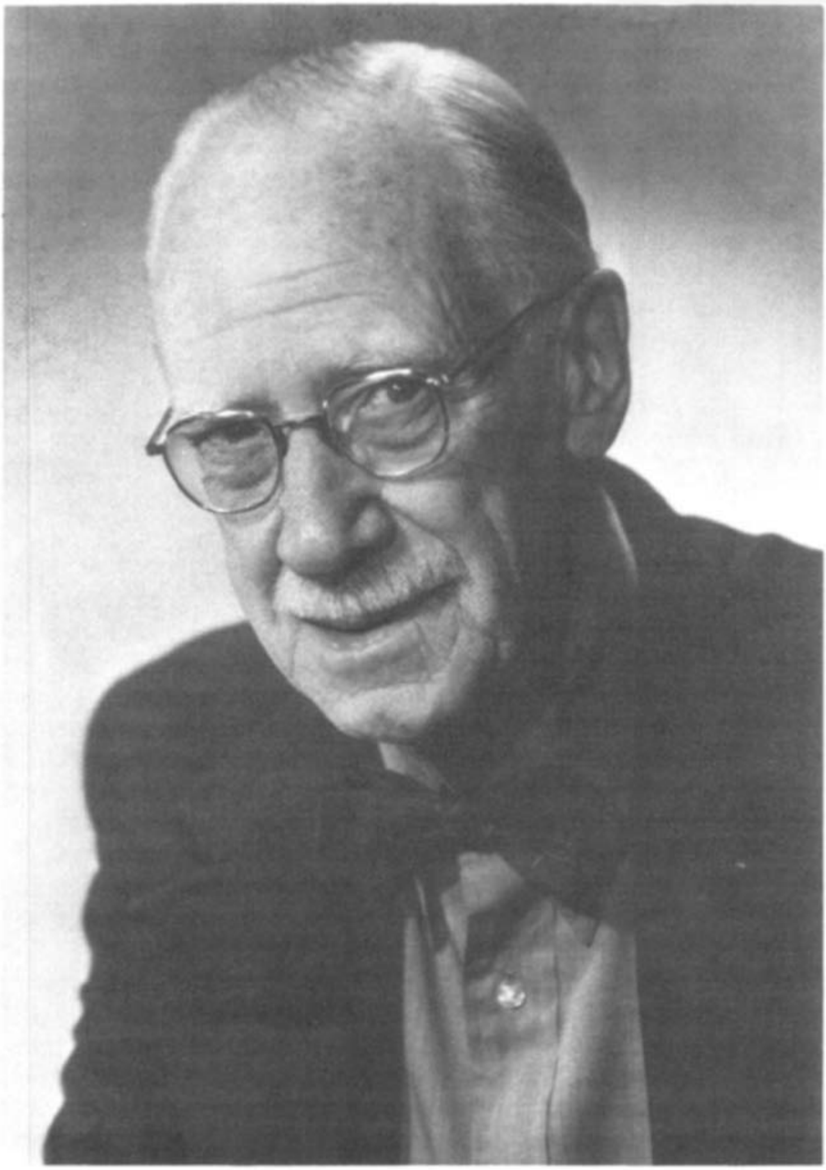

K S Cole

Ann. Rev. Physiol. 1979. 41:1–24

MOSTLY MEMBRANES[1] ♦1202

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My first formal connection with physiology, and my first job, began in 1929 when I became Assistant Professor of Physiology at Columbia's College of Physicians and Surgeons in New York City. The association with physiology has been very happy and rewarding. Physiology and physiologists have been kind, generous, and forgiving. Now I am invited to write the Prefatory Chapter of the *Annual Review* which, in the words of the editor "is traditionally authored by a physiologist of great distinction." I am highly honored to join this group and more than a little flattered.

I switched to biology after I obtained a degree in physics in 1926; but I had been committed after the first summer at Woods Hole in 1924. I had gone to Woods Hole because I liked my first taste of biophysics at the Cleveland Clinic the summer before.

I had decided on physics research during the more than a year at the General Electric Research Laboratory, 1920–1922. There I saw electrical engineers at work and it was not for me, in spite of the fact that earlier, during a five week inspection as a merchant seaman, I had been inspired by the magnificence of the Panama Canal, and during a trip with Dad I'd felt the grandeur of the generators and the thrill of molten aluminum being cast at Niagara Falls.

As a youngster I had been lonesome but too busy to worry about it. Even then, although I spent summers as a machinist and as a deck hand on the Great Lakes, I was an electrician. I produced sparks and shocks with worn out parts from the telephone company and put together a licensed wireless station with a Ford spark coil and galena (for a detector) begged from the head of the Geology Department.

It all goes back to my amazing parents—a Mother who, when I asked her why the big lumps came to the top when I jiggled the sugar bowl, said "Maybe they don't," and a Father who devoted his career to shaping the academic excellence of Oberlin College. As a parent and a Dean he must have been sorely tried by my pranks—especially by those he suspected but I didn't get caught at. When I asked about a couple of faculty members, he told me they could keep warm on a very cold day just by talking about him. But I don't remember ever acting against paternal advice!

COLLEGE

My scientific career really began with the year at Schenectady. S. R. Williams at Oberlin persuaded me to write for a summer job to the Bureau of Standards, which promptly turned me down, and to General Electric, where W. R. Whitney asked me to visit and promised me a job if I *had* to work there. It was a marvelous experience. I worked on my own on high frequency heating of silicon steel and evolved gas analysis in high vacuum. The techniques were all new to me. Come fall, I didn't have my first analysis.

Dad suggested I take a year off from college, and GE raised my salary so that I could quit my job as a boarding-house waiter. At the research laboratory I got to know everyone and what they were doing. I prowled the works from a battleship turbo-generator to tests of a rolling mill motor. I was properly chewed out for indiscretions and mistakes but I was really hurt when Irving Langmuir ignored me after a glance at my puzzling data. The next time he said "You *do* have a problem," and we worked on it. When I said I was interested in his octet atom, he spent the afternoon explaining and defending it, and we became friends! During this period, solo canoeing on the Mohawk out of the Edison Club and a vacation up Schoharie Creek were my principal diversions.

By far my luckiest move was to take a course at Union College on "Modern Physical Theories" by F. K. Richtmyer of Cornell. He was consultant to GE and gave several lectures on each visit. His book became the first year grad student's bible for several decades and a model for mine almost fifty years later.

My senior year was spent catching up on sophomore and junior year courses I'd missed while in the Army and on the high seas. Dad was Oberlin representative to Farrand's inauguration at Cornell. As he departed for the occasion in academic regalia and soup and fish, I told him that I didn't care about the ceremonies but that he must meet the rough-hewn Richtmyer. He was as much impressed by the man as I, and advised me to take the half-time instructorship Richtmyer had offered me. So, having considered MIT, Chicago, and Harvard, I settled on Cornell. That summer my favorite girlfriend was married, and I went on the Lakes, a rough, tough high-seas bos'n—aged 22.

