A SILVER SPOON

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An invitation to write the prefatory chapter for the Annual Review of Physiology provokes mixed feelings. There is no question as to the honor it confers; a glance at the list of previous invitees attests to that. On the other hand, it signals the unwanted passage of time, and it implies that the invitee, after 50 years of physiology, should have profound and useful things to say about the past and future. Alas, I must confess at the outset that the pearls of wisdom within my shell have been slow to mature, and they are still too small to spread before the sophisticated readers of this Annual Reviews volume. I can only use them as decorations for a personal narrative.

PRELUDE

I was born in 1915 in New York City. My father, Alwin M. Pappenheimer, Sr., was Professor of Pathology at Columbia University and one of the leading experimental pathologists of his day. He came from a well-to-do family and had every opportunity to make use of his natural talents for both science and the art of living. The summers of his youth were spent travelling in Europe, and he spoke French and German fluently. He made many drawings, etchings, and paintings, and he played the violin and viola well enough to participate in most of the classical literature of chamber music. I grew up with the sound of string quartets in the living room. My mother had a similar background, and she too was proficient in languages and music. My elder brother, who later became Professor of Biology and Master of Dunster House at Harvard, already played the violin well at the time I was started on the cello in 1922. On several occasions my scientific career has been influenced indirectly, but importantly, by music.
My father loved his work, and the excitement of his research permeated our family life. Students and colleagues from many parts of the world came to visit, and as far back as I can remember our conversations at home included science. Sometimes I was taken to the lab to share the excitement firsthand and listen to scientific palaver over a sandwich lunch with my father's colleagues. Much of the vocabulary of biology was mine by the time I was twelve years old, and about this time, my father began taking me to meetings, including Harvey Lectures at the Academy and evening joint sessions of FASEB when they were in New York. We went to these lectures in the same spirit as we went to concerts. My father often complained ruefully that he did not know enough chemistry and physics to solve his research problems, and perhaps it was for this reason that I inclined towards physiology, which depends so heavily on the exact sciences.

On sabbatical years my father travelled extensively in Europe, Russia, and the Far East. I began my schooling at the École Alsacienne in Paris in 1921. Classes were from 8:30 to 4:30 with daily homework as well. The pace was faster than in America, and on returning home I skipped one and one-half grades at our local elementary school in Scarsdale. Later I was sent to the Lincoln School in New York City, one of the leading progressive schools of its period. I entered Harvard at 16, intellectually prepared but too young to enjoy fully the broad educational and social opportunities Harvard had to offer. My father was a devoted Harvard man, and it did not occur to any of his children to apply elsewhere. It was 1932 and we, the freshmen, were observers of the Great Depression, but few of us were a part of it. Harvard had yet to reach out for the best and brightest, and we took for granted a Certificate of Admission and full financial support from our parents. To paraphrase T. S. Eliot (3):

We came this way, taking the route we were most likely to take
From the place we would most likely come from . . .
Either we had no purpose or the purpose was beyond the end we had figured and was altered in fulfillment.

I concentrated heavily in science but did not do particularly well in formal courses and in the end failed to obtain honors. My tutor was Jeffries Wyman, Jr., who introduced me to quantitative biology in general and to the physical chemistry of proteins and amino acids in particular. In the parlance of the 1980s, Wyman would be considered a molecular biologist, and indeed, his contributions to the mechanism of the Bohr effect and the general theory of allosteric reactions of proteins are cornerstones in modern theory of protein function (27). I was in awe of his command of thermodynamics and mathematics. Our joint work on the surface tension of solutions of dipolar ions was
published in the *Journal of the American Chemical Society* (23) in 1936. Jeffries (though of course I did not then address him so) wrote the first draft and gave it to me for criticism. I rewrote some of it, added a whole new section, and handed back the manuscript in fear and trepidation. He studied the changes and without hesitation or emotion said, “It is much improved, but now you must be the senior author.” Not long ago I was flattered on two counts when a well-known biophysicist in England asked me whether my father had written this enduring paper.

