

Living history of physiology: Bodil Schmidt-Nielsen

William H. Dantzler

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In 2005, The American Physiological Society initiated The Living History of Physiology Project to recognize senior members who have made extraordinary contributions during their career to the advancement of the discipline and profession of physiology. Each physiologist will be interviewed for archival purposes, and the video tape will be available from the American Physiological Society Headquarters. In addition, a biographical profile of the recipient will be published in *Advances in Physiology Education*.

LIVING HISTORY OF PHYSIOLOGY: BODIL SCHMIDT-NIELSEN

Bodil Schmidt-Nielsen was born on November 3, 1918, in Copenhagen, Denmark, and was the youngest of four children of two other eminent physiologists, the Nobel Laureate August Krogh and Marie Krogh, whose lives she has chronicled in a significant biography (19). Because her parents were both physiologists and because most of the visitors and guests in their home were physiologists, she and her siblings were exposed regularly to conversations dealing with physiology. Moreover, because she was educated at home with a private teacher from ages 6 to 11, she regularly lunched with her parents when they came home from the laboratory and heard their discussions of the research problems of the day. At age 11, she entered the Rysensteen Gymnasium in Copenhagen, from which she graduated in 1937, having specialized in mathematics and science. She has frequently commented on the excellent teachers she had in the gymnasium. Bodil Schmidt-Nielsen, An Eminent Physiologist.

Although originally considering medicine, she instead chose to enter the School of Dentistry at the University of Copenhagen, from which she received her Doctor of Dental Surgery degree in 1941. During her studies, she became particularly intrigued by physiology, tutored fellow students, and began her initial physiological research on the exchange of calcium and phosphorus in human teeth (15). Because she married Knut Schmidt-Nielsen in 1939 (this marriage ended in divorce in 1966; in 1968, she married Roger G. Chagnon) and had the first of her three children shortly after receiving her dental degree, she gave up plans to continue studies in medicine and concentrated on research in the School of Dentistry during the years of World War II. These studies were again largely focused on calcium and phosphorus metabolism. However, she has frequently remarked that even at this time she saw her work in the broader terms of fluid and ion balance. In 1946, she became the first person to receive the new Doctor of Odontology degree from the University of Copenhagen. She received her Doctor of Philosophy degree, also from the University of Copenhagen, in 1955.

Dr. Schmidt-Nielsen's interests expanded further in the direction of fluid and electrolyte balance after Laurence Irving and Per F. Scholander invited her and her husband to work with them at Swarthmore College in 1946. She became a Research Associate, first at Swarthmore (1946–1948), then at Stanford (1948–1949), next at Cincinnati (1949–1952), and finally at Duke (1952–1957). She was an Associate Research Professor at Duke from 1957 to 1964 (first in Zoology and then in Zoology and Physiology). It was during these years (1946–

1964) that she performed some of her most significant studies on fluid and ion balance and renal physiology. Given her father's interest in finding animal species that best illustrated physiological principles, it is not surprising that she took a broadly comparative approach to her work. Indeed, she worked with invertebrates as well as amphibians, reptiles, birds, and mammals throughout her career.

Her first significant work on fluid balance, and the work that brought her national and international attention, occurred when Irving, in the spring of 1947, suggested that she and her husband study the water metabolism of kangaroo rats in southern Arizona. They carried out field studies on kangaroo rats (*Dipodomys*), pocket mice (*Perognathus*), and wood rats (*Neotoma*) during the summers of 1947 and 1948 and then carried out further experiments at Swarthmore and Stanford. The studies indicated how kangaroo rats live in the desert without drinking water (31). They found that this depended on both physiological and behavioral mechanisms. These animals obtain water almost entirely from oxidation of the dry food they eat. They reduce water output by producing highly concentrated urine and reducing evaporative water loss. The latter occurs because the expired air is saturated with water vapor at the temperature of the nose, which is maintained 10°C below their body temperature, and because there is little evaporation from the skin. These physiological processes allow them to maintain a water balance at 25°C with no drinking water as long as the relative humidity is above 10%. From a behavioral stand point, the animals are nocturnal and burrowing. The burrows have a relatively constant temperature, never above 30°C, and a relative humidity three to four times that of the outside air. Thus the animals avoid the heat of the day (and, therefore, the need for additional evaporative cooling) and further reduce respiratory water loss because of the high humidity. They also eat seeds that have gained extra preformed water from the relatively high humidity of the burrows. These studies were remarkable in their completeness and set a new standard for understanding water balance in animals living in diverse environments. They and later similar studies on camels in the Sahara desert formed the basis for Dr. Schmidt-Nielsen's Bowditch Award Lecture (of which she was the second recipient) in 1957.

