FOR LIVING HISTORY

As a rock-ribbed, dyed in the wool biochemist I was surprised, pleased and felt greatly honored to be included in the Living History program together with such a distinguished group of physiologists.

It came about because

(1) On April 1, 1966, I journeyed back to my homeland, New Jersey, to become the founding Chairman of the Department of Physiology (later. and Biophysics) at Rutgers University Medical School, now the Robert Wood Johnson Medical School, a component of the University of Medicine and Dentistry of New Jersey. On assuming the post, I felt comfortable with my degree from Harvard since it was in Medical Science, not specifically in Biochemistry, the same as it would have been had my major been Physiology. Nonetheless, I quickly sought some more specific credentials and asked, first, for membership in The Society of General Physiologists and then in The American Physiological Society.

(2) On August 24, 1960 in a lecture presented at Prague during a Symposium on Membrane Transport and Metabolism I proposed for the first time anywhere that the fluxes of an ion and a substrate could be coupled by combining with the same reversible transport carrier in the cell membrane. In the intestinal epithelial cells that I was studying the ion was sodium and the substrate was glucose. Because of the coupling, glucose accumulation to high levels in the cells, i.e. active transport, was seen to be powered by the ATP-driven efflux of sodium ions elsewhere. Figure 1 below is a photocopy of what I drew for my notes on that day and displayed to the audience as I gave my talk. It was later redrawn more formally (Figure 2) and published in the proceedings of the symposium (Crane, R. K., Miller, D. and Bihler, I., in A .Kleinzeller and A. Kotyk, Eds., Membrane Transport and Metabolism, Academic Press, New York, 1961, pp. 439-449.

In later publications I adopted the term cotransport as a descriptive name for the process.

(3) The Executive Director of the American Physiological Society, Martin Frank, took note of (1) and the later developments from (2) and invited me to join the program.

