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SARAH RATNER
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A Biographical Memoir by

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Sarah Ratner

SARAH RATNER

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BY RONALD BENTLEY

To a remarkable extent Sarah Ratner's career as a biochemist largely paralleled the development of her discipline. She became a graduate student in the early 1930s, when biochemistry was mainly rooted in physiology and organic chemistry; about all that organic chemists knew of proteins was that they contained amino acids. Nucleic acids were even more of a mystery, and the catalytic action of enzymes was an enigma. The chemical structures and modes of action of vitamins and hormones were unclear. When she published her last paper in 1987, biochemistry had come of age.

The discipline of biochemistry developed slowly as new and improved technologies became available after World War II. Beginning about 1950 and continuing for two to three decades there was an astonishing acquisition of knowledge; this period was the golden age of biochemistry. The suggestion of one possible structural arrangement for DNA in 1953 was followed by the development of a new discipline, or perhaps more accurately a collection of disciplines, under the rubric "molecular biology." To a major extent biochemistry was subsumed as a most important component of molecular biology. Beginning with an organic chem-

istry problem for her Ph.D. thesis, Sarah Ratner grew into biochemistry. Her work contributed mightily to one important new technology, and she unraveled many details of important biochemical problems. She is the epitome of a classical biochemist.

In this memoir I take the liberty to call her Sarah. That she was commonly so known does not imply condescension; rather, it attests to the warm affection and deep respect with which she was universally regarded. Her own quotations are taken from an autobiographical article, "A Long View of Nitrogen Metabolism" (Ratner, 1977) and from an autobiographical résumé made available by the National Academy of Sciences. Quotations from the Festschrift for her eightieth birthday (Pullman, 1983) are identified by FSR and page number.

Sarah's productive life of 96 years encompassed both world wars as well as other major upheavals on the worldwide scene. In the year of her birth, 1903, the telephone and gasoline-powered automobile were relatively young inventions. It was in that year that the Wrights made the first successful airplane flight. When she died in 1999, the world was totally transformed by such developments as atomic energy, jet and manned space flight, gene cloning, and the Internet. Her family home library "included books on the great technical inventions: electricity, the telegraph and telephone, the incandescent light and the internal combustion engine." These works, part of her childhood reading, stimulated her interest in new technologies.

Her parents emigrated from a poor Russian village well before 1900. Her father, self-educated except for a few years of early Hebrew biblical studies, was an omnivorous reader and collector of Hebraic and late nineteenth-century classics (history, literature, philosophy). He was a strong influence on his children. Her "gentle and self-effacing" mother

was much concerned with family care. After the birth of three sons came twins: a fourth son and only daughter, Sarah. Of these five children she was the only one to choose an academic education.

Sarah attended a "new and excellent" high school in New York City, preferring courses in science and mathematics. Her desire to attend a university open to women centered on Cornell, not only for its strong chemistry department but also for scholarship possibilities. In fact, it was the award of a scholarship that convinced her parents to withdraw their objections to a university career. When she entered Cornell in 1920, as a chemistry major, almost all of the students were men focusing on industrial careers. She was the only woman in many of her chemistry and physics classes, and while she would have liked to exchange impressions and ideas with fellow students, "co-eds were generally placed in the pale and I was easily discouraged, being innately very shy." The situation was not easy for her; her college friends were liberal arts students with whom chemical discussions were impossible.

On graduation in 1924 neither medical school nor an industrial position seemed possible for Sarah. She gained laboratory experience in New York City in two positions requiring analytical chemistry. One was the Department of Pediatrics of the Long Island College Hospital. In 1932, collaborating with C. A. Weymuller, she reported on the acid-base metabolism of a nine-year-old child on diets with different ratios of "ketogenic to antiketogenic substances." Seventeen different analytical methods were used for determination of a wide variety of parameters in blood serum and feces (Weymuller and Ratner, 1932). One can only shudder at the amount of routine work involved. In work with R. Kurzrok (Departments of Biochemistry and of Obstetrics and Gynecology, Sloane Hospital for Women) it was

found that in cases of amenorrhea accompanied by genital hypoplasia, excretion of follicular hormone in urine was slightly greater than normal. In this work a biological assay system was used (Kurzrok and Ratner, 1932). Other work with Kurzrok is discussed later.