During the course of these studies, Dr. Schmidt-Nielsen became more and more intrigued by renal function, particularly by the ability of various animals to produce a dilute or concentrated urine and by the relationship of the excretory end products of nitrogen metabolism (especially urea and uric acid) to renal water conservation. Indeed, it was her observation in the summer of 1947 that kangaroo rats can concentrate urea to 3,500 mmol/l, whereas humans can only concentrate urea to 400 mmol/l, that convinced her that she must try to understand renal function (23). She started by reading Homer W. Smith's 1937 book (23), *The Physiology of the Kidney* (36), the

Address for reprint requests and other correspondence: W. H. Dantzler, Department of Physiology, College of Medicine, University of Arizona, Tucson, AZ 85724-5051 (E-mail: dantzler@email.arizona.edu).



Fig. 1. Picture of Bodil Schmidt-Nielsen taken in 2003.

precursor to his 1951 book, *The Kidney: Structure and Function in Health and Disease* (37), and essentially the only general source of information on the kidney. She was really intrigued by the clearance technique, as described in this book, and by the evidence suggesting that in the mammalian kidney urea is filtered and a major fraction is reabsorbed (23). In 1951, after completing most of the work on water balance in desert rodents, she started to explore the process by which the kidney of the kangaroo rat excretes urea (23). Thus began a series of studies on urea excretion and the urine-concentrating mechanism that had a profound impact on our understanding of mammalian renal function.

The prevailing view before Dr. Schmidt-Nielsen's studies was that urea was freely filtered at the glomerulus and that some was then passively reabsorbed along the renal tubules by simple diffusion, with the remainder being excreted. Using the clearance technique, she initially demonstrated that the renal tubules of kangaroo rats secrete urea (20). This paper attracted only modest attention. However, she confirmed this finding and extended her clearance studies on tubular transport of urea in both kangaroo rats and white rats in the following years. Her work was published in a landmark paper in the *American Journal of Physiology* in 1955 that forced people to reevaluate their concepts on the way in which urea was processed by the mammalian kidney (21). In this paper, she again showed that kangaroo rats could excrete more urea than the amount filtered (i.e., the urea clearance exceeded the inulin clearance). Of equal significance, she demonstrated that urea clearance varies independently of glomerular filtration rate and tubular reabsorption of water in both kangaroo rats and white rats (which did not excrete more urea than that filtered). Of particular note, she showed that urea clearance decreased relative to insulin clearance with excitement and a low-protein diet. From these results, she concluded that in at least some mammals a "mechanism other than filtration-passive back diffusion is involved in the renal excretion of urea," and she tentatively suggested "that urea can be excreted by active tubular secretion" (21). In a later micropuncture study with Karl Ullrich, she proposed that urea

was actively reabsorbed from the collecting ducts in rats on a low-protein diet but not in rats on a high-protein diet (43).

In the early phase of these studies, in 1952, Homer Smith visited her laboratory and, observing what she was working on, invited her to spend the summer at Mount Desert Island Biological Laboratory (MDIBL) in Maine, thus beginning her long association with that institution (23). During that summer, she and Roy P. Forster reinvestigated E. K. Marshall's finding that frog renal tubules actively secrete urea and found urea clearances 6 to 10 times the glomerular filtration rate in these animals (26).