PHYSICS

The first semester at Cornell was so grim that I was ready to quit, but Dad told me I couldn't quit as a loser. Then a notice appeared on the bulletin board: "Wanted—Two biophysicists at the Cleveland Clinic." I knew of the Clinic and of G. W. Crile. Richtmyer said "Darned if I know what a biophysicist is, but I'll tell you something I think is biophysics." He told me of a day at Woods Hole when W. J. V. Osterhout explained the electrical conductivity of the kelp, *Laminaria*. "I think he's right," Richtmyer concluded, "and it looks like darned good fun." But Hugo Fricke wanted two physics PhDs, not a summering first year grad student. He went on vacation to Denmark with no word of what I was to do, so I had to talk myself into the job twice.

Fricke (10) measured the resistance and capacity of blood and calculated the cell membrane at nearly 1 μF cm^{-2}, to give a lipid thickness of 33 Å. He published this finding in the spring of 1923—barely ahead of the extraction and spreading experiments of Gorter & Grendel. I recalibrated his bridge and struggled futilely with his analysis, but it was a good summer. I liked Fricke and admired his history-making combination of theory and experiment. I also learned something of his principal love, the chemical effects of X rays. I knew most of the staff, including several who died in the Clinic fire a few years later. The medical atmosphere was interesting and exciting.

I spent the next summer at the Marine Biology Laboratory at Woods Hole. C. G. Rogers took me in to work on heat production of the eggs of the sea urchin, *Arbacia*. R. A. Budington told me that he was glad to see me interested in a live subject. Rogers had superb measuring equipment, but I had to design and make my first thermopile and stirring gadget while the new Lillie building was being built. The results of the *Arbacia* work were solid and spectacular, but they were first repeated and confirmed 50 years later—at my urging—by Ed Prosen of the National Bureau of Standards.

I went to most of the Physiology and Friday evening lectures as well as the MBL Club dances. I bought a decrepit sailing dory and taught myself to sail while I eased into the sailing crowd led by Ghosty Bridges, of genetics fame. I saw so many interesting and useful things that I thought I could do and had such a wonderful time that I became a Woods Hole addict and set out to try to mix biology with my physics.

Back at Cornell I turned to doing a thesis that involved chasing electrons in circles onto photographic emulsions in a brass box. Most of my fellow graduate students were in the graduate fraternity but, as I found out later, my name was always blackballed. I wasn't even curious about this; I joined a group of fellow barbarians that included a couple of my first-year students. We had some hilarious times to more than compensate for living at home during college.

In the mad scramble to finish up I applied for an NRC post-doc fellowship that would let me follow Fricke and measure the membrane capacity of sea urchin eggs. It seemed easy because they were large and beautifully spherical. But the physics division said that eggs weren't in their jurisdiction; they told me to try biology. Biology said that I didn't have the appropriate training; they told me to try physics. Richtmyer somehow persuaded the sporting biology board to play the long shot and support me at Harvard and Woods Hole under W. J. Crozier and E. L. Chaffee. When my diploma came, Dad said "It's very pretty but it doesn't mean a thing —except that now you won't have to explain why you don't have one."

BIOLOGY

So I became a biologist. Tramping the hot sidewalks of Cambridge looking for a room was discouraging until I came to the last place on my list— opposite Radcliffe—on the second day. Jack Fife clattered down, invited me in, made me a cup of tea, and sold me on the other third floor room. Then he sold his landlady on me as a roomer, and I moved in to the center of my social activities for two happy years. Lucky? Jack was an English grad student. Mrs. Williams, the landlady, had been a student of Osterhout's, was the widow of a Harvard anatomist, and was putting their two children through Radcliffe and Harvard. Her husband had done his thesis on "The Anatomy of the Common Squid, *Loligo,*" in which he discovered and described the giant nerve system. But I didn't see the monograph for ten years; I don't know why I didn't cite it in my book.

While I was trying to duplicate Fricke's bridge, my roommate at Cruft, H. B. Vincent, suggested that I use two vacuum thermocouples such as he was using for his shot-noise work. I tried the idea out on Fricke's data and it gave me his result with half of his data. So I designed and built an oscillator and an egg cell—where stirring and aerating the egg suspension were problems, as were electrodes—and got to Woods Hole before the *Arbacia.* I visited New York to meet Osterhout and Selig Hecht, who were to become lifelong friends.

The work went well with minor modifications, but the cell required the eggs from as many as five females. Preliminary calculations following M.

Philippson showed a large dependence of capacity on frequency—contrary to postulate. But I was stuck with the experiment and took as much data as possible on both unfertilized and fertilized eggs. I hoped to sort it out later. I made many friends. E. N. Harvey was a lab neighbor and listened to my woes. When Keffer Hartline complained about his experiment, my vacuum tube and circuit cured the troubles; he upbraided me some years later when his amplifier misbehaved: "It's your fault, you started me on this miserable business." I got another old sailing dory, promptly christened "Hunky"; we sailed as much and as often as possible in it and in Ghosty's beautiful Herreschoff "Virge."

The next year was mixed. In trying to make sense out of my data, I spent long periods in Widner Library. I went back into the fundamentals and tried to derive the relations that (as I didn't know) Kramer & Kronig were just then publishing. But I was very lucky. Browsing through Maxwell's text I discovered his neat derivation for the resistance of a suspension of spheres and then, a few pages earlier, his expression for a two-phase sphere. Extrapolating the outer phase to a thin capacitor and putting it into the suspension, I arrived at considerable improvements on Fricke.

From K. S. Johnson of Bell Labs, who was a visiting professor, I learned about equivalent circuits and complex plane plots. Gildemeister had plotted human skin impedance on the complex plane to give a small, short, straight line; I was able to show that for a constant phase angle impedance this became the circular arc with a depressed center that has since been widely used. I wrote up the two papers alone in Randall Cottage—where, in one of his puckish moods, G. W. Pierce designated me Director. L. R. Blinks came up from Rockefeller with a thermos full of *Laminaria* to check out their high-frequency behavior. I got some understanding of Crozier's thermal coefficients and became acquainted with Hudson Hoagland and Gregory Pincus, who later did "the pill." Crozier really went to work on my two manuscripts. He whipped them and me into shape, both grammatically and logically, for which I've been very grateful. The theory paper (2) is still useful. The experimental one only reminds me to be generous with brash youngsters.

I was intrigued by what little I knew of nerve. I got a fellowship to work with A. V. Hill, but he wouldn't have me unless I'd go back to heat. Then Osterhout called from Washington to ask if I'd like a year with Peter Debye in Leipzig. Would I ever! "Get an application in the mail today and maybe you'll get a fellowship." I missed the last mail, but a long telegram did the trick—except that Debye wouldn't have me. Then Richtmyer interceded, and I had a fabulous year. I worked over my head on Nernst-Planck theory. When I asked what one problem had to do with membranes, Debye stomped to the window muttering "You and your damned membranes."

We both laughed and that was our password. But Debye was frustrated; in a letter to Richtmyer he said, "I've enjoyed having Cole—but please don't send me any more like him." Working with Debye was a rare privilege; I was convinced that he, like Langmuir, was a different kind of mortal.

