would have been unacceptable. His remarkable life is even more impressive upon closer examination. It is this writer's honor and privilege to offer a brief biographical memoir of my friend and mentor, Rudi Schmid.



Rudi Schmid

By Robert K. Ockner

Origins: the Alps, the Andes, and America

Rudi's birth in Glarus as the son of two practicing physicians placed him squarely in an environment that challenged him intellectually in the world of medicine and physically through the rigorous demands inherent in accessing the surrounding peaks. Heredity and environment thus combined early and uniquely to instill in him a lifelong devotion to science and inquiry, and to the year-round pursuit of mountain adventures.

As a young man, he excelled in the latter arena, just as he was destined to excel years later in science and medicine. From 1941 to 1944 he was a member of the Swiss national ski team, specializing in the downhill and slalom events. Although World War II precluded competition in the Olympic Games, he and his team mates somehow managed to travel to other southern European countries to find like-minded competitors in Olympic events. During summer, his interests turned to climbing. He was twice elected president of the University of Zürich's elite Academic Alpine Club, and in 1946 he was one of a group of climbers who were the first to scale the formidable west face of Mont Blanc.

Rudi graduated from the University of Zürich Medical School in 1947. In 1948, he served as assistant leader and organizer of the 1948 Swiss Academic Club Alpine expedition to the Peruvian Andes to scale the largely unexplored Cordillera Blanca range. On that expedition, a mishap at an altitude of over 5,000 meters caused him to fall more than 100 meters and to sustain moderate but not life-threatening injury. The catastrophe, which could easily have proved fatal to one less durable, was the consequence of an unfortunate team decision regarding the choice of a climbing route. While Rudi strenuously disagreed with the decision on the grounds of safety, he acquiesced for the sake of unity in the enterprise. Certainly, this event, and possibly others similar to it, must have played a formative role in the development of Rudi's independence and trust in his own judgment.

As it turned out, the Swiss Andean expedition also helped to bring about a crucial linkage between the physical and the intellectual components of Rudi's life. While convalescing from his injuries in Peru, Rudi met a member of the Department of Medicine faculty of the University of California, San Francisco (UCSF), School of Medicine—Salvatore Lucia—who happened to be touring in the area. This contact led to Rudi's application and acceptance in 1948 to the UCSF internship program in Internal Medicine. It also marked his entry into postgraduate American medicine that, in turn, would lead to the career decisions and accomplishments for which he is best known.

Medicine and medical science

Rudi's survival skills proved again to be invaluable in 1949 as he completed his internship and applied successfully for acceptance to a combined program as medical resident and doctoral candidate at the University of Minnesota under the late Cecil Watson. This transition also provided the opportunity for Rudi to persuade his Swiss sweetheart, Sonja Wild, also an outstanding skier and mountaineer, to come to America and be his wife. She and Rudi were married in Sacramento, California, where relatives lived, and began their new life together in America.

As a doctoral candidate in association with Cecil Watson and Samuel Schwartz, Rudi developed an important experimental model of porphyria and conducted a landmark series of studies of clinical and experimental porphyria (1952a, 1952b, 1955a). At that time, the porphyrias were a poorly understood group of disorders, described primarily in clinical terms with little conception of their pathophysiology or of their relationship to heme biosynthesis. Rudi's research clarified much about these conditions and provided the foundation for their rational classification (1954). Thus, the rare erythropoietic



Rudi Schmid mid-career.

protoporphyrin reflected an abnormality of heme biosynthesis in bone marrow normoblasts. Excessive production of the formed porphyrin accounted for the photosensitivity and pigmented urine that are characteristic of this form of the disease. In contrast, the more common hepatic forms, which reflect overproduction of porphyrin precursors and earlier porphyrins in liver, were characterized by 1) abdominal pain or neurological signs (“intermittent acute”) 2) a second type, in which the liver produced excessive amounts of preformed porphyrin intermediates that are associated with photosensitization (thus, “cutanea tarda”) or 3) a “mixed” variant in which either of the other two clinical patterns might predominate at different times.