The scientific community readily accepted the frog data on tubule secretion but was intensely critical of the mammalian data and particularly of Dr. Schmidt-Nielsen's suggestion that both active tubular secretion and active tubular reabsorption of urea occur. However, we now know that she was correct on both counts. More than 30 years after her pioneering work, studies with isolated, perfused segments of inner medullary collecting ducts (IMCD) from rats produced evidence of carrier-mediated urea reabsorption that was stimulated by vasopressin (1, 2, 18), and, a few years later, You et al. (48) cloned urea transporters fitting these characteristics. Further studies with isolated, perfused tubule segments from rats demonstrated that sodium-dependent active secretion of urea that is reduced by a low-protein diet occurs in the terminal IMCD and that sodium-dependent active reabsorption that is apparent only with a low-protein diet occurs in the initial IMCD (8, 10). A reduction in active secretion and an increase in active reabsorption could have contributed to the reduction in urea clearance with a low-protein diet first reported by Dr. Schmidt-Nielsen in her 1955 paper (21).

While Dr. Schmidt-Nielsen was carrying out these early studies, she was, of course, also studying the degree to which and the mechanism by which mammals as diverse as kangaroo rats and camels reduce renal water losses. In other words, she was intrigued by the ability of the mammalian kidney to produce concentrated urine and the then recent proposal by Hargitay and Kuhn (6) that this could be achieved in part through the function of the loops of Henle as countercurrent multipliers. By 1957, she believed that comparative analyses of loop length (or relative medullary thickness) and concentrating ability among mammalian species (studies which she had begun performing and later published) (28) as well as initial experimental data by others (42, 45, 46, 47) strongly supported the theory of Hargitay and Kuhn (6, 22). Moreover, she thought that urea must be involved in this concentrating process and, on the basis of her increasing evidence for urea secretion by the renal tubules (21), she even suggested that active transport of urea might be involved as a driving force in countercurrent multiplication in her influential 1958 review on urea excretion in mammals (22). She was right about the importance of urea, although she was apparently wrong about active urea transport as the driving force in countercurrent multiplication.

However, she contributed further to the understanding of the concentrating process and to the significance of urea when she invited Karl Ullrich to visit her laboratory at Duke in 1960, and they teamed with Carl W. Gottschalk at the University of North Carolina to carry out two important micropuncture studies, one on rats and one on desert rodents (golden hamsters, *Mesocricetus auratus*, and fat sand rats, *Psammomys obesus*) (4, 44).

The first study confirmed earlier work from Gottschalk's laboratory (13) showing that urea was recycled in the medulla and showed that the recycled urea came from urea reabsorption in the medullary collecting ducts. The second study, on animals in which the loops of Henle could be readily approached for micropuncture (the August Krogh approach of finding the correct animal for study), provided the first unambiguous evidence that sodium is actively reabsorbed from the water impermeable thick ascending limb of Henle's loop. These and earlier studies by Gottschalk (e.g., Ref. 5) confirmed the role of countercurrent multiplication in the urine-concentrating process.

However, although many studies have now demonstrated in some detail how countercurrent multiplication and the urine-concentrating process work in the outer medulla, the process in the inner medulla, where both urine osmolality and urea concentration reach their highest levels, remains a mystery to this day. Nevertheless, Dr. Schmidt-Nielsen's work on the significance of urea in this process certainly formed a basis for later influential theoretical models for the inner medullary concentrating process (12, 38). Urea still plays an important role in more recent models of how this process might work (14). In addition, when I was in Dr. Schmidt-Nielsen's laboratory in the early 1960s, our discussions on the inner medullary concentrating process raised the possibility that the production of some other metabolite, not just urea, could be involved in generating the osmotic gradient. Although this idea was never presented publicly, she was again prescient. This mechanism was later shown to be at least theoretically effective (9), and it has recently been proposed, with supporting model studies but no definitive experimental proof, that the generation of lactate in the inner medulla could be the critical factor in the inner medullary concentrating process (7, 41).

In 1964, Dr. Schmidt-Nielsen left Duke University to become a professor of biology at Case Western Reserve University, but, in 1971, after a year as chair of the department, she resigned her tenured professorship, to become the first permanent research scientist at MDIBL because "I wanted to spend all of my time on research rather than administrative duties" (comments in her Curriculum Vitae). She retained this position until 1986, when she closed her active research laboratory. From 1971 to 1975, she maintained adjunct professorships at Brown and Case Western Reserve Universities. Although she closed her active laboratory in 1986, she was still present and contributing to scientific discussions at MDIBL during the summer and held an adjunct appointment in the Physiology Department at the University of Florida, where she spends her winters, until 1997 when she became emeritus adjunct professor.