PHYSIOLOGY

Soon I was to take my first real job as a physiologist. During the winter in Leipzig I'd had a very satisfactory offer from H. B. Williams at Columbia P & S. I accepted twice—once in a letter from Athens that didn't arrive. Williams had battled for the position for a physicist and had asked Richtmyer for a recommendation once he'd gotten it. More luck! The other two PhDs on the P & S faculty, Hans Clarke and Michael Heidelberger, were chemists; I was an oddball. (But Williams himself had been a math major, had been in charge of sound ranging in World War I, and had written a couple of papers on string galvanometer theory and design.) Williams' help and understanding were nearly unbelievable. He took me to the Mens Faculty Club occasionally; usually we ate at the Attendings Dining Room of Presbyterian Hospital. My next best friend was Ross Golden of radiology. He gave me the job of calibrating his therapy machines, and soon I was consulting physicist to the hospital.

We'd had an ethylene explosion in an Operating Room soon after I arrived. Williams and I made recommendations, which fell by the wayside. A fatal cyclopropane explosion some years later was devastating. The Executive Vice President decreed there would be no more cyclo operations until I could assure him that they would be absolutely safe. When we had things under reasonable control I told him I could make the rooms safe for cyclo only by means that would make surgery impossible. I told him I would give the surgeons a probability of an explosion, which they could then consider along with all the other hazards—including those of other anesthetics. He was disgusted but convinced.

I did all sorts of odd jobs. I measured potential differences between teeth, calibrated a skin-temperature gadget, overhauled (with Williams and Hoyt) the first-year medical physiology laboratory, and gave a few of the lectures. The Department was then concentrated on circulatory physiology. B. G. King and E. Oppenheimer injected some 100 dogs with Evans Blue dye and took blood samples between a few minutes and 24 hours afterward. I found the concentrations were beautiful linear functions of the square root of time and wrote up a picture for diffusion of the serum albumin that bound the dye. But this was against the local establishment and also the journal wouldn't publish anything so absurd.

I've been very proud of my aortic aneurysm operation. After being bombarded by reports about everything that had been tried, I finally realized that a wire laid down on the wall and heated to a controlled temperature might work. We used enamelled wire, pushed the bight through a needle and heated it electrically in a bridge. After animal experiments and our first patient we had a long series of successful immobilizations. Our chief of surgery, Alan Whipple, came in once, watched the wire being inserted, looked at me and my rheostats, galvanometer, slide rule, and log-log graph paper, and, twinkling, said "I've seen strange things in operating rooms, but this is the damnedest yet." I was let down when my collaborators wrote up the operation; they gave me credit only for the circuit.

It was Ashley Weech who finally sold me to the Center staff. According to him, I could diagnose, prescribe and cure a patient by phone. He told me of his new and expensive glass electrode pH meter. I kept my reservations to myself. During the summer he reported that his meter was completely unreliable. I told him how to keep the quartz insulation dry, and that did it.

RESEARCH

My own work was slow starting. I got minimum equipment and set up a crude bridge that I used to measure everything from potato, to nerve, to a cat's diaphragm. Then I managed to approximate them on the impedance plane by depressed-center circular arcs. At Woods Hole Harvey was working on *Arbacia* eggs in the centrifuge microscope he'd built (following the design I'd sent him from Leipzig). He came up with an incredibly low value for the surface tension. This I confirmed by dropping a bit of cover slip onto eggs in a dish. I spent much of the winter building an "egg crusher" designed around specially rolled gold wire from a friend at Leeds & Northrup. The results gave me the internal pressure and elasticity I'd long wanted. Harvey hurried me into publication in the *Journal of Cellular & Comparative Physiology,* Vol. 1, No. 1, p. 1, 1932. With no little sentiment I remember that the symposium, which W. J. Adelman, R. A. Sjodin, and R. E. Taylor arranged around my 65th birthday at Woods Hole, appeared as a supplement to the last issue of the *Journal* before it changed its name. This was also about the time that M. Yoneda et al showed I'd probably been too lazy in not integrating the moment of the profile of the egg—which I had built a balance to do. They found the membrane tension independent of the area. (Recently, this question became controversial again!)

The next winter I improved the crusher. Eva Michaelis came with me to work on fertilized eggs during the summer. My brother, R. H. Cole, came to work on a fancy but stupid idea of mine to measure *Arbacia* heat. I'd shopped most of the Cape to find a knockabout I could afford; I called it "Nike." About the first thing I did was to sail it down from Monument Beach single-handed in enough of a breeze to cause Ed Norman to allow as how I must be a good sailor. He had a Herreschoff "S" and was about to rejuvenate the long-dormant Woods Hole Yacht Club. Once, when ballast shifted, my brother Bob and I were dumped in the Hole! That summer Elizabeth Roberts, a Chicago attorney whom I'd known since she was two years old, came to New York and we were married. I took her to Woods Hole. She complained that all I cared about was sailing; she got sea sick. We were to share our lives happily, through thick and thin, for a third of a century. She died with her boots on.

R. G. Harris asked me to help with a symposium he was organizing at Cold Spring Harbor in late '32. I came up with the name, Cold Spring Harbor Symposium on Quantitative Biology, and gave three papers to replace dropouts. It seems a shame to me that lately there have been so many pressures as to preclude the leisurely eight-week programs that were the rule until Reg died.

Bruce Hogg, a medical student, had volunteered to help in New York. Using a micropipette, he and C. M. Goss had explored potentials around a heart-muscle culture. The 2 μm tip killed the cells when he tried to cross a membrane, but there were one or two hot spots in some cultures where the action potentials exceeded the rest potential. He came with me to work on *Laminaria* the first Cold Spring Harbor summer in Fricke's lab. We collected the kelp by diving off Eaton's Neck at chilly dawn and repeated some of Osterhout's experiments. The kinetics were provocative but I couldn't understand them. So the graphs sat in our lab collecting Medical Center grime until we found the answers with *Nitella.* The next summer Bob Cole helped Emil Bozler and me on frog sartorius with a rather good bridge I'd put together. I calculated the resistance and capacity for parallel cylinders following Maxwell, only to find later that Rayleigh had given my resistance as his first approximation. Again we had a constant phase angle impedance, but I finally realized that this gave no information on the absolute value of the frequency-dependent capacity. Remembering my '28 trick for calculating this, I went to work before breakfast to see if the exponents checked. To my vast relief, they did. By sugar substitution, we got an early value of membrane resistance as 40 Ω cm^2.

I'd been remembering E. N. Harvey's telling me of a big white Bermuda sea urchin, then called *Hipponoë,* which he'd found with a few eggs at Christmas. When Dr. Horace Davenport told us of the delights of the Bermuda Station, Elizabeth and I decided to go on a working vacation in the fall. Will Beebe and his group were recovering from their bathysphere deep dive and included us in all their fun, from helmet diving at Almost Island to motor boating to St. Georges for dinner and moonlight dancing. Elizabeth had a rough time with her bicycle and was black and blue from running into ditches and hibiscus bushes. With the captain of the Bermuda water polo team we collected eggs from every possible source. Our last collection gave two ripe female *Hipponoë* and 100% fertilization, as Harvey had suspected. So we planned another expedition the next fall and the H. J. Curtises came along for a couple of weeks. One memory is of the four of us racing our bikes back from Swizzle Inn.