These analytical experiences fostered an interest in physiological chemistry. The decisive step was her acceptance in the early 1930s as a Ph.D. student by H. T. Clarke in the Department of Biochemistry, College of Physicians and Surgeons (P&S), Columbia University. Clarke, usually termed "H.T.," had a distinguished career as an organic chemist with Eastman Kodak (Vickery, 1975). In 1928 he was appointed head of the department at P&S, then termed "Biological Chemistry," with a mission to upgrade facilities and to appoint new faculty, a task at which he succeeded brilliantly. H.T. believed in a strong role for organic chemistry and, as a historian has noted, "a conscious effort was made to introduce ideas and techniques from organic chemistry into medical research" (Kohler, 1977). The Columbia medical school had moved uptown in 1928 to Washington Heights to form part of the Columbia Presbyterian Medical Center.

The only requirement for admission to graduate study in that department was to survive an interview with H.T., at the end of which the potential student was immediately informed of the outcome. No other extraneous factors entered into his decision. He apparently based his judgment on the student's chemical knowledge and "ability to recall and coordinate his chemical experiences" (Fruton, 1990). H.T. had an uncanny sense of quality and was almost never wrong in his choices. The interview was hard to prepare for. The aspiring student might be asked "how he would make sulfuric acid or something of similar import" (Chargaff, 1978, p. 65). In Sarah's case H.T. clearly excelled himself.

H.T. provided Sarah a part-time job in the department so that she might complete course work and also involved her in the previously described work with Kurzrok. The latter and H.T. had collaborated on some work, and the Rube Goldberg-style apparatus diagrammed by Kurzrok and Ratner (1932) for continuous extraction of follicular hormone with ethyl acetate and subsequent evaporation could only have been constructed by H.T., a skilled glassblower.

A 1935 paper was the first for which she was the sole author. Also heavily dependent on analytical work, the iron content of the teeth of anemic animals was found to be about half that of the controls (Ratner, 1935). At this time she held a Wm. J. Gies Fellowship (1934-35); both Gies and H.T. were thanked "for their generous interest and advice."

Sarah was also involved in work for which she did not receive authorship. She stated that in 1930, working with Kurzrok, she discovered a low molecular mass compound in human semen that could produce uterine contractions. Much later, and in retrospect, she noted that this work "constituted the first recorded description of the uterine contracting properties of a prostaglandin." Her "List of Publications" (provided by the National Academy of Sciences) contained no paper describing this work. Examination of Kurzrok's publications shows that Sarah was indeed involved. In a 1930 paper (Kurzrok and Lieb, 1930) the authors are listed in large capital letters as RAPHAEL KURZROK and CHARLES C. LIEB. Immediately following, in parentheses and in very much smaller type, is the brief statement "With the assistance of Sarah Ratner." This 1930 paper is notable, being the very first in which her name appears in connection with research in the scientific literature. Perhaps Sarah singled out this work in her autobiographical material since she felt that her "assistance" deserved coauthorship or at least a much warmer acknowledgment. In later papers

Kurzrok and his colleagues made no further mention of Sarah.

Her Ph.D. thesis work was straight organic chemistry: a study of the reaction of cysteine with formaldehyde to form a thiazolidine-4-carboxylic acid (Ratner and Clarke, 1937). Much later Sarah took pride in the fact that this work was of great interest in connection with the structure of penicillin. A penicillin degradation product, penicillamine, reacted smoothly with acetone. Penicillamine was found to be ßß-dimethylcysteine, and the reaction product was a thiazolidine carboxylic acid structure formed exactly as in the reaction of cysteine with formaldehyde. The thiazolidine ring is an important component of the ß-lactam structure for penicillin.

In late 1936 Sarah sought postdoctoral research positions but again encountered problems, apparently as a result of her gender. She notes that "other students finishing up at that time were men, and they had been well placed." A research position distant from New York City was accepted reluctantly in view of her father's ill health. When he died, she returned to New York to assume responsibility for her mother's care.

In 1937 Sarah had "the professional good fortune to be invited back to P&S to work with Rudolf Schoenheimer." Finally she was on the right track, and she never looked back. H.T.'s humanism and lack of prejudice had opened his department to many scholars who were refugees from the nightmare policies of the Nazis. Schoenheimer was one such individual. Together with David Rittenberg (Bentley, 2001) he had developed the use of the heavy isotope of hydrogen as a tracer of metabolic processes. When Sarah was asked to join the group, similar work was just beginning with the heavy isotope of nitrogen. Tracer isotope techniques with both stable and radioactive isotopes came to

play a most vital role in the new technologies exploited in biochemistry. The leadership role of Schoenheimer in this development has been extensively described, notably by Kohler (1977).