In the summer of 1935 I took the Physiology course at Woods Hole under the direction of Laurence Irving. Our instructors included such distinguished biophysical chemists as Leonor Michaelis and Rudolf Höber; the latter taught me how to prefuse frog kidneys via the portal system and how to cannulate a frog’s ureter. Later, the 1945 edition of Höber’s *Physical Chemistry of Cells and Tissues* became one of the most well-worn books in my scientific library. At the end of the course, I was awarded the Collecting Net Prize ($50 was a lot in those days) to come back the next summer to work on the kinetics of CO₂ transport and carbamino formation in fish blood with J. K. W. Ferguson, who had just published important work with Roughton on carbamino hemoglobin in human blood. We did not find carbamino hemoglobin in fish blood, but we did find an anomalous distribution of HCΟ₃⁻ and Cl⁻ in elasmobranch red cells and duly published in the *Biological Bulletin* (5).

**ROOTS IN ENGLAND**

In the autumn of 1936 I sailed for England with a letter of introduction to Sir Joseph Barcroft from Jeffries Wyman. An aunt had left me a legacy of about $2000 a year, and this was more than sufficient to support a research student in pre-war England. What would I have done without it? I arrived in Cambridge not yet 21 but eager to begin work in the laboratory. I learned, however, that Sir Joseph was in the United States and would not return until October. I spent the next few weeks practicing the cello and reading old Norse poetry in the University library. When Sir Joseph returned, he was extremely kind to me, perhaps because he was fond of my brother-in-law, Will Forbes, who had worked with him ten years previously. He gave me a small research project on fetal red cells and arranged for me to take the Part II honors course in Physiology, an experience for which I am endlessly grateful. I was dreadfully self-conscious, and I admired Sir Joseph so much that I could scarcely speak in his presence. He seemed to sense this and made a point of sitting next to me at laboratory teas and trying to put me at ease by telling funny stories and anecdotes. There were eight Part II students, selected from some 300 who had taken Part I. Our instructors included E. D. Adrian, B. H. C. Matthews, F. R. Winton, E. B. Verney, W. A. H. Rushton, and F. J. W.
Roughton, and I developed lifelong associations with all of them. Alan Hodgkin was a teaching assistant in the practical class; his job was to come in early in the morning to decerebrate cats for our class experiments. There were five lectures a week for three full terms, and each lecture involved analysis of significant papers in the field. We came to know the important literature in almost every aspect of physiology and in three languages. During the spring term I was introduced to F. R. Winton’s experiments on isolated perfused mammalian kidneys, and this opened the door to a new world for me.

Winton was then Reader in Physiology at Cambridge and the author, with L. E. Bayliss, of a widely used elementary textbook of physiology. He had trained at University College, London, under Starling, W. M. Bayliss, Verney, Lovatt Evans, and A. V. Hill. Sir William Bayliss’s “Principles of General Physiology” represented for me (and still does) the essence of all that is good in physiology, but I thought of Bayliss as someone who had lived long ago. It was amazing and thrilling for me to talk with someone who had been a close friend of both Starling and Bayliss. In Winton’s hands the original Starling-Verney heart-lung preparation developed into a sophisticated technique for perfusing isolated organs from a pump-lung circulation; it was the forerunner of modern artificial heart and life-support systems. I was spellbound by the sight of an isolated dog kidney sitting on a glass plate and producing clear golden urine from thick red blood.