Our second experiment gave a 90° phase angle—*Hipponoë's* membrane was a perfect capacitor, altogether different from my *Arbacia*. Also the capacity increased on fertilization and decreased on swelling. (Bob Taylor recently asked about the capacity per egg—not per square cm—and it was near enough constant to suggest microscopic dimples and pimples or wrinkles and crinkles.) So we had to do *Arbacia* again. The next summer Bob and I imposed on Fricke's hospitality again; for eggs from starfish we found the same result as for *Hipponoë*. When we used urchins from Woods Hole it was the same story. Why did three echinoderm eggs have a perfect capacity while all tissues showed what I've come to call dielectric loss? And how did the capacity increase on fertilization? And what was the high-frequency dispersion at several MHz?

My ideas on a wheatstone bridge had jelled enough to justify my taking 1935 off to design and build it. Dottie Curtis and Elizabeth decided that Curtis should work with me. The Rockefeller Foundation supported the idea; he arrived at New Years, just in time to solder a few of the last joints. Joe Spencer had been dropped from Princeton, and he was volunteered to help us; we'd been invited to give a paper at the '36 CSH Symposium on nerve and muscle; Ted Jahn wanted to work on grasshopper egg cuticle during this summer: We had a feverish rush.

We knew that muscle fibers varied considerably in size and, since cell radius is a factor, whole muscles could give an apparent membrane loss. Years later, Paul Fatt showed, gently but firmly by calculation, that the contribution of the size spread was negligible. In our paper we also derived the longitudinal impedance of a single nerve fiber with narrow and also with wide electrodes. The wide-electrode result looked too difficult to be useful.

At Woods Hole, Joe Spencer did a precision job on *Arbacia* eggs. He confirmed the findings of *Hipponoë* and *Asterias* while showing that Bob and I had tried to do too much on too few eggs at Cold Spring Harbor. As Curtis worked with single eggs at Woods Hole, Rita Guttman studied frog eggs in New York. One of these was held in a cylindrical hole in the disc between the electrodes. I couldn't solve the potential theory so she got an analog solution using progressively larger glass beads as a model system. But I thought the resistance effect would be too small to measure with red cells when Coulter proposed his counter. How wrong can you be? Recently it was found that W. R. Smythe had solved the problem in an entirely different connection. Smythe was certainly pleased when I told him our data agreed with his solution. How widespread has been the use of the Coulter counter! (Then Smythe was bewildered and deeply grateful when I pointed out an old mistake in the last edition of his book!)

SQUID

The spectacular events of the summer of 1936 involved J. Z. Young and his squid giant axon. Squid were brought from the south shore of Long Island in milk cans; they arrived thoroughly inked and more dead than alive. The two axons we tried looked just like sea water but Young convinced us of their importance. "If you want to find out about nerve, you've got to work on this axon." When I asked how everyone had missed this half-mm tube as an axon, Young said he'd not done the literature until he'd mostly finished at Naples and then had found a 1912 monograph—by an American—on the giant axon system of squid. "Would that American be L. W. Williams?" I asked. I told him the story of my landlady's husband—to his utter amazement.

Elizabeth became pregnant and our lives were going to be different for a while. We went to England on an elegant small Cunarder because U.S. lines were struck, taking with us *Time* magazine with its center spread on Wallis Simpson and King Edward. This was all news to Britain and we kept current with the Paris Herald. We had a delightful lunch with J. Z. Young at Oxford, and I probably first met Alan Hodgkin in Cambridge during this visit. We took one of the first ferry trains to Paris where we visited A. M. Monnier and his wife. Elizabeth had her first, and I my second, encounter with bitter winter weather in the Atlantic in a small American freighter coming back. We were four or five days late, but home by Christmas.

The squid axon was a bigger break by far than we knew then. Our first interest was to see if 1 $\mu F\ cm^{-2}$ and dielectric loss were characteristic of a single cell membrane. Curtis suggested that we use *Nitella* during the winter. We got the 1 $\mu F\ cm^{-2}$ and a considerable loss—as had Blinks—but the *Nitella* had far too low a resistance. Finally when we pulled the cellulose sheath over a glass rod we found we had what came to be called an ion exchanger—the conductivity was nearly independent of that of the medium, as has been confirmed.

We arrived at Woods Hole with the squid and soon had another 1 $\mu F\ cm^{-2}$ with considerable loss—70° to 80°. Out of plate glass Curtis ground a new cell with much larger electrodes; it made no difference to our findings. We also had a second, high-frequency dispersion, which we ignored. More disturbing was the fact that there was no change of impedance during excitation nor during deterioration until an hour or so after the axon became inexcitable (9). A constant critic kept his record clean: "I always thought you were carefully measuring something quite unimportant!"

We went back to *Nitella* in the fall of '37; using narrow electrodes we saw the transverse impedance decrease as an impulse went past. For the first time, I calculated the effect of a pure membrane resistance decrease. Our points taken from movies of the unbalance Lissajous figures during impulses could be interpreted as an average 15% decrease of membrane capacity from its resting value of 0.9 μF cm^{-2} and an average maximum resistance decrease of 500 Ωcm^2 which was independent of frequency. So the capacity change seemed negligible compared to the 200-fold decrease of membrane resistance. But the lowest resistance (500 Ωcm^2) was considerable. It was also interesting to do some analysis on the characteristics of a partial short circuit travelling with constant speed. The paper we wrote is a pride and joy to me (5). If (as we've been accused of doing) we started a new era of axonology, it was in this paper that we had to be original.

We built a new cell and a new amplifier; we modified our first commercial oscilloscope to give single, but highly nonlinear, sweeps. Then we waited, miserably, at Woods Hole for the first squid. Our first two axons showed nothing. We put in the whole nerve. With everything wide open we observed a very slight change. Curtis swore it was a decrease; I wasn't sure. But it got larger and larger as we used better and better axons, until finally we got the picture shown in Figure 1 (6). The photo was taken in the dark with my '29 Leica. I set and tripped the Lucas spring rheotome some twenty times for the impedance change, ΔZ, and half a dozen times for the action potential, V. I had a bloody thumb sometimes. Hodgkin visited when we had ΔZ on the scope. He was as excited as I've ever seen him, jumping up and down as we explained it. He also appreciated the importance of the resting membrane resistance and thought longitudinal measurements between long electrodes could give it. He assembled the equipment in New York and took the data back to Cambridge to find about 1000 Ωcm^2 (7).

On my way to the 1938 Zurich congress I stopped in London; Otto Schmitt was there; Bernard Katz had just come from Leipzig; A. V. Hill instructed me on talking to the multilingual audience I would face. Brian Matthews and I travelled together and talked sailboats most of the way. After a bad case of jitters I was truly surprised by the enthusiastic reception of my talk.