A special social organization was necessary for the tracer work: an interdisciplinary group (Kohler, 1977). The separated isotopes were provided by a physicist, labeled organic molecules were synthesized by an organic chemist, instrumentation for assay required a physical chemist, and finally a biochemist was needed to define metabolic problems and to interpret results. The group at P&S was a very early example of exemplary interdisciplinary research. In this group Sarah initially played the role of the organic chemist and in 1939 coauthored a paper with Schoenheimer describing the synthesis of amino acids containing ^{15}N. She was, moreover, rapidly "growing into biochemistry" and specifically the biochemistry of nitrogen compounds. From 1937 to 1939 she was supported by a Macy research fellowship and from 1939 to 1946 had titles of instructor and assistant professor.

There was, however, an unhappy development; Schoenheimer took his own life in 1941. He was to have delivered three lectures at Harvard's Medical School later that year, and Sarah and Rittenberg assisted H.T. in preparing Schoenheimer's drafts for delivery (by H.T.) and publication as *The Dynamic State of Body Constituents* (1942). This book is a landmark in biochemical writing. The isotope group had also begun work on the synthesis of antibody protein before Schoenheimer's death. Sarah felt this work did not receive enough acclaim and she later expanded on it in a lecture (Ratner, 1979).

Beginning in 1942 she worked with D. E. Green on amino and hydroxy acid oxidases and on a peptide form of *p*-aminobenzoic acid. A purified L-amino acid oxidase from rat kidney was shown to have broad specificity and to be a

flavoprotein. Also present in liver, this enzyme did not have a major role in amino acid deamination. While the overall outcome was disappointing, this research was instrumental in stimulating her interest in enzymology. She became "very eager to pursue new facets of nitrogen metabolism."

Sarah was recruited by S. Ochoa as an assistant professor of pharmacology at New York University's School of Medicine in 1946. She was 43 years old and finally was able to strike out on her own. One year later she published a brief but most important paper on the mechanism of the formation of arginine from citrulline. It marked the beginning of her comprehensive study of urea biosynthesis (see later) that occupied her over the next four decades. It was a late start to be sure but one leading to splendid conclusions with observations of great significance.

When Ochoa became chair of the New York University Medical School's Department of Biochemistry and moved to a new building, Sarah "was left in a dilemma which was happily solved by the return of Efraim Racker to New York." Racker was to head and reorganize the Department of Biochemistry at the Public Health Research Institute of New York. Sarah joined the institute that finally became her scientific home; it was her last move. She remained as a staff member until retirement in 1992, when she was close to 90 years old.

The urea story began in 1932 when H. A. Krebs and K. Henseleit studied urea formation in respiring liver slices in the presence of oxygen, discovering a cyclic process. Ornithine, CO_2, and NH_3 reacted to form citrulline. With a second NH_3 the latter produced arginine and finally arginine was decomposed with the enzyme arginase to form urea and ornithine; the latter could initiate the cycle again (see Figure 1). Sarah demonstrated that the citrulline → arginine reaction was more complex than it appeared. The ni-

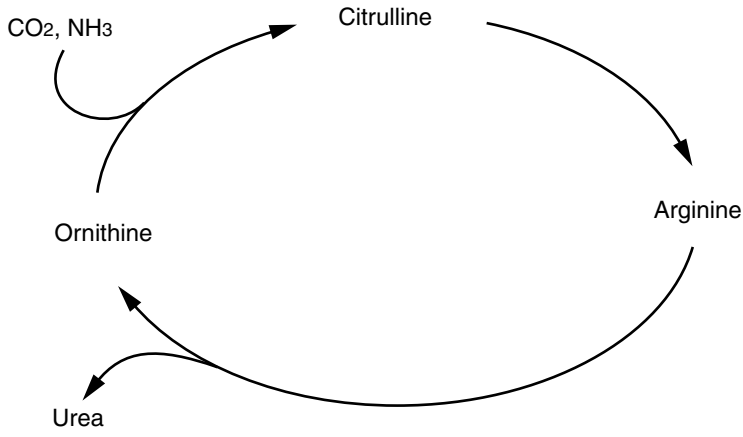

FIGURE 1 The original Krebs/Henseleit proposal for urea synthesis.

trogen donor was not NH_3 but aspartic acid, and the reaction with citrulline led to formation of a previously undiscovered amino acid, argininosuccinic acid. Two further enzymes were necessary for urea formation: argininosuccinate synthetase catalyzing the formation of argininosuccinate and argininosuccinate lyase catalyzing argininosuccinate decomposition (see Figure 2). A major part of her achievement was to purify these enzymes from various sources, to study their molecular structures, and to determine the catalytic mechanisms by which they acted.