Upon completion of his fellowship at the University of Minnesota in 1954, Rudi was awarded a PhD and became an American citizen. He continued his research, focusing on heme biosynthesis, with a brief postdoctoral fellowship in the laboratory of David Shemin at

Columbia University. There, he identified key steps in the biosynthetic formation of heme (protoporphyrin IX α), specifically the conversion of δ -aminolevulinic acid to the monopyrrole porphobilinogen, and of the latter to the tetrapyrrole heme (1955b).

Rudi then accepted an appointment at the National Institutes of Health (NIH), where he began a phase of his research into what could be considered the catabolic side of tetrapyrrole metabolism: the degradation of heme to bilirubin and the latter’s excretion in bile and urine.

In the complex world of tetrapyrrole metabolism, Rudi’s research generated new understanding of both its anabolic processes (i.e., those involved in heme biosynthesis and its disorders underlying the clinical porphyrias) and its catabolic phase (i.e., heme degradation and bilirubin metabolism). In studies of the catabolic phase, Rudi made critically important contributions to the understanding of heme and bilirubin physiology and therefore to the understanding and clinical diagnosis of jaundice. Thus, he demonstrated, simultaneously with European investigators, that “direct-reacting” and “indirect-reacting” bilirubin, as measured in the standard laboratory test, reflected bilirubin’s conjugation with glucuronic acid, or lack thereof, respectively. This conjugate took the form of an ester glucuronide between bilirubin carboxyl and glucuronic acid hydroxyl (1956, 1957).

Shortly after completing his landmark studies at the NIH, Rudi accepted a position as assistant professor of medicine at the Thorndike Memorial Laboratory of the

Harvard Medical Unit at Boston City Hospital. The Thorndike was directed at that time by Professor William B. Castle, the highly respected hematologist and discoverer of intrinsic factor, the gastric secretory product essential to the absorption of vitamin B12 that is lacking in classical pernicious anemia. At the Thorndike, Rudi—in association with his trainees and colleagues Roger Lester, Don Ostrow, Steve Robinson, and Steve Schenker—provided additional insights into bilirubin metabolism, including its transport in plasma and the physiological significance of its conjugation with glucuronic acid (1961a, 1962).

It was during this period that I, as a student at Harvard Medical School who was fascinated by Rudi's lectures on liver physiology and bilirubin, approached him in hope of doing research in his laboratory. He kindly accepted me for a ten- to twelve-week hiatus that the clinical program permitted between my third and fourth years. At that time, he had recently completed a visit to southeastern Turkey at the invitation of Turkish authorities to investigate a most unusual phenomenon, the widespread outbreak of what generally was regarded as a rare condition, cutaneous porphyria. This occurred in the setting of a wheat scarcity due to poor harvests over several years.

The involved Turkish physicians considered the possibility that seed wheat (i.e., that treated with the fungicide hexachlorobenzene and stored for the subsequent year's planting) might have found its way via the black market into the supply of wheat destined for consumption. But because such a fungicide-induced epidemic of this rare disease had never been described, the opinion of Rudi, a widely recognized expert in this group of diseases, was solicited (1960).

My summer research project, given encouragement by some of Rudi's preliminary experiments, was to test the hypothesis that a porphyria-like syndrome could be induced in laboratory rats by hexachlorobenzene. If so, it would lend critical support to the concept that this agent was in fact responsible for the outbreak. The experiment confirmed the hypothesis and permitted crystallization of large amounts of porphobilinogen from rat urine. The summer's research was an exciting and exhilarating scientific adventure, and it was published in *Nature* the following spring as my first formal scientific publication (1961b).

In 1962, Rudi accepted a position as professor of medicine in the Division of Gastroenterology at the University of Chicago, where his studies of experimental bilirubin encephalopathy with Ivan Diamond were completed (1966). In 1966, he was recruited by his former colleague at Harvard Medical School, the recently recruited chair of the



Rudi reviewing data with long-standing research assistant and lab supervisor, the late Lydia Hammaker.