Near the end of the Congress a cable sent me to Vienna. Elizabeth's sister had married a Viennese doctor, and they wanted me to bring his mother back with me. It was very distressing that Frau Frey, her relatives, and her friends could only go to each other's homes in the evenings and talk about the Nazi restrictions and what had happened to whom. I could only get transit visas for Switzerland and France when we had to leave—two weeks before our boat sailed. The inspector on the boat train nearly had apoplexy when I showed him Frau Frey's passport. Frau Frey was the belle of the boat; she could go anywhere, do anything, and talk to everybody—which she did. Then we were met in Hoboken by the Jewish Relief, who insisted I was not an adequate escort! Frau Frey had a wonderful time in Chicago with her children, going to tea rooms and movies for the few years she had left.

Curtis had talked with Hodgkin about recording the internal potential of an axon but I wasn't enthusiastic. Why bother about an upside down action potential? We used a metal core needle. Hodgkin and Huxley got a certain overshoot, with a micropipette and reported this in a note in *Nature.* We did better the next summer (except for an overcompensation of the 100 μm glass tube).

It most certainly was a serious mistake in general for us to have directed so much attention to our single exception to the mean behavior of all our other axons. Hodgkin (11) blames it and the dextrose effect for a year's delay in proposing the "sodium hypothesis." The dextrose effect I neither understand nor remember.

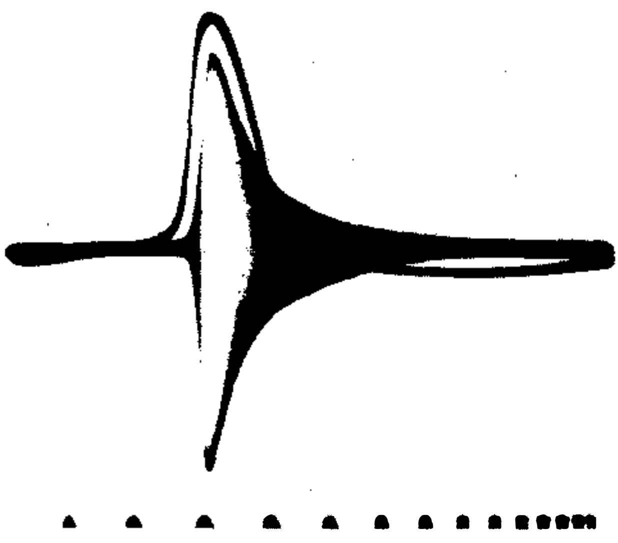

Figure 1 Oscillograms from passing squid-axon impulse. Action potential is the single line, V; impedance decrease, ΔZ, is the band; time mark are 1 msec apart. [After (6), 1938.]

But the Battle of Britain had begun. Curtis and I measured the potential under an external electrode and I found a neat trick to get the membrane *V-I* rectification curve. Hodgkin dubbed it Cole's Theorem. Years later I was disgusted to find I'd assumed linearity in one step; I'm still puzzled about why several better derivations give the same answer.

Curtis wanted to become a real physiologist and went to Johns Hopkins with Phil Bard. R. F. Baker came to us having written a mass-spectrometer thesis; we found that impedance changes by current flow duplicated those during a passing impulse at intermediate frequencies. We also measured the inductive reactance that Hodgkin and I had found in the membrane. It could be explained by the time needed to establish a nonlinear steady state and could also be a capacitive reactance.

As Baker became interested in microscopic spectroscopy and electron microscopy, George Marmont came from Cal Tech. We investigated the effects of K^+ and Ca^{2+} on longitudinal impedance. The results were striking (4) but were only published in abstract at the time. I thought the capacitive and inductive reactances might be permanent structures, seen only as allowed by shunt or series resistances, but the complexity was hideous. The time constant of nonlinearity and Mott's semiconductor theory adapted for K^+ made much more sense.

I'd studied the calculus of variations under Marston Morse at Cornell (along with I. I. Rabi) and had listened to his lectures on mechanics at Harvard. Still, I was surprised to have him suggest that I come to the Institute for Advanced Study on leave after he'd been there a while. I was tired of the medical atmosphere at the College of Physicians and Surgeons, and I got a Guggenheim for one of our very happy years. We had just moved to the Bronx, but we moved again with our very new little girl. I was set up in Fine Hall in mathematics with physics next door and the joint library upstairs. L. A. MacColl of Bell Labs had told me of V. Bush's lecture, "The Engineer Grapples with Nonlinearity." With that and Mott's semiconductor theory for starts, I chased nonlinearity and negative resistances through the mostly Japanese and Russian literature. John Tukey set up an IBM card-sort solution for a membrane, but I couldn't tell him the membrane characteristics. Riding into New York one day, I sat with Solomon Lefschetz. I told him I was planning to bring him a question.

"What is it?"

"How to tell one side of a line from the other."

"That's a good question for a topologist. Why do you want to know?"

"I want to know what makes a nerve impulse go."

"You come see me day after tomorrow and we'll talk."

Talk we did for practically a solid week. After a few days he said that because he wanted to know more, he would give a course. After the second week he had decided to translate the pertinent Russian literature. Decades later, shortly before he died, he introduced me to a friend as the man who had started him on the work he'd been doing for the past 25–30 years.

WAR

There were all kinds of visits and phone calls to enlist me in war work, but I was determined to finish the sabbatical that was starting so well. Luring me to Chicago for consultation, A. H. Compton and N. Hillberry told me the story of nuclear fission and demanded that I take charge of the biomedical problems. I knew at least how to start; and after I had persuaded them I could take no medical responsibility, it was an exciting four years. Our group grew exponentially to nearly 400 before staffing Site X (Oak Ridge). It was six months before our first laboratory was ready. It occupied the disinfected stable of an extinct ice plant on the south side of the Midway, and it was extended twice. Soon we had the first practical hunk of uranium from Spedding. We fought battles for survival with Groves; we struggled to get support from DuPont. Meanwhile the pile went critical.

Soon after R. E. Zinkle came with me, we interviewed Pat Lear for the job of animal farm manager. She told Ray she could cook. She was a tower of strength—even though she could not cook.

George Svihla and I decided to try an autoradiograph for fission product dose. An exposed guinea pig was frozen, sawed into thick sections, and reassembled with X-ray film between the sections. Svihla noticed that the machinist who had watched the procedure put on gloves to replace the band saw blade. Joe Hamilton, who supplied much of our distribution data from Berkeley, could never understand why we used thick sections.

I stole Curtis from an aviation project to head up Site X biology. In a sea of mud in the early days I had to be carried by men in hip boots. Ladd Prosser was my unhappy, able, number two at Chicago. Jo Graff was our beautiful administrator, who kept things going while her husband was interning. Only by the few times she wept on my shoulder could I guess what it cost her to be so tough.

It was all tightly programmed—except for the free 10% man days I insisted upon—but after Hiroshima and Nagasaki the place blew up. Everybody had kept his pet hates to himself until the war was won.

War is so disgusting, so futile.