Also of great significance was the finding that ATP was necessary for the urea cycle operation, thus explaining the need for O_2 in the Krebs-Henseleit experiments; argininosuccinate formation required ATP. Indeed, the ATP-generating activity of the citric acid cycle was metabolically related to urea synthesis. In addition, two ketoacids of the citric acid cycle, oxaloacetic acid and α-ketoglutaric acid,

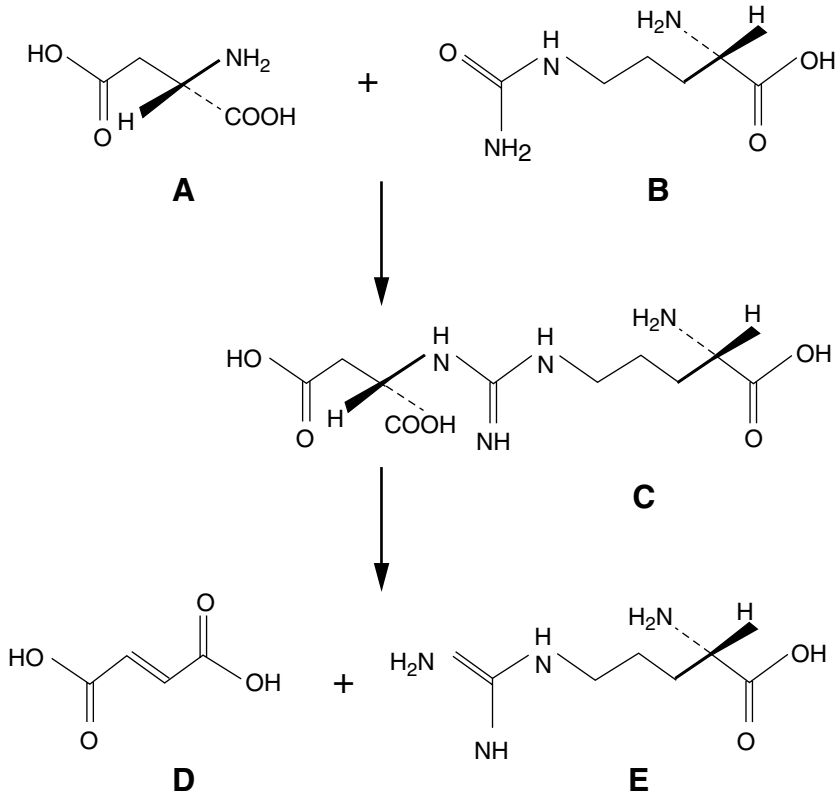

FIGURE 2 The Ratner portion of the urea cycle. *A* = aspartate, *B* = citrulline, *C* = argininosuccinate, *D* = fumarate, *E* = arginine. The formation of *C* from aspartate and citrulline is catalyzed by argininosuccinate synthetase and requires ATP. Its decomposition is catalyzed by argininosuccinate lyase.

played important roles. The interrelationships between the two cycles (citric acid and urea) are best visualized by consulting Figure 3. An excellent summary by Sarah herself is also available (Ratner, 1976).