Winton was an expert with instrumentation, and he designed most of his own transducers, amplifiers, recording oscillographs, etc. The perfusion apparatus was itself a complex, inorganic organism—a maze of motors, plumbing, and electrical devices for measuring, recording, and controlling flows, pressures, temperatures, ion concentrations, and blood oxygen saturation. All of this appealed enormously to my scientific senses; it seemed to me to be the ideal compromise between in vitro research and the unsatisfying complexities of whole animal research. I was swayed, also, by the fact that Winton was a fine cellist and his wife, Bessie Rawlins, was one of the foremost concert violinists in England. They invited me home to play second cello in the great Schubert C major quintet (Opus 163), and this settled matters for me. I had been brought up with the Schubert but never had I played it with such accomplished musicians. Winton, together with Grace Eggleton (later to become Mrs. Leonard Bayliss), was about to start an investigation of renal oxygen consumption as a function of osmotic work of urine formation. He welcomed me as a graduate student, possibly because of my previous training in physical chemistry and blood-gas transport; or was it because of my interest in string quartets? Two foreign postdoctoral fellows were working with Winton at this time: Jim Shannon (later Director of NIH) was there to compare inulin with creatinine clearances in the isolated kidney, and Kurt Kramer from Göttingen was there to develop, with Winton and
Glenn Millikan, a spectrophotometric device for continuous recording of arteriovenous oxygen differences in flowing blood. It must be remembered that in 1936 solid-state photocells were in their infancy, and the success of this project depended on the spectral characteristics of a prototype selenium barrier cell made only in Germany. Five years later Kurt Kramer in Germany and Glenn Millikan and I in the United States used this experience to develop the ear oximeter (15). In the meantime, Winton, Eggleton, and I produced a series of papers on the mechanisms of urine formation in perfused kidneys. It was the start of a close personal relationship, which lasted until Frank Winton’s death in 1985. Winton’s ingenious techniques for estimating renal glomerular pressure (2, 26) provided the basis for my own first contributions to capillary physiology a decade later.

In this period, also, I came to enjoy student life in Cambridge. I played in the University Orchestra and took part in activities at Clare College. On a dark, cold winter’s night we (the University Orchestra with soloists from London) performed Verdi’s Requiem in King’s Chapel, the most beautiful setting imaginable for this gorgeous music. William and Marjorie Rushton also played in the orchestra, and through them, I was invited to Music Camp in the Berkshire Downs. This, too, opened the way for life-long friendships. I was an avid skier and spent memorable winter holidays in the Alps and in the rugged Jotunheimen of central Norway. At Finse I raced in the downhill (Class C), coming in 89th in a field of 115 entrants. I was the only foreigner, as was duly noted by the Oslo and Bergen newspapers.

In 1938 Winton moved to the Chair of Pharmacology at University College, and he took me with him as research student on leave from Cambridge. Hermann Rein, one of the most prominent physiologists in Germany (and Kurt Kramer’s chief), had just published a paper alleging that metabolism of resting muscle was regulated by the sympathetic nervous system. Winton suggested that I look into this in perfused hindlimb preparations, utilizing the methods for recording blood oxygen we had used for studies of renal metabolism. I was able to confirm Rein’s surprising results, but I found a much simpler explanation for them that was based on sympathetic control of the microcirculation rather than on metabolism (17). This project gave me experience with the perfused hindlimb preparation, which I eventually used for studies of capillary permeability.

Of course we worked under the constant threat of war and with nagging inner voices telling us to stop everything worthwhile to prepare for it.

**WAR YEARS**

War came on September 2, 1939. I was on vacation at a music houseparty in Harvard, Massachusetts, and I intended to return to University College as
Demonstrator in Pharmacology. Passports were cancelled, along with my job. Winton became Dean of the Medical School, which was removed to Surrey before its buildings were destroyed during the Blitz of 1940. I sought help from A. N. Richards at the University of Pennsylvania. When I came for an interview, I launched into a detailed account of my work on perfused muscle, but he soon interrupted. “All I want to know,” he said, “is whether you are a good experimenter.” Torn between outward modesty and inner faith, I finally opted for the latter, and that was the end of the interview. He set me up with a temporary appointment in Bazett’s Department of Physiology and an emergency research grant of $250, which enabled me to complete work begun in England and to send in two papers to the *Journal of Physiology*. At the same time, I joined forces with Glenn Millikan to help develop the ear oximeter. Glenn, like myself, had been cast adrift from his position in England, and he sought help from Detlev Bronk at the Johnson Foundation for Medical Physics. It seemed obvious that the US would soon be in the war, and all of us wanted to contribute what we could as scientists as soon as possible. For the next six years, Glenn and I worked closely together on oximetry, on oxygen demand valves, chemical oxygen generators, carbon monoxide poisoning in tanks and military aircraft, positive pressure breathing, and other problems in applied physiology for the military.