PEACE

The University of Chicago set up the new Institutes. Zinkle became head of Radiobiology and Biophysics, and I resigned from Columbia to head up

Biophysics. It was a real wrench. At Columbia I'd found myself, I'd been happy. The years there were the best I've had.

George Marmont came to Chicago; we took equipment to Woods Hole for squid studies in 1946. It was not a good summer; we tried futilely to extend our prewar results on longitudinal impedance to low-frequency effects of current flow. Jimmie Savage had worked with Warren Weaver, who had thrust upon Jimmie a fellowship to work with me. Savage visited us late in the summer; after listening to our woes, he suggested putting a long current-carrying electrode inside the axon. I explained how the electrode polarization would probably defeat us; but Marmont took him seriously and soon proposed a reduced silver axial electrode, a central outside electrode with a guard at each end, and electronic control of the membrane current. I promptly added the inverse of membrane potential control.

In 1947 Carlos Chagas had invited me to Rio de Janeiro to lecture and consult at the new Instituto de Biofisica. It was a long, hard trip, but I was met by an enthusiastic delegation. During a courtesy visit to the Rector it was decided that my lectures would be published as the first of a series. There have been several reprints of the *Four Lectures on Biophysics.* I was able to help E. Leão with his spreading-depression impedance decrease; it could be interpreted as a membrane-resistance decrease. I couldn't do anything with the Instituto's favorite electric eel and I got back in time to go to Woods Hole.

After the usual start-up troubles but with Will Rall's help, we had the Mach I cell in operation in 1947. We confirmed the 1 μF cm^{-2} and 1000 Ωcm^2 findings and ran strength-duration curves with direct data. We found the initial resistance to be much too high unless there was a series resistance associated with the membrane; we had trouble with anode block of an impulse. My dream of making excitation stand still in space and time was half-fulfilled; it was not until J. W. Moore showed that excitation for the squid axon in iso-osmotic KCl and $CaCl_2$ was stable in time that I had the other half. However, Marmont was firmly opposed to my insistance on membrane potential control, and I got only a few runs—including that shown in Figure 2 (3). These I found spectacular. There was no trace of a threshold; the early inward current was a mystery, but it was a transient negative resistance that could account—at least qualitatively—for the rise and height of a spike and its propagation. The outward currents corresponded to our ideas about K^+.

In the fall Hodgkin told me of his Na^+ results with Katz; but I was more impressed by my own data, which I told him about. He wanted to visit us; still, he wasn't altogether happy to find I'd booked him for the annual biology division lecture, which he gave on the Na^+ work—to a full house. We went over the equipment and my results in great detail. He vigorously

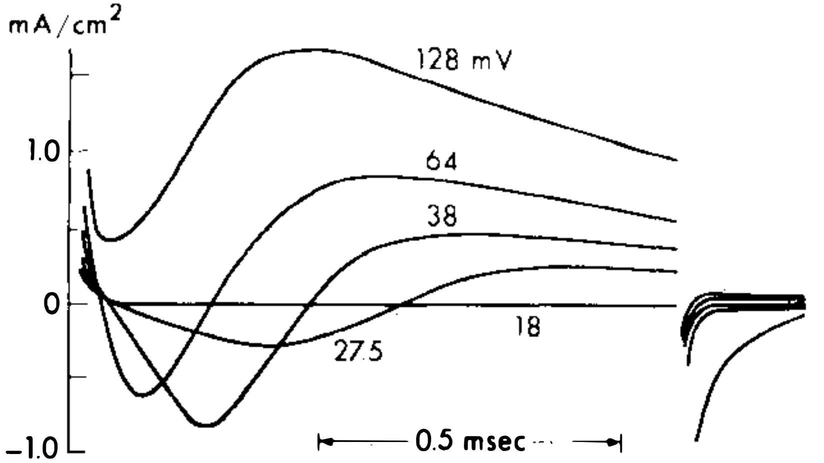

Figure 2 Squid-axon membrane currents after step depolarizations as indicated from resting potential (voltage clamps). [After (3), 1947.]

defended his and A. L. Huxley's carrier theory and blamed the slow rise of inward current on apparatus; but I believed my results, and he later confirmed them. I also pointed out troubles with electrode polarization (which they corrected) and with the membrane resistance (which they compensated for).

Through the winter, while Marmont designed and built the elegant Mach II cell, I tried all sorts of outrageous schemes to explain the potential-control data and did various Institute chores. We got a new Director, who didn't care what biophysics was, so long as it was physical chemistry. He told Savage to go back to mathematics where he belonged; Jimmie became Mr. Statistics, first at Chicago and then at Yale. The Director didn't mind having me, but he didn't want any more like me. I felt less than wanted at Chicago and our friends agreed.

DEFENSE

It was a most auspicious time for Admiral Clarence Brown to offer me the new position of Technical Director at the Naval Medical Research Institute in Bethesda and announce that he was going to stay in Chicago until I accepted. From the latter intention he was dissuaded; he sat out my indecision in Washington. Leaving the Institute was not easy—the breadth of the University was so great, and we had many good friends—but I felt I had to try the unknown again. I had not realized how discouraged Elizabeth had been in Chicago; she was delighted to be going to Washington.

I had to interrupt making friends and enemies at NMRI to go to Paris by way of London for the electrophysiology conference in honor of Louis Lapicque and his gallant war stand. I spoke for the visitors and included an April-in-Paris note. It was my first chance to present my '47 results, which I could only do briefly as an introduction, really, for Hodgkin, Huxley and Katz (14). In a little over a year they had corrected most of my difficulties, caught up and run past me. I was pleased that we had been their starting point and that they had confirmed my results, although I was not entirely happy to have the concept and the technique dubbed the "voltage clamp."

My simple plan for NMRI was to have a group of small, strong centers of research distributed as well over the medical field as possible so that any emergency would be within reach of one or perhaps two staffed working laboratories. This would avoid some of what caused our slow start up at Chicago. Manuel Morales was a fountain of good ideas (e.g. that we should invite Terrell Hill to join us). Moore, one of several students of Jesse Beams who turned to biology, came with us to work on muscle impedance; we had Dave Goldman, who started to construct an analog computer. The energetic submariner Al Behnke kept things moving as Executive Officer. Early on, Admiral Brown transferred to us his long-time right-hand man, Vic King, with instructions to get done the things we wanted done. W. E. (Bill) Kellum became CO and soon had the admiration and respect of civilians and military alike. Although he confessed it took him a year to understand what I was trying to do, he could straighten out my mistakes almost before I made them. But it was slow business, with much diversion, backtracking, and backbiting. Then we lost momentum. Ed Condon was hounded out of the Bureau of Standards; McCarthy forced out two of the most unlikely subversives of our staff—one now a full professor at Yale; A. V. Astin was only saved in the battery additive fiasco at the NBS after a slow protest from outside government and the Bureau was weakened by fragmentation; the Office of Naval Research was being forced to curtail its broad effectiveness to "man in the fleet" problems; and good rumor had it that NMRI was next. We were losing key personnel in the antiintellectual movement and couldn't get adequate replacements. I tried to get a more prestigious replacement for me but I couldn't get even medical support in my office. We seemed to be in an apparently endless decline.