In 1958 Sarah learned of an unfortunate child with

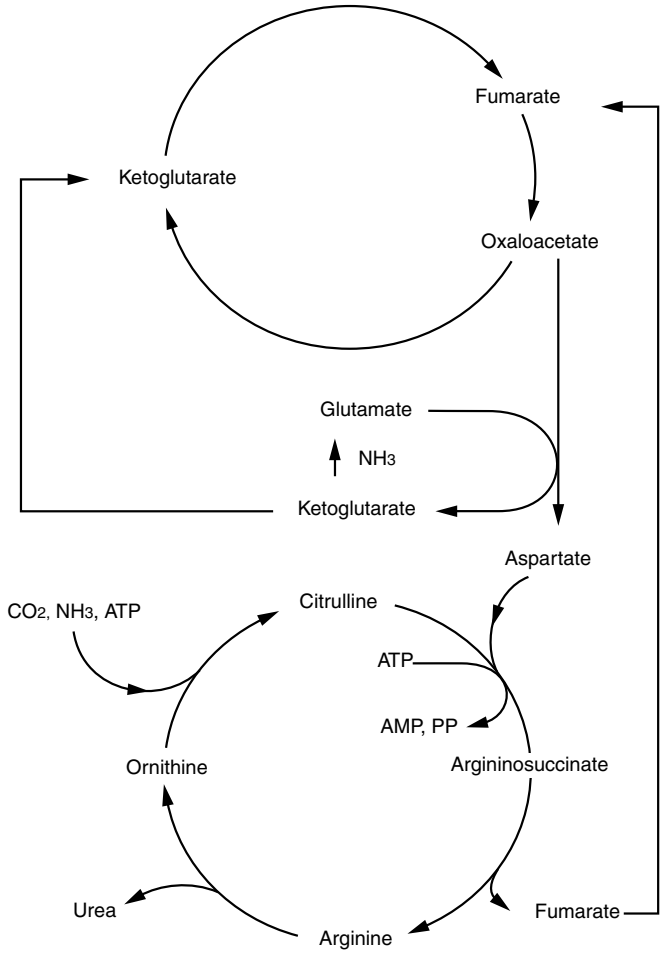

FIGURE 3 Interrelationships between the Krebs/Henseleit/Ratner cycle and the citric acid cycle. The top circle shows a much abbreviated form of the citric acid cycle emphasizing the three components of most interest. Coupled with the reactions of oxidative phosphorylation, this cycle leads to formation of ATP (required for argininosuccinate synthetase). CO_2 and NH_3 actually enter the cycle through carbamoyl phosphate; synthesis of the latter is also dependent on ATP.

mental retardation and marked derangements of nitrogen metabolism who excreted some 3 grams per day of argininosuccinate. This was probably the earliest description of an inborn metabolic error involving the urea cycle. This particular problem is now known as argininosuccinate aciduria. Similarly, citrullinemia, an autosomal recessive genetic disease, involves a deficiency of argininosuccinate synthetase and produces excessive levels of citrulline in plasma and urine, and neurological damage and mental retardation. Few individuals have discovered two enzymes with such significant consequences.

Sarah's work on isotope tracer techniques contributed to the extensive flowering of biochemistry between 1950 and 1970. It is not easy in the twenty-first century to realize how few instrumental capabilities were available before World War II. As a Ph.D. student the major tools available to her were elemental analysis, melting and boiling point determinations as indications of purity, and the intellectual gift to interpret results, often by analogy with previous findings. Apparatus was very simple and only slowly did glassware with standard ground joints come into use. Her thesis advisor, H.T., was "a very good organic chemist of the old observance; one of those who liked to putter around in the laboratory with test tubes and small beakers and watch glasses and who was happy when crystals appeared" (Chargaff, 1978, p. 67). A snapshot of that time is provided by Sarah (personal communication, letter, December 3, 1989, from Sarah Ratner). She was "reminded how primitive our instruments were at that time. For example, all the pH measurements were carried out with a very thin glass membrane drawn out by the department's technician guided by a description which had just been published by someone at another university."

Although placing a high value on teaching for student

and lecturer alike, Sarah was uncomfortable as a lecturer. Her manner of speaking was deliberate and thoughtful. Colleague H. Waelsch remarked, "Sarah, I always know when you are calling because the phone rings more slowly" (FSR, p. 243). She taught pharmacology at New York University after spending part of a summer reading "the monumental pharmacology text by Goodman and Gilman." She regretted that she had not taught biochemistry in a lecture course. She was too modest to claim that at a different level she was, in fact, a most gifted teacher who excelled in mentoring and guiding those associated with her. Her research was accomplished by herself or by a rather small group. Her style "tended toward longer papers and less frequent publications."

Sarah had a relatively late start as an independent investigator and later in life stated that "my career as a biochemist has been a more difficult one because of my sex." She believed that she received relatively few applications for postdoctoral positions in her laboratory for the same reason. Incredible as it may seem today, when she went to Cornell in the 1920s there were many universities that did not admit women; Cornell was a happy exception. T. C. Stadtman has noted that "the obstacles that had to be overcome to achieve scientific recognition when Sarah started her career were of an entirely different magnitude than they are now. Every woman biochemist who has followed Sarah Ratner has benefited from her example of excellence and perseverance and owes her a debt of gratitude" (FSR, p. 233). A revealing interchange between mentor, H.T., and student, Sarah, has been noted. "When 'H. T.' [Clarke] (bless his heart!) sincerely intending to be complimentary, remarked, 'Sarah thinks like a man,' Sarah's response was a somewhat disdainful, 'hrumph'" (FSR, p. 3).