Let me digress for a moment to pay tribute to Glenn Millikan, who was killed in a mountain climbing accident in 1947. He was the son of Robert A. Millikan, President of the California Institute of Technology, who was famous for the oil drop experiment used to measure the charge of the electron. Glenn was known as “the little oil drop.” He was probably the most well-known and charismatic young physiologist of his day in Europe and America. He exuded energy, curiosity, and *joie de vivre*. He found his way from Harvard to Cambridge, England, where he did highly original and important work on myoglobin, which culminated in a Physiological Review in 1939 (14). He was elected to a Fellowship at Trinity College, where he became a source of inspiration to students of physiology. He is still remembered with affection by colleagues in both Europe and America, and certainly his premature death deprived American physiology of one of its most promising young scientists.

In 1939, our Air Force was woefully lacking in equipment for high-altitude flying, and only a few physiologists had the knowledge and the vision to understand what was needed. Among these few were Bruce Dill, Detlev Bronk, and Walter Boothby. The Aeromedical Research Laboratory at Wright Field consisted of one altitude chamber and two or three poorly equipped laboratories staffed by a few junior medical officers and enlisted men. There was no formal provision or support for civilian research in this area, and during 1940 Glenn and I usually made the long trip out to Dayton in our own
car. Operational aircraft seldom flew above 18,000 feet, and in most cases they were equipped with rudimentary oxygen equipment. Only three years later, the USAF sent more than 10,000 fighting men aloft daily in unpressurized aircraft to operate for many hours at altitudes where consciousness would fail within a few seconds without supplementary oxygen. The enterprise as a whole required vast training programs in the use of oxygen, as well as continual work to improve the design and efficiency of oxygen equipment, which competed in weight with the load of gasoline and armament.

Bronk saw the magnitude of these problems at an early stage, and he became a leader for both the military and civilian effort. Most of the time he worked directly out of the Air Surgeon’s office in Washington, but he retained a small group at the Johnson Foundation to carry out applied research on oxygen equipment and on visual problems. Those of us who worked in his home laboratory as civilians had continual access to operational problems and to the flight testing facilities of the services and the aircraft industry. We spent hundreds of unhealthy hypoxic hours testing experimental equipment at simulated altitudes of 40,000 feet or more and temperatures of \(-40^\circ\) in the altitude chamber in Philadelphia.

I also participated in experimental flights to extreme altitudes in stripped down B-17s and in the first prototype B-29 heavy bomber just prior to its disastrous loss with all hands aboard in December 1942. I did a survey of carbon monoxide from gunfire in tanks and aircraft, and the Navy asked me to test a chemical oxygen generator retrieved from a Japanese Zero shot down in the Pacific. I found 0.1% CO in the oxygen. The Navy broadcast this result to the Japanese, hoping it might shake the confidence of their pilots in their equipment; at the same time, my report was classified as secret in the US, so I could no longer read it or keep it in my files.

Most of the time, at least up to 1944, we worked long hours and with a sense of urgency. Bronk was tireless; he would often arrive from Washington late in the day, talk with us until midnight and then return to Washington. I, too, led a somewhat frenetic and heady life of travel to military establishments and aircraft factories all over the country, not to mention frequent trips to Washington. Nevertheless, I remained in touch with a saner world through playing in string quartets, mostly with Catherine Drinker Bowen and with Helen Rice, who later founded the Association of Amateur Chamber Music Players, an international organization which now has more than 6000 members.

I had been brought up in an academic world that emphasized distinctions between “pure” and “applied” science. I was surprised and excited by the rapidity with which knowledge, previously considered interesting but useless, could be transformed to practical use on a large scale. Conversely, exposure
to practical problems often stimulated new questions in the realm of fundamental science. Certainly, this was true of respiratory physiology, which advanced rapidly in fundamental ways under the stimulus of applied research for the military. This was a lesson for my generation of academic scientists, a lesson which in its broader context was transformed into public policy after the War.