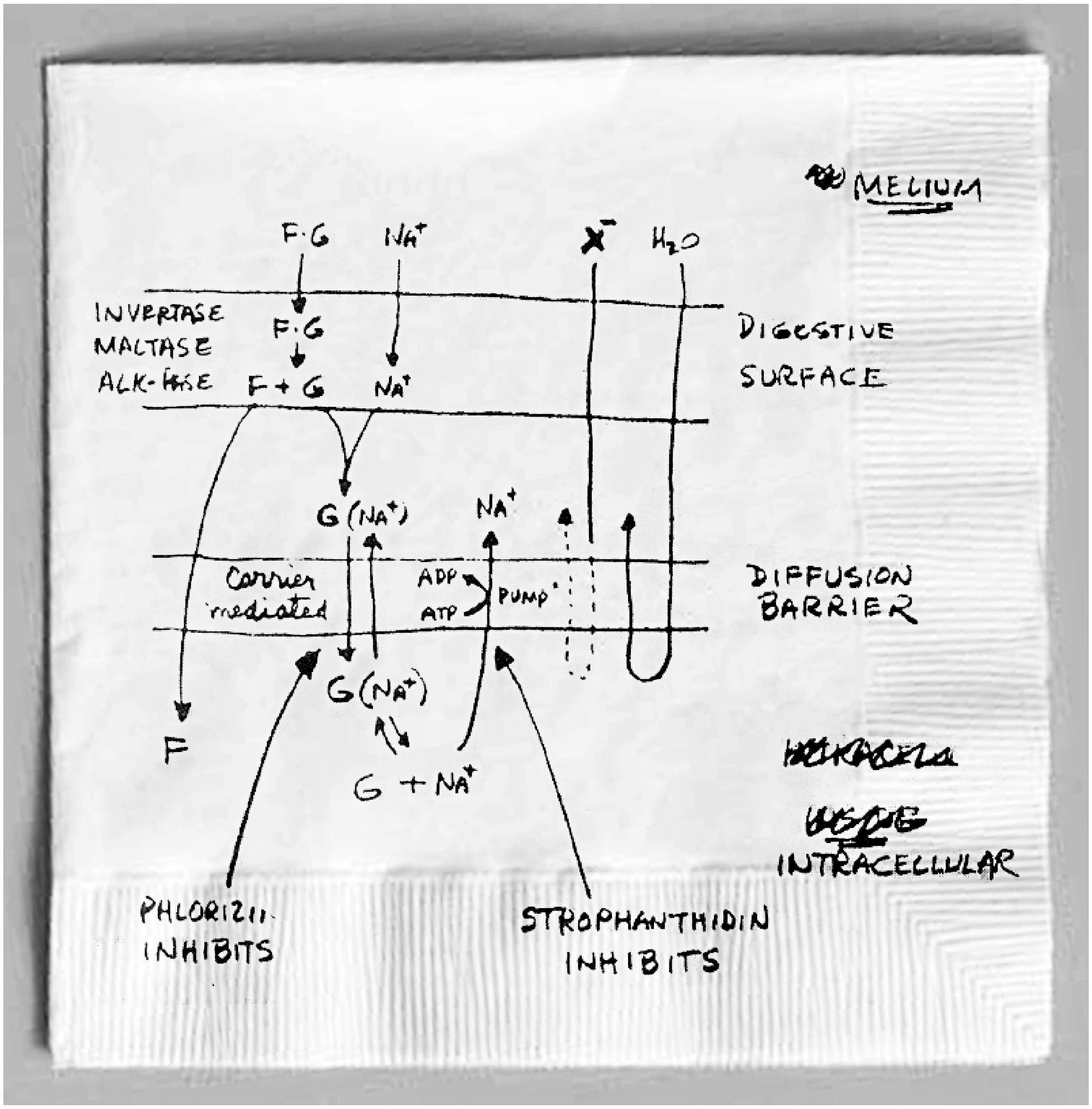

Figure 1. Photocopy of my notes for the proposal of flux coupling between Na ions and glucose in the mucosal cells of the small intestine.

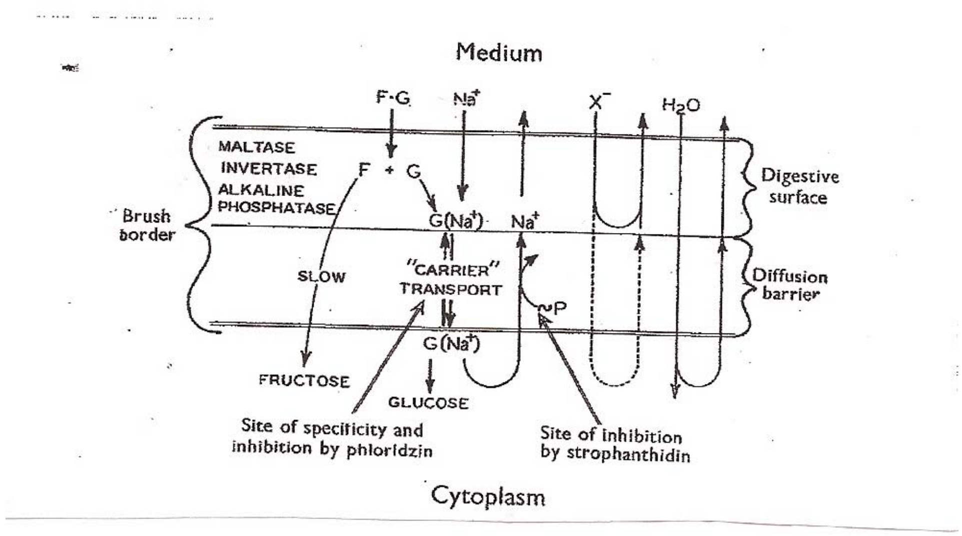

Figure 2. Photocopy of my proposal of flux coupling between sodium ions and glucose (Figure 1) as rendered more formally and printed in Crane, Miller and Bihler.

The Ups and Downs of Cotransport

The ups of cotransport come from people who have read the original literature. The downs come from people who have not read the original literature and believe that the later literature is fair and unbiased or from people who, though familiar with the original literature, want it to be different and set about changing it or making substitutions which tell a different story.

On the day of the symposium, cotransport was just an idea. It had no experimental support. It was based on the failure of many experiments to support any known mechanism and my belief that I knew enough to propose it. There were no experimental results which denied the possibility. Over the years it slowly gained acceptance but absolute proof has taken nearly 50 years to achieve.

Peter Mitchell (Nobel Prize '78) was in the audience at the symposium and, as I gave my talk he reacted and blurted out, "You've got it!" as I have described in "The Road to Ion-coupled Membrane Processes". Following the symposium the earliest event was the adoption by Peter Mitchell of flux coupling, i.e., cotransport , in a lecture delivered on September 20 (in T.W.Goodwin and O. Lindberg (eds), Biological Structure and Function, Vol.II, Academic Press, London, 1961 pp. 581-603) with however, protons instead of Na+ for a revision of what he had called the chemiosmotic hypothesis. He gave up his concept of vectorial enzymology. However, he retained the name. The downer was that Mitchell did not cite my cotransport as the origin of the concept.

The second downer came two years later when Mitchell claimed (Biochemical Society Symposium No. 22, 1963, pp 158-159) that the Crane, Miller, Bihler paper gave only a hint of cotransport. He redrew the coupling we had shown and renamed cotransport as symport.