Five of us flew Navy via Gander, Azores, Port Leyouty, and London to the 1951 Copenhagen physiological congress. At the Congress dinner, Lord Adrian said that if we were to rank our national preferences he was sure Denmark would be the unanimous choice for second place. One spectacular achievement reported was Ussing's electrochemical identification of an ion pump. But I was much more interested in the preliminary curves Huxley showed me of their Na^+ and K^+ conductances-vs-potential from voltage-clamp data.

The next summer (1952) there was a Cold Spring Harbor repeat run on nerve and nerve systems. Hodgkin sent me near-to-final drafts of their five *Journal of Physiology* manuscripts, and at last I realized fully what they were doing and how enormously successful they had been. Hodgkin gave the paper with his usual calm, convincing enthusiasm. After ten minutes the Chairman, Frank Schmitt, co-opted me to handle the discussion. I infuriated Hodgkin by counting the number of ad hoc analytical forms and numerical values in their equations (12). But he also said they had fully confirmed my 1947 results and had used essentially our experimental approach. Lorente de No said that it was a powerful picture and might be right but that it couldn't work for a frog axon. John Eccles dominated the rest of the all-too-short symposium and won at least grudging admiration from everyone by producing three new theories in three days.

On our way back to Woods Hole I was feeling very sorry for myself because Hodgkin and Huxley (HH) had done all that I had ever hoped to do. Consolingly, Hodgkin said they had just followed my lead. Later Huxley was to say he was only Hodgkin's student, while Eccles only claimed to apply their results. At Woods Hole, Moore and I were trying to clamp with external electrodes. Hodgkin wasn't sympathetic, but he dissected axons for us and tried to teach our other guest, I. Tasaki, to do it—even using Tasaki's favorite needles.

In 1952 the Standards Eastern Automatic Computer was in somewhat erratic operation at NBS. H. A. Antosiewicz and I explored all four quadrants of the HH equations (13) and found a saddle point that was an undoubted threshold. I passed the word to Bonhoeffer, and to his translator, Max Delbrück, that his thermochemical analogy would have to have a threshold. Huxley agreed with Richard FitzHugh's phantom saddle point, and they both thought I was wrong. Several years later I ran onto some unaccountable bumps in the curves. FitzHugh & Antosiewicz finally traced these to an absurd programming mistake that had produced the saddle point. Although important theoretically, the threshold was only 1 part in 10^8 wide and only made a percent or so change in any physiological parameter, but I had to explain and apologize as widely as possible. It was only a decade and a half later when Rita Guttman was getting much more gradual thresholds at temperatures in the 30s C, which F. Bezanilla confirmed with HH calculations.

Moore saw an advantage in using a microcapillary for the internal axon potential, and we practiced on "open chest" squid with intact circulation. Harvey had mixed feelings: "Here is a perfectly good biological experiment being done by two physicists." The undershoot recovery was delayed so much that we could expect it to disappear along with the HH leakage in an undisturbed animal. This Hodgkin and Keynes did find by boring through the mantle directly to the axon!

NATIONAL INSTITUTES OF HEALTH

Seymour Kety was intramural director for the NINDB and NIMH joint operation at National Institutes of Health and planned a biophysics laboratory. I was a very discouraged administrator after four years of war and six of defense, and the squid work I wanted to do was more than I could support at NMRI. So Moore and I moved across the street. With me I took considerable regrets that the Navy might not get what it needed and deserved for some time; I also took a pay cut!

Once again we were starting a new lab from scratch. It is not easy to sort out the apparently intertwining threads of the past twenty-three years at NIH. The most compelling strand has been the voltage clamp, with the squid axon a close second. If (as I've been accused of doing) I revolutionized electrobiology in 1947, Hodgkin and Huxley certainly took the giant step in 1952. Hodgkin (11) recounted it for the centenary of the Physiological Society in 1976. As the concept of the clamp has been accepted, many new techniques (some good, some not so good) have been developed. I guess there are well over 100 voltage clamps around the world; the published papers relying on them must be in the thousands. And now solid-state programming and data reduction are rapidly taking over manipulations far beyond my wildest dreams.

The "abominable notch" was still with us. Moore, Taylor, and I spent a couple of years on it—spurred on by Frankenhauser and Hodgkin, who ignored it, and by Tasaki and collaborators, who insisted that all good axons showed it. (Who wants to work on less than the best?) Although it almost certainly comes from poor electrodes, it is still the constant threat that I, and Hodgkin and Huxley, only narrowly avoided before 1950. Moore and I had been keeping our axons hyperpolarized between pulses to maximize the sodium currents, but all too soon the polarizing currents would begin to run away or the axial electrode would bubble. Only a few msec of prepolarization were adequate to prevent these troubles and prepotential had little effect on the initial sodium current. But after -212 mV the potassium currents were delayed by up to 0.2 msec. Didn't this prove HH were wrong? No, only limited! Our article (8) seems to have been a good start for the *Biophysical Journal,* first volume, first number, first page, 1960. The Cole-Moore delay has been confirmed for squid (Figure 3) and has been a

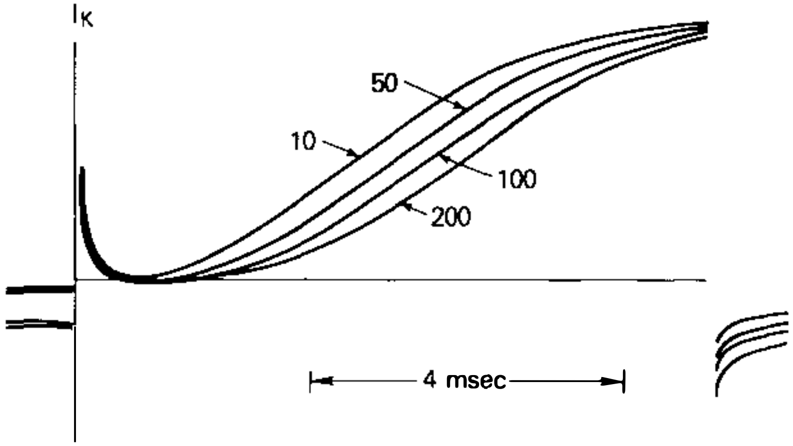

Figure 3 Depolarizations of squid axon with TTX after 3 msec hyperpolarizations to indicated potentials from holding potential. [After Keynes, Kimura & Lecar, unpublished.]

major challenge for theory. For several years there have been rumors that a frog node is different. So it may be that our simple delay is the exception rather than the rule; theorists can then let out their belts.

The work of our group on squid was hampered and finally broken up by dissension that I was unable to ease or prevent without more space. So I made everyone a section chief and went on alone.

We had only the simple analog computer—a descendant of V. Bush's mechanical differential analyzer, which I'd admired—and with it I learned the lessons I got from v. Neumann and E. Teller. The computer succeeds calculus as a way of intellectual life. Richard FitzHugh took it over—he'd always wanted one—and worked up to solutions of the HH equations before turning to keep pace with the digital developments. He worked on topology, developed the BVP (Bonhoeffer–van der Pol) analogy, and moved on to the relatively recent economics of nerve and muscle action. I've loved his teaching gadgets and his cartoons—the "Drink MyxiCola" gag, and the coy squid (which I've stolen).