My own experience with applied research during the War was immensely enriched by close association with Detlev Bronk and the small group of biophysicists in his entourage, including Keffer Hartline, Frank Brink, Martin Larrabee, John Hervey, Glenn Millikan, and John Lilly. They were all experts in instrumentation, especially electronics. We were a close-knit family, and one would have to be very impermeable indeed not to learn by osmosis from daily association with such alert and knowledgeable minds.

By 1945, however, the War's end was in sight and all of us were "de-exhilarated" and eager to return to academic life. The project I was then working on, the storage of oxygen in the form of perchlorates, was already in pilot production in Pittsburgh, but it seemed unlikely to me that it would ever be used for its intended purpose as a source of emergency oxygen for aircraft or for portable welding apparatus. I was anxious to resume studies of the microcirculation, and after V-J Day it was natural for me to apply to E. M. Landis, an authority on capillary circulation who had just succeeded W. B. Cannon as the Higgison Professor of Physiology at Harvard. He had not yet made new appointments of faculty rank, and I had the good fortune to be selected as his right-hand man.

CAPILLARIES AND MEMBRANE PERMEABILITY (1946–1954)

I arrived in Boston in December 1945 to start a new life. There was a heavy load of teaching awaiting me. Gene Landis had organized a super course in mammalian physiology; all chapters of the fat textbooks of physiology were represented in both lecture and lab. It was a veritable dinosaur of a course, doomed to extinction as new branches of biology evolved to dominate the medical curriculum. For me it meant another period of intensive work and learning; I was frequently on deck at 6 AM to prepare live demonstrations or student labs prior to my 9 AM lecture.

It was not until June 1946 that I found time to resume experimental work. I had a vague plan for studying edema formation in isolated perfused muscle but without any clearly defined goal. NIH had not yet started large-scale support for university-based medical research, but even if it had, I don't think I could have written an acceptable request for a grant. Certainly I had no inkling that the project would lead rather swiftly to a logical sequence of
enduring advances in the physiology of the microcirculation and the biophysics of membrane transport. After only a few experiments, I saw how to set the mean capillary pressure to known values, how to measure the effective osmotic pressure exerted by the plasma proteins across capillary walls, and how to relate these to rates of net filtration and absorption. In the following year, these preliminary experiments were verified and extended in detail with Armando Soto-Rivera; they were first presented at the 17th International Congress of Physiology held in Oxford in 1947. It was the first Congress after the War, and physiologists were happily reunited after many years of forced separation. It was a moving contrast to the grim Congress in Zurich which I had attended in 1938, just prior to the invasion of Czechoslovakia. August Krogh listened to my paper at Oxford; afterwards he came "backstage" to say nice things about it, and of course I was thrilled because his work in respiratory, comparative, and capillary physiology was (and still is) such a large part of our heritage. At the closing plenary session in the beautiful Sheldonian Theatre, Albert Szent-Gyorgi gave a speech of thanks in nine different languages.

The methods developed for measurement of capillary pressure and effective transcapillary protein osmotic pressure were soon extended to the analysis of transcapillary concentration gradients during diffusional exchange of hydrophilic solutes between blood and tissues. This, in turn, led to a general theoretical analysis of the relations between restricted diffusion, hydrodynamic flow, and molecular sieving—an analysis applicable to a wide variety of biological and artificial membranes. The theory and preliminary results were first presented (with E. M. Renkin and L. Borrero) at the 18th International Congress of Physiology in Copenhagen in 1950, under the title *Filtration and Molecular Diffusion concerning the Number and Dimensions of Ultramicroscopic Openings in the Capillary Wall*. The complete paper subsequently appeared in the *American Journal of Physiology* (25). I recently wrote a history of this development and its relation to the parallel development of irreversible thermodynamics as applied to membrane transport (21). The American Physiological Society Handbook volumes on *Microcirculation* (edited by E. M. Renkin and C. C. Michel) provide full review of the many modifications and extensions of the original theory that have been made in the last 35 years.