During the same time period a very clear upper appeared as gastroenterologists and others recognized that my formulation (see figures 1 and 2) clearly suggested the possibility that addition of glucose would enhance the uptake of sodium ions. This was relevant to the search for an oral rehydration therapy that could combat the water and salt losses in severe diarrhea as occurs in cholera. Captain Robert Philips had spent years fruitlessly searching for a solution but scored the first success in 1964 when he tried a glucose and saline solution on cholera victims. Over the years this success was repeated and led to the development of a glucose-saline solution adopted by the World Health Organization. Millions of lives have been saved and this record was editorially recognized by the Lancet in 1978 with the statement that my proposal of coupling between the fluxes of sodium ion and glucose, i.e., cotransport, which led directly to Oral Rehydration Therapy was potentially the most important medical advance of the 20th century.

Work on cotranport continued in many places and resulted in a symposium sponsored by the New York Academy of Sciences in 1984 and a symposium sponsored by Inserm in Aussois, France in 1985 clearly identified as the 25th anniversary of my proposal of 1960.

After my retirement in 1986 there was a brief hiatus and then a variety of uppers and downers.

First was a Wellcome Witness to 20th Century Medicine Symposium on Intestinal Absorption , Vol. 8, 2000 during which the attendees wondered how I got to cotransport first when there were a number of graduates from David Smyth's department at Sheffield who were working in the same research area.. This is definitely an upper though one of the attendees, a Roy Levin, repeatedly said that I had not shown Figure 1 at Prague but scribbled it on an envelope at a later time. This is nonsense. Levin was not at Prague and apparently hadn't read my article "The Road to Ion-coupled Membrane Processes" in which I described Mitchell's response when I displayed Figure 1 at Prague.

A most serious downer was provided by Bruce H. Weber. In an article in Bioscience Reports , 11, 1991, praising Mitchell, he wrote on page 584 the following

"As can be seen by his precirculated contribution at the Prague Symposium, Mitchell had already reached the general conclusion that the driving of the transport of one ligand by another required only that the two ligands be (literally) coupled together, either directly or through an intermediary component, and that their compound or complex be free to diffuse through a common catalytic translocation pathway traversing the osmotic barrier. It would be irrelevant whether the coupling of the ligands involved primary and/or secondary valencies"..

There is nothing in Mitchell's Prague paper which even remotely resembles what Weber claimed is there. On questioning Weber it turned out that what he had written was put together from conversations he had with Mitchell and Arnost Kleinzeller some thirty years after the fact. Such a subversion of the truth is surely rare in the annals of science and may even be unique. Weber has never recanted.

Moreover, while managing with falsehood to enhance Mitchell's reputation, grave damage to my scientific reputation was done as I have learned from a major member of the bioenergetics community who first drew my attention to the Weber quotation above and whom I quote: "I think Weber's historical perspective is also a fair reflection of what the bioenergetics community would consider appropriate".

The next downer came with the publication of a book by Weber together with John Prebble. In this book,Wandering in the Gardens of the Mind, Oxford Univ, Press, 2003 they try to show that Mitchell came independently to cotransport (symport) No one can know what was in Mitchell's mind before I presented cotransport at Prague. Afterward, we can be certain that he understood cotransport and saw how to use it to get started on his march to the Nobel Prize.with a revised version of his chemiosmotic hypothesis.

It is now 50 years since I proposed cotransport and finally we have the biggest upper of them all; cotransporters have been crystallized and their structures determined. Cotransport is proved without doubt thanks to another graduate of David Smyth's department, Ernest M.Wright FRS.(see The Wright Lab on the internet)and others (Forrest, L.R.and Rudnick, G., The Rocking Bundle, A Mechanism for Ion-coupled Solute Flux by Symmetrical Transporters, Physiology 24, 377-386, 2009)

My Personal History

I was born December 20, 1919 at 700 Highland Avenue, Palmyra, New Jersey in the second floor bedroom which I continued to occupy for the next 15 years. My parents were Wilbur Fiske Crane, Jr. farm building architect and engineer, and Mary Elizabeth McHale Crane, housewife.

I attended the Palmyra public schools through the second year of high school when I was given the opportunity to apply, by examination, for entry and a scholarship to St. Andrew's School in Middletown, Delaware. I was accepted and I spent three years during which I received superb schooling especially in English as taught by William Cameron. I graduated in 1938.

In the fall, I enrolled in Washington College, Chestertown, MD I have already written the history of my college years and the following years up to 1962 in The Road to Ion-coupled Membrane Processes, Comprehensive Biochemistry, 35, Selected Topics in the History of Biochemistry, Personal Recollections, I., G. Semenza, Ed., Chapter 3, 1983, Elsevier Science Publishers. Here, I will mention only a few highlights.