Sarah received several awards: William J. Gies fellow in

biological chemistry (1934-35), Schoenheimer lecturer (1956), Carl Neuberg Medal (1959), Garvan Medal of the American Chemical Society (1961), and Freedman Award in Biochemistry, New York Academy of Sciences (1975). She was one of the relatively few women to have been elected to the National Academy of Sciences (in 1974). From 1978 to 1979 she was a Fogarty scholar in residence at the National Institutes of Health. She served on boards and committees at various times: member of the Editorial Board and Editorial Committee, *Journal of Biological Chemistry*; Editorial Board, *Analytical Biochemistry*; Executive Committee of the American Chemical Society, Division of Biochemistry; and member of the Extramural Science Advisory Council, National Heart and Lung Institute, National Institutes of Health. She received an honorary D.Sc. degree in 1984 from the State University of New York, Stony Brook. The citation read in part as follows:

> Known to your colleagues as a scientist's scientist, you have pursued a long and successful career in unravelling the complexities of amino acid metabolism. Your way of going about scientific investigation combines determination to arrive at a complete molecular description of a biochemical process with clarity of vision and exquisite attention to detail.

Since I never had the privilege of working with Sarah Ratner, knowing her mainly as a result of my wife's abiding affection for her, I may not be her best biographer. It is appropriate, therefore, to let her colleagues remedy my deficiencies by quoting at length from the 1983 Festschrift in her honor.

> M. L. Blanchard: "She was an effective teacher and what I learned from her helped to shape my life" (FSR, p. 4).

> M. J. Coon: "I became impressed with her dedication to science, the meticulous care she devoted to experimentation, and her thoughtful approach to problems both scientific and nonscientific" (FSR, p. 41).

M. E. Jones: "Her stature is great as an innovator and as a scientist who has made critical and important contributions to the study of nitrogen and amino acid metabolism. Her personal attributes may be less well known but are cherished by those of us who have had the opportunity to know her and to discuss science with her" (FSR, p. 81).

C. J. Lusty: "To me Sarah Ratner represents scientific excellence. She is a scholar, mentor and a friend" (FSR, p. 103).

H. S. Penefsky: "I am speaking of her intense commitment to the highest standards of scientific excellence and the natural way in which these standards are expressed and communicated by example. Those of us privileged to know her could not, I think, fail to absorb and be influenced by those lessons. Thank you, Sarah" (FSR, p. 145).

B. Petrack: "My respect for Sarah continues to grow, not just for her considerable scientific achievements, but also for her many admirable personal qualities, among which integrity, kindness, and courage stand out" (FSR, p. 147).

F. Lipmann: "A fascination with science was surely the center of her life's interest, but I would like to mention that it still left time for her to become, for example, an expert in the fine art of bookbinding, to name only one of her side interests" (FSR, p. 167).

M. E. Pullman: "[Sarah] has been a wise and generous friend and colleague for many years. Her uncompromising devotion to the highest standards of scientific excellence has been and continues to be an inspiration to those of us privileged to know her" (FSR, p. 181).

E. Racker: "Sarah's interest in music and the arts is manifest in her writings which are compositions of a very individualistic scientist. Her contributions are recognized all over the world. Her laughter and warmth are cherished by all who know her" (FSR, p. 185).

O. M. Rochovansky: "She tried to instill in me the qualities of a good researcher: an unprejudiced mind, logical thinking, experimental care and the need of that extra dash—the insight that makes a difficult problem suddenly become beautifully clear. These are qualities that Sarah has in abundance" (FSR, p. 187).

S. Gluecksohn-Waelsch: "I remember visiting you in your parents' house on Shakespeare Avenue in the Bronx—a home notable for its high standards of tradition and hospitality, standards that you have maintained and continue to do through the years" (FSR, p. 243).

The portrait is very clear: extraordinary insight, uncompromising standards and integrity, a most distinguished biochemist especially concerned with nitrogen metabolism, gifted mentor to many, and above all a very warm and vibrant human being. Unhappily, her health declined somewhat following retirement; Sarah Ratner's long and most productive life ended on July 28, 1999.

J. W. BENNETT kindly read a draft of this memoir, and I am grateful to her for valuable suggestions.

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