In 1949 I married Hylie Palmer, a violinist at the Julliard School of Music and a pupil of Galamian. She has been first fiddle in my life ever since.

Alexander Forbes was still in the Department of Physiology at Harvard when I arrived in 1946, and it was a great privilege to come to know him. He was a pioneer in electrophysiology and one of its most distinguished leaders for more than 50 years (13). He was the first to use vacuum tube amplifiers in conjunction with the string galvanometer for recording nerve action potentials...
(6), which set the stage for the classic work of Gasser and Erlanger on peripheral nerve and of Adrian, Bronk, Zotterman, Matthews, and others on single unit analysis in sensory systems (8). Alex was also a pioneer of oblique photogammetry from the air and an authority on off-shore navigation. In 1935 he mapped northern Labrador and Baffin Land from his own plane, thus charting the way for the northern air route to Europe during World War II (7). He was awarded the Charles Daly Medal of the Geographical Society, and his election to the National Academy of Sciences might equally well have been for his contributions to geographical science as to neurophysiology. He seemed to know every inch of the New England coast and how it had changed during the sixty years he sailed it. He was a marvelous raconteur. In the evening, after a long day’s sail, he would relax over a “Chickatawbut” cocktail in the cabin of his ketch Stormsvala and draw on an endless repertoire of stories and anecdotes, which he always introduced by saying who had told it to him and when. There must have been dozens of young people, including my wife and me, who thought of him affectionately as Uncle Alex.

During the 1950s the American Heart Association established some fellowships designed to relieve young professors from administrative duties, and I was selected for one of these generous lifetime awards. This allowed me to continue laboratory work on a small scale in company with occasional graduate students and postdoctoral fellows. It also gave me the freedom to explore novel ideas without worrying about short-term success or failure. My first effort was indeed a failure. I had the idea that several puzzling features of the renal circulation might be explained by plasma skimming in the interlobular arteries and afferent arterioles. This idea turned out to be incorrect, at least in the renal cortex. Although my theory, which was presented as a Bowditch Lecture and elsewhere (22), failed to survive, it nevertheless stimulated lively discussion and experimentation for several years and I do not regret being wrong in this case.

GOATS

Beginning in 1957 I undertook development of techniques for perfusion of the ventricular system in unanesthetized animals. I was stimulated by the work of I. Leusen from Ghent, who had shown that perfusion of the ventricles with acid solutions caused hyperventilation in anesthetized animals even though the arterial blood became alkaline (11). Previous theories of chemical regulation of breathing were concerned solely with the composition of blood, and it seemed to me that Leusen’s experiments had some exceptionally important implications for this field. No one had ever perfused the brain ventricular system in unanesthetized animals, and I had no experience with surgery for
chronic experiments. My friends in the Neurosurgery Department were very skeptical about the feasibility of chronic cannulation of the cisterna magna. We found, however, that the size and shape of the skull in goats or sheep make possible the implantation of guide tubes through thick occipital bone pointing towards the atlanto-occipital membrane. The cistern could then be punctured at will through the guide tube without causing pain to the unanesthetized animals. At the same time, Feldberg, in England, described techniques for chronic implantation of cannulae in cerebral ventricles (4); so the stage was set for ventriculo-cisternal perfusions in goats. Nevertheless, it took us almost five years to perfect the surgical techniques and to learn how to carry out perfusions of the brain for long periods in healthy, confident animals. Eventually, the project was productive in three disparate fields of physiology, as follows:

1. Exchange of materials between blood and cerebrospinal fluid (CSF), including the first measurements of CSF production and absorption by clearance techniques. The results were first presented in 1961 at the International Congress of Pharmacology in Stockholm and have since been described in reviews and textbooks.