We had been going along happily with *Loligo* at Woods Hole when I heard (around 1960) that the Humbolt *Dosidicus* off Chile weren't as impossible to work with as I'd been led to believe. Our first expedition didn't come off; but the second, in the fall of '63 with Dan Gilbert in charge, was a good start. Our groups had excellent seasons at Vina del Mar with E. Rojas in spite of crude collecting and laboratory facilities, fantastic logistics, and a tidal wave. But in 1971, with a capacity crowd waiting, not one single *Dosidicus* was to be found—nor have they reappeared. The unlikely troika of Keynes, Rojas, and Taylor has, however, continued to function. In Chile, efforts have been diverted to the giant barnacle muscle fiber; at Bethesda, Leonard Binstock discovered and promoted the cord of the worm, *Myxicola,* which has become a mainstay of the laboratory.

Ross Bean, whom I'd met at a bilayer meeting, came to see us at Bethesda. We persuaded him to try a very low concentration of additives; this gave impressive unit conductances. These studies, along with studies of fluctuations, have continued to expand in the lab under Gerry Ehrenstein and Harold Lecar.

For some time I'd decided that I should step aside at 65—as insurance against mistakes and to let young blood take over. I almost made it. Taylor became Acting Lab Chief in '63 and continued until '71. Adelman came back as Lab Chief and, after considerable shuffling around, moved with two sections to Woods Hole year round, leaving a section in Bethesda.

BIOPHYSICS

My first attempt at formal biophysics was a discussion group I chaired at the first summer meeting of the American Physical Society in 1927 at Cornell. During the war I tangled with Leo Szilard, who had been about to switch from physics to biology when artificial radioactivity was discovered. He dismissed my simple approach to biophysics, and it was only after many hours that I caught on: Biophysics was whatever Szilard did in biology, and that settled the argument. He started to work on phage after the war. When peace came, departments, laboratories, institutes, divisions, and branches of biophysics burst into the open. Many plans arose for national organization and publication. I managed to keep in touch with the more active people and groups, but so much time and effort were wasted in attempting definitions that I finally was able to get them ruled out of order. I was in favor of affiliating with the Institute of Physics; this notion was bitterly attacked. Alan Burton, then President of the American Physiological Society, told me what APS could offer, but I knew that a number of noisy physicists and engineers would have none of it. I had to do the best I could, even though I was a loyal member of the Society.

It was finally obvious that biophysics had to proceed without assistance or entangling alliances. An informal but considerable group at the '56 Federation meeting voted for a trial meeting to be run by the Committee of Four, E. Pollard, O. Schmitt, S. Talbot, and me. We held the first meeting at Columbus with Air Force funds from Colonel A. P. Gagge; Pollard produced the required *Proceedings.* When Hartline said that we had more people he knew and more he wanted to know than any meeting he'd been to, I was sure we had succeeded. Elizabeth and I wrote up both the

Constitution and Bylaws. I worked for their adoption, item by item. After an evening without adverse discussion at Cambridge, the Biophysical Society came into being. It has been very interesting to watch the completely independent development of a division of biological physics in the American Physical Society and the current trial of joint sponsorship of the *Biophysical Journal*. I do hope that the casual cooperation can go on.

H. B. Steinbach was commissioned to organize an ad hoc National Research Council committee to keep track of international biophysics. After considerable manipulation, the first congress was held in Stockholm. United States financing was an important factor in assuring its success, and I was relieved of one of my longest ad hoc services. The organization joined UNESCO to become the International Union of Pure and Applied Biophysics and now meets regularly.

A major effort was made in 1969 to bring MBL up to date. Steinbach and I had talked for some time about having a voltage-clamp researcher working with students at Woods Hole through the winter. Finally Adelman put together a summer program in 1969—the Excitable Membrane Training Program. He edited the book of lectures, *Biophysics and Physiology of Excitable Membranes* (1). Ernie Wright was the angel who kept it going for six years before it was ruled out. It was well worthwhile.

I was named Regents' Professor at the University of California at Berkeley for the first semester of 1963–64, and Elizabeth was determined to go with me. We had a lovely apartment near campus. It overlooked San Francisco Bay and the Golden Gate, which I'd steered a West Coast War Emergency boat in and out of long before there was a bridge. I usually got home early so we could put up our feet at cocktail time and watch the glorious sunsets. I'd decided to write up my lectures as a book, but I was not prepared for what became a five year stint.

I've been back to Berkeley almost every year for the winter quarter. I have gradually entrusted my seminar to C. A. Tobias and have added La Jolla and Galveston to my visiting list. P. E. Lilienthal of Cal Press saw me through the book *Membranes, Ions and Impulses* and its reprinting in 1972 (4). I'm almost convinced it was worth the time and effort. By the time I had recovered it was mandatory retirement time.

RETIRED AND REHIRED

My 70th birthday was ushered in with flair at the Gilberts' by the Piet Oostings' singing Happy Birthday in Dutch at midnight, and I became a rehired annuitant. As an experimentalist I've increasingly depended on Woods Hole, where for some years I've had relative peace and quiet in 150 square feet of space. I've not only gotten my hands dirty, I've cut, burned, and otherwise maltreated them on my own.

I had been somewhat querulous about various aspects of the electrical and electron-micrographic estimates of the Schwann sheath at 1.5 Ωcm^2 until I ran onto a paper Curtis and I published in '38 on the axon-impedance locus with its incomplete high-frequency tail. Could it be the Schwann sheath? Probably so; I calculated the resistance to be 1.6 Ωcm^2. Before 1970, Choh lu Li, Tony Bak, and I had run analogs to show that the low-concentration Rayleigh and Maxwell resistance equations applied to up to 100% volume concentrations of several close-packing cylinders and three dimensional forms. If cylinders made up the sheath, then the extra-cellular space constitutes about one half of one percent of cell volume. But what about the 4 MHz dispersion capacity? Might the low-frequency Rayleigh capacity equation work up to 100%? An analog said it did. Thus, if the membrane capacities are 1 $\mu F\ cm^{-2}$, the sheath should be six cells thick—except that the cells aren't cylinders! Membrane-covered cubes followed the Maxwell capacity up to 100%. This completes at least a sketch of Fricke's beginning in 1923. The 1935 bridge reappeared, after 18 years in hiding and minus crucial transformers, to make it possible, at least, to test guard arrangements and perhaps to find out more about dielectric loss!

IN CONCLUSION

I've had busy and exciting times with membranes since I first heard of them in 1923. In spite of my mistakes, I'm very happy to have had the good luck to participate in the development of the present widespread enthusiasm for them. I'm only slightly modest about the many and good friends who've helped so much and who share in my distinctions. These days I find it difficult to keep track of new concepts, powerful techniques, and obvious conclusions—but I keep on trying.

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