To satisfy a curricular requirement I enrolled in Chemistry for my freshman year. Up until then I had developed little interest in science but I found the lectures by Kenneth Buxton compelling One thing led to another and I ended up taking all the chemistry courses and branched out to do nearly the same with biology under Julian Corrington and physics under Jesse Coop. I graduated in 1942 with a BS in chemistry.

Kenneth Buxton steered me toward a job with the Reynolds Experimental Laboratory of the Atlas Powder Company in Tamaqua, PA. where the training program was designed to provide leaders for the TNT plants in Paducah and Weldon Springs. The intensive course turned me into a competent analytical chemist.

Toward the end of my first year I was offered a chance to teach chemistry at the Northeast Missouri State Teachers College in Kirksville, MO, the permanent staff having all gone off to the war. I accepted and spent the next year teaching every course in chemistry by myself. Along the way, however, I decided I should get directly into the war effort.

I applied for a commission in the U.S. Navy and volunteered for the draft.
I also passed the Eddy Test and was sent off to Great Lakes Naval Training Station as a seaman 1st class. Toward the end of the ninety days training, my commission came through and I was sent to the Officers Training School at Plattsburg NY. for another ninety days.

After that I was sent to Norfolk VA and then to Hollywood Beach FL for training as a Combat Information Center Officer. A week or two later I became very sick with joint pains and severe night sweats. Unable to diagnose me, the medical staff labeled me as malingering. I was able to keep going on my own until I completed the course and returned to Norfolk where I was immediately placed in sick bay and then transferred to the Portsmouth Naval Hospital. There it was determined that I had meningococcemia and was placed on a regimen of penicillin which was quickly effective.

I spent several months in recuperation and was then sent to Hunters Point near San Francisco to become a deck officer on the USS Killen, DD593 (see wikipedia). Killen had two years of active service. The first year ended with her taking a bomb at Surigao. The second year began after repairs at Hunters Point and I was with her until she was docked at San Diego for decommissioning.

After being released to inactive duty I want off to graduate school at Harvard in the medical science program at the medical school, there being no biochemistry on the main campus. At that time, there were few to choose from as preceptor for a thesis. Eric Ball offered to take me on provided I would study C14 incorporation into retinal tissue. I accepted and spent a little over two years on the project until I was allowed to accept an offer from Fritz Lipmann to be the Assistant Biochemist at the Massachusetts General Hospital.

I spent a year with Lipmann and got very little done experimentally but got great exercise for my brain and my imagination. When he was home, Lipmann formed the habit of coming into my cubby hole laboratory every afternoon about 4 o’clock and starting a conversation. About mid-year, Carl Cori showed up, looked at me, nodded his head and shortly after I received an invitation to join his department in St. Louis.

I was appointed an instructor in Cori’s department and set to work on a variety of projects with a number of colleagues. Approximately the first two and one-half years were spent with Alberto Sols on hexokinase. I was raised to Assistant Professor. Then Alberto went home to Spain and Richard Field showed up from Boston...We worked on transport in Ascites Tumor Cells until Richard left and then Cori and I joined efforts to produce what some (e.g, Erich Heinz) felt was the definitive study at the time.

Shortly after, I broke with Cori and set off to study the active transport of sugars by the intestine. First with Stephen Crane and then with Ivan Bihler we were able to demonstrate that covalent bond formation was not a part of the mechanism. With David Miller we identified and isolated brush borders. I became an Associate Professor.

Finding that sodium ion was essential for sugar active transport and knowing that animal cells continuously pumped sodium ions out, I was convinced that this was the needed energy source but how was it used. I spent over a year considering various possibilities (see Crane, R.K., Intestinal Absorption of Sugars, Physiological Reviews, Vol. 40, No, 4 , October 1960) but arrived at the solution at Prague only hours before it was my turn to lecture the assemblage. I proposed cotransport, the ups and downs of which are treated separately.

From that time on I did little else experimentally but to try to prove or disprove my proposal. Two years later I accepted the Chairmanship of Biochemistry at the Chicago Medical School. John Scheinin, the president of the school, was somewhat persuasive but what really caught my interest was Philip Shubik and the handsome new research building constructed by the National Cancer Institute. I thought there was great potential. Four years later I decided that the potential was not going to be realized and I left to accept the Chairmanship of Physiology in the brand new Rutgers Medical School.

During the twenty years I spent at Rutgers my colleagues and I pursued a proof of cotransport without being able to achieve it. I spent a lot of time dealing with the problems of developing a medical school from scratch. I retired in 1986 and turned my attention and labors for the next ten years to the sequential development of horse farms devoted to dressage.

I have just turned 90 years of age and I don’t work anymore.

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