2. Central chemical control of breathing [reviewed in a Harvey Lecture, 1967 (18)].

3. Investigation of sleep-inducing factors released into CSF during sleep deprivation [reviewed for Scientific American, 1976 (19) and in a Bayliss-Starling Lecture, 1982 (20)].

It would be difficult to initiate a project of this kind at a reputable medical school of the 1980s. My assistant, Jim Nicholl, never went to college, but he was a jack-of-all-trades who could do everything from metal spinning in the machine shop to milking goats. In fact, he became more adept than I at implanting cisternal guide tubes. Together we built a goat shed and fences amid the ventilators on the roof of the Medical School, and we did not even ask permission from Buildings and Grounds. We found farmers (within a radius of 100 miles) who would supply us with their “surplus” goats free of charge. We transported goats and hay in my station wagon. In summer the operated animals (with neckbands to protect their carotid loops and aluminum hats attached to their horns to protect ventricular guide tubes) travelled with us for vacations at our summer home in the Berkshires. Astonishment, laughter, and curiosity were plain to see in the faces of motorists who passed our station wagon with its cargo of capped goats and children. At about this time I began to serve on national committees in Washington and elsewhere, and the airplanes often passed over the Medical School, where I could look down to see my goats capering on the roof.
All of this would be illegal today, and the cost of purchase and care of more than a hundred goats in accredited facilities would be quite out of line with the potential of the project as it was viewed at the time.

SLEEP

It was my habit to spend Saturday mornings browsing amongst the journals of the week. That was how I stumbled on an article by Monnier and Hosli with the intriguing title *Humoral transmission of sleep and wakefulness; hemodialysis of a sleep-inducing humor during stimulation of the thalamic somnogenic area* (16). That article referred me to Pieron’s early work on the sleep-inducing properties of CSF drawn from sleep-deprived animals. A copy of Pieron’s 1913 monograph *Le problème physiologique du sommeil* was at hand in our departmental library. On several occasions I have been to the library to browse or to look up a specific reference and was led by chance to an unrelated paper that changed the course of my subsequent research. This sort of serendipity is something the computer cannot supply and I am reminded again of the quotation from T. S. Eliot’s *Four Quartets* paraphrased in the prelude to this essay. In this case I realized at once that my colony of goats provided the means for collecting large quantities of CSF from sleep-deprived animals, and I resolved to “give it a fling.” Jim Nicholl and I rigged up a system to keep the goats awake while Tracy Miller and Cecilie Goodrich implanted ventricular cannulae in cats to enable us to introduce CSF from the goats into the cats. To our surprise, the very first experiments corroborated the findings of Pieron: CSF from a sleep-deprived goat infused into the ventricles of a cat appeared to make the cat torporous for several hours, whereas normal fluid from the same goat had no effect. Of course we had no EEG to judge the nature of the induced sleep, but we all agreed about the behavioral effects in the three cats tested.

Our first publication in this field was in 1967 (24), and it was followed by 15 years of frustrating attempts to isolate and identify “the” sleep factor. Early in the project I was joined by Manfred Karnovsky, a distinguished biochemist who was (and still is) sympathetic to old-fashioned physiology and physiologists. Our starting material changed from CSF derived from sleep-deprived goats (six liters obtained laboriously from 25 goats over a three-year period), to the brains of 15,000 sleep-deprived rabbits, to 5000 liters of normal human urine. We had many collaborators, but much of the credit for the final isolation and identification of an active muramyl tetrapeptide from urine belongs to Dr. James Krueger (10, 12). The natural product and certain synthetic muramyl peptides have now been shown to induce high-amplitude, slow-wave sleep in rats, rabbits, cats, and squirrel monkeys. I am still not
convinced, however, that the material isolated from urine is related to the 
sleep-inducing Factor S we originally found in the CSF of sleep-deprived 
animals. The latter is surely of importance to normal physiology, but there are 
reasons to believe that the muramyl peptides are involved in immunological 
reactions to bacterial infection, including fever as well as sleep. The history of 
this still controversial subject has been reviewed in several recent publications 
(1, 9, 10, 19, 20).