Throughout the years, Dr. Schmidt-Nielsen continued her comparative studies, especially on the excretion of water, electrolytes, and nitrogenous substances (ammonia, urea, and uric acid) in fishes (e.g., Refs. 29, 33, and 39), reptiles (e.g., Refs. 3, 17, 25, 30, 32, and 40), and birds (e.g., Refs. 34 and 35). However, the most significant studies that Dr. Schmidt-Nielsen performed during her last active period of experimental research at MDIBL were again related to the mammalian mechanism for concentrating urine. It had long been noted that exposing the renal papilla by cutting away the ureter and thus eliminating the contractions of the renal pelvis reduced the urine-concentrating ability of the mammalian kidney. During

this time, the collecting ducts remain full and urine flow is continuous. However, Dr. Schmidt-Nielsen was fully aware that the intact pelvis had peristaltic contractions. She wondered about exactly what effect these contractions might have on fluid and solute movements in the papilla. Therefore, she and her co-workers performed a series of studies involving determinations of flow of surface fluid and fluid in the papillary structures, of external pressure exerted on the papilla, and of structural changes (16, 24, 27). They found that the peristaltic contractions of the pelvic wall tend to "milk" the papilla, having a profound effect on flow in collecting ducts, loops of Henle, vasa recta, and capillaries. These contractions also influence the size of cells and intercellular spaces. She suggested that fluid moves into the cells during contraction when urine is flowing through the collecting ducts and into the interstitium during relaxation (27) and that such movements might influence the concentrating mechanism. She did not propose an exact mechanism for the coupling of the pelvic contractions to the urine-concentrating process in the inner medulla. However, Knepper and colleagues (11) have recently proposed that interstitial hyaluronan can function as a mechanosmotic transducer to couple contractions to the concentrating process. There are as yet no experimental data to support this exact model, but Dr. Schmidt-Nielsen's work continues to have a profound affect on contemporary thinking regarding the mammalian urine-concentrating mechanism.

Finally, I can comment personally on Dr. Schmidt-Nielsen's creativity and her abilities as a mentor. She was not the sort of mentor who paid much attention to the mundane practical requirements of most graduate programs (meeting deadlines, courses to take, etc.). Those details were left up to us. She believed that creative research was the only thing of any importance and that any other aspect of graduate education was relatively unimportant. She was an ideal mentor for the highly independent student. Those of us who were fortunate enough to work with her were always amazed at the range of interpretations and novel ideas she came up with as she examined the data from our experiments—a point that should be obvious from my description of her research contributions above. Of course, many of these ideas proved to be incorrect, but she generated so many that usually at least one important, often novel, conclusion emerged from each study. Her laboratory was an extraordinarily stimulating environment in which to work. She was an inspirational mentor!

In addition to the Bowditch Award Lectureship in 1957, Dr. Schmidt-Nielsen was selected as the first August Krogh Distinguished Lecturer of the Comparative Physiology Section of the American Physiological Society in 1994. Over the years, she has received many other honors acknowledging her outstanding contributions to physiology, including election as a fellow of the New York Academy of Sciences (1958), AAAS (1959), and the American Academy of Arts and Sciences (1973). She was also a Guggenheim Fellow (1953–1954), Established Investigator of the American Heart Association (1954–1962), and National Institutes of Health Career Awardee (1962–1964). She received an honorary Doctorate of Science from Bates College in Lewiston, Maine, in 1983 and an honorary M.D. from Aarhus University in Denmark in 1997. She has served the American Physiological Society as a Member of Council and, in 1975–1976, as its 48th President. She was the Society's first and, for the next 28 years, only

woman President. For her contributions to physiology and her service to the American Physiological Society, she received the Ray G. Daggs Award from the American Physiological Society in 1989.

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William H. Dantzer
Department of Physiology
College of Medicine
University of Arizona
Tucson, AZ 85724-5051
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