UCSF Department of Medicine, Lloyd Hollingsworth (“Holly”) Smith, to accept the position of Professor of Medicine and Chief of Gastroenterology. This event marked Rudi’s return to his San Francisco roots. Two years later, after completing my Boston fellowship in gastroenterology, I joined Rudi’s division in San Francisco, where I spent the remainder of my career.

Not surprisingly, Rudi’s research program was quickly re-established in San Francisco. His focus returned to heme, but this time in the context of its role as a component of cytochrome P450, and the crucial heme-containing enzyme heme oxygenase and its role in drug metabolism. He and his colleagues Raimo Tenhunen and Harvey Marver characterized and reported a previously undescribed microsomal enzyme system in spleen, liver, and other tissues (1968, 1969). The microsomal heme oxygenase system catalyzed the oxidative cleavage of protoporphyrin IX α , resulting in the NADPH-dependent release of carbon monoxide and biliverdin in equimolar amounts. The biliverdin then was converted rapidly to bilirubin by NADPH-dependent biliverdin reductase at a rate such that the heme oxygenase,

not biliverdin reductase, was rate determining for the complete system. All evidence suggested that the microsomal heme oxygenase played a major role in the physiological degradation of heme, whether derived from hemoglobin in senescent erythrocytes or from other hemoproteins in diverse tissues, including macrophages and small intestine (1971, 1975, 1976).

Additional studies demonstrated that not only endogenously synthesized heme, but also heme supplied exogenously, are utilized in reconstitution of functionally active heme oxygenase in which the heme moiety has been chemically destroyed. This effect of exogenous heme is dependent upon its prior incorporation, biosynthetically, into the complete microsomal heme oxygenase complex. (1979a, 1981) In addition, new insights into the formation of bilirubin diglucuronide were provided by experiments conducted in association with Norbert Blanckaert and John Gollan (1979b).

In the mid-1970's, Rudi recognized the opportunities presented by a new NIH program that encouraged the establishment of multidisciplinary liver research centers. With the support available through this program, he organized the UCSF Liver Center and served as its founding director.

Together, these selected reports, authored by Rudi Schmid and his associates, demonstrate a sustained line of investigation conducted over a period of more than thirty years in five major academic institutions. They have provided significant new insights into a critically important, broad aspect of biology and medicine namely, the biochemistry, physiology, and pathophysiology of heme biosynthesis, function, and degradation.

Leadership and honors

As division chief at UCSF, Rudi was confronted with new responsibilities unlike those he had carried previously. Not only was it necessary for him to re-establish his active research program, but he also faced important administrative challenges, including organization and oversight of basic and clinical teaching and patient-care responsibilities.

For the latter, he proved to be remarkably successful in encouraging outstanding practicing gastroenterologists in San Francisco and the surrounding areas to accept one or two months of weekly attending physician responsibilities, thereby enriching the overall training and experience of gastroenterology fellows, medical residents, and students, and promoting the delivery of high-quality medical care. He correctly predicted that first-rate practicing physicians, given an appropriate degree of professional respect, responsibility and the opportunity to play a significant role in patient management and conferences, would gladly participate in a program that otherwise was not remunerative. In addition, teaching and patient-management conferences were established to address other important areas such as histopathology and medical-surgical case review, grand rounds, inpatient rounds, and ambulatory patient care. In these diverse administrative activities,



Rudi, in a relaxed moment.

Rudi's personal qualities, as described above, were applied in a remarkably successful way to the benefit of all concerned.

In the mid-1970's, Rudi recognized the opportunities presented by a new NIH program that encouraged the establishment of multi-disciplinary liver research centers. With the support available through this program, he organized the UCSF Liver Center and served as its founding director. The Liver Center made it possible to integrate, in a more formal and extensive way, individuals in other departments and units with liver-related research interests at the university. My own research interests had by this time become firmly oriented toward studies of fatty acid metabolism and the fatty acid binding proteins, not limited to liver. Rudi generously allowed me complete independence and substantial support to my studies, which might have been considered to divert space and funding away from his own interests. In fact, this was never a problem, and quite the opposite my work was encouraged.