INTERNATIONAL

The romance of travel to international meetings has been badly tarnished by 
the jet. The up-and-coming young physiologist thinks nothing of waltzing off 
to Europe for three-day meetings several times a year, attaché case and 2 × 2 
slides in hand. There is prestige value when the secretary can answer phone 
calls with “Dr. S. is out of the country until Thursday. Do you want him to 
call?” The airport at landing is the same as the one at take-off, and Hilton-
Budapest is not much different from Hilton-San Diego or New Delhi.

It was not always so. Less than 40 years ago the triennial International 
Congress of Physiology were about the only international meetings for 
biochemists, endocrinologists, nutritionists, and pharmacologists, as well as 
physiologists; and there was no such word as neuroscience. Biological sci-
entists, young and old, saved their pennies for the triennial treat. It was 
unethical to use research funds for travel to meetings, even to local FASEB 
meetings. It took a week to cross the Atlantic (depending on the weather), and 
it did not make sense to embark on such a long trip without spending at least a 
month on the other side. How to compare the excitement of a midnight 
sailing, the sound of the bugle warning visitors off the ship, the rattle of 
chains as the gangplank is raised and the hawser cast away, cutting one loose 
from home with no way of quick return even in emergency—how to compare 
this, I say, with the long line of tired, vetted passengers boarding Flight 6339, 
which might just as well be going to Kansas City as to Paris or Copenhagen?

The scientists I admired most, both in England and America, were inter-
nationally minded, and my generation of physiologists inherited a strong 
tradition of loyalty to THE International Congress of Physiology. I attended 
most of these Congresses from 1938 onwards. In 1964, when Wallace Fenn 
asked me to be Program Director for the 1968 Congress in Washington, D.C., 
I jumped at the chance. From then until 1983 I had the joy and privilege of 
working with Councils of the IUPS together with my counterparts from the 
USSR, Poland, Hungary, South America, India, Australia, and Japan, as well 
as those from Western Europe and Scandinavia whom I already knew well. 
One of my main concerns in this period was to maintain strong representation
of “Neuroscience” within IUPS, in hopes that this most exciting part of physiology would not break away into a separate union. It seems to me that physiology in the United States has suffered greatly by the establishment of separate departments or divisions of neuroscience within universities, national societies, and academies. This has not occurred in other countries, where departments and societies have moved with the times to incorporate the enlarged scope of modern neurophysiology in which immunology, peptide chemistry, embryology, etc play such important roles. It may be that the size and success of developments in neuroscience within the United States made fission inevitable, but whatever the reason, it has adversely affected many departments of physiology across the land.

In addition to service with IUPS, I have had many other opportunities to participate in international meetings or projects, some in exotic places. In 1957, after a lecture tour of Swedish universities, I revisited Jotunheimen on skis to replay the adventures of 20 years previously. Björn Folkow from Göteborg accompanied me on this expedition, during which we skied to Storbreen glacier. There my old friend Per Scholander was extracting gas bubbles from the ice to estimate the composition of the atmosphere at the time the glacier ice was laid down. In 1942 Scholander and I almost lost our lives when we were caught for three days in a severe blizzard on the summit of Mt. Mansfield in sub-zero temperatures and high winds. Other memorable expeditions, all in the name of Physiology, were in Kashmir, in the foothills of the Himalayas; in the alps of Southern New Zealand; and in Valdivia, 16 hours by train south of Santiago, Chile.

On two occasions I returned to England for full years; first as Overseas Fellow of Churchill College, Cambridge, and subsequently as Eastman Professor and Supernumerary Fellow of Balliol College, Oxford. These were years for renewal of old friendships, cementing of new ones, and the sharing of both with my wife and children. Three of our children continued for five years or more in England to complete their schooling and university educations. All of them chose art, music, or literature as a life work: not an easy way to earn a living, and I admire their courage and idealism. It seems unlikely that the Arts will ever receive even a small fraction of the support given to Science in the second half of the 20th century.

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