During the months that I spent in Rudi's lab at the Thorndike and the years that I spent in his division at UCSF, the personal qualities that I have already noted were applied in a remarkably successful way to the guidance of fellows and faculty colleagues alike. His interactions with us were characterized by warmth and enthusiasm and always with insistence on the highest standards of scholarship.

Rudi's unit in San Francisco was also highly productive, in terms of the success of its members and former members. Among these have been editors of leading journals including *The Journal of Clinical Investigation and Gastroenterology*, as well as former presidents of leading organizations such as the American Association for the Study of Liver Disease and the American Society for Clinical Investigation.

In 1983, Rudi was recruited to serve as dean of the UCSF School of Medicine. Although this represented the first time in his decades-long career that he would leave active research, he accepted the new challenge with characteristic enthusiasm and energy. At the very beginning of his deanship, Rudi was asked to chair an NIH committee charged with a review of the status of liver transplantation with regard to its possible suitability for more widespread application. Under Rudi's leadership, the committee concluded that the procedure should no longer be considered experimental and therefore could be recommended for appropriately selected patients as treatment for acute or chronic end-stage liver disease and certain metabolic disorders. This decision was an important stimulus to increase global establishment of liver transplant centers and thus to the increased availability of this life-saving procedure.



Rudi, Sonja, son Peter, and daughter-in-law Diane, trekking in Tibet.

During the more than six years of his deanship, he essentially overhauled the leadership of the UCSF School of Medicine through his appointment of fourteen key departmental and institute chairs, who guided UCSF to continuing excellence. Holly Smith, now retired after having served a term as associate dean, and who is an ongoing source of wisdom and humor for the UCSF community, has commented that "...the last good dean was Gunga Din: at least he brought water to the troops!"

While Rudi did not carry much water, he did engender at UCSF a new commitment to excellence in teaching, a remarkable achievement for this institution, which has a reputation built primarily on excellence in research. His success in this endeavor was enhanced and reflected by two new programs that he instituted: 1) a two-day annual retreat for department chairs and program directors at the Asilomar Conference Center in Monterey, California; and 2) the establishment of the Dean's Seminar Series, through which selected medical topics were addressed from both a clinical and basic science perspective. Both of these innovative programs, which contributed to Rudi's "stamp" on his deanship, served to enhance a spirit of



Rudi, daughter Isabelle Franzen, Sonja, and son Peter.

learning, interaction, and cooperation among the departments and research programs of the medical school.

Among Rudi's more noteworthy appointments was that of Haile Debas as chair of the Department of Surgery. Debas was a widely respected academic gastrointestinal surgeon and clinical investigator, who subsequently served as dean of the UCSF School of Medicine and chancellor of UCSF.

In addition to his other endeavors and achievements, Rudi turned his ability, knowledge, and experience in the international arena to establishing an important new focus for UCSF: the Pacific Rim. Thus, in 1986 he helped to establish and served as director of the Cheng Scholars Program, helping to make it possible for promising young biomedical scientists from the People's Republic of China to pursue postgraduate studies in the United States. After retiring as dean in 1989, Rudi continued his international work as associate dean for international relations in the UCSF School of Medicine and School of Pharmacy.

Rudi Schmid was recognized for his accomplishments by numerous awards and honors. Among these are the UCSF Medal (UCSF's highest honor) and the Friedenwald Medal of the American Gastroenterological Association; presidencies of the Association of American Physicians and the American Association for the Study of Liver Diseases; membership in scholarly societies including the National Academy of Sciences (elected in 1974), the Institute of Medicine, the American Academy of Arts and Sciences, the German Academy of Sciences Leopoldina, and the Swiss Academy of Medical Sciences; and numerous consultant and editorial appointments.

Throughout Rudi's remarkable career, a major asset was his family, including his wife Sonja, daughter Isabelle Franzen, son Peter, and grandson (Isabelle's son) Alexander. He shared with them a companionship and love of travel and outdoors, including skiing, hiking, and the care of their beautiful garden in Kent Woodlands, Marin County, California.

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