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An Unanswered 2003 Letter Appealing on Behalf of all Mankind to Nobel Laureate Roderick McKinnon to Use His Newfound Fame and Visibility to Begin Restoring Honesty and Integrity to Basic Biomedical Science by Rebutting or Correcting Suspected Plagiarism in His Nobel-Prize-Winning Work

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Abstract: The centerpiece of this document is an unanswered letter of appeal from the author to Professor Roderick MacKinnon of the Rockefeller University dated November 17, 2003. The aim of the appeal is summarized in the title of this communication. In addition to the 2003 letter, there are also two follow-up letters in this communication, each containing a copy of the 2003 letter and each repeating the appeal. The follow-up letters, dated February 22, 2008 and April 2, 2008 respectively, were also unanswered. To make sure that these letters reached their destination, each was certified with delivery time and date affirmed. Thus the February 22 letter was delivered on the February 24 by the US Postal Service. Two copies of the April 2 follow-up letter were sent. The first copy was delivered by Federal Express on April 4. The second copy of the April 2 letter was delivered by the US Postal Service on the same day. Thus all told three additional copies of the 2003 letters were delivered to, and must be in the hand of Professor MacKinnnon. All these efforts were made to make certain that Professor MacKinnon's refusal to answer my registered 2003 letter was not due to his not having received a copy of that letter.

November 17, 2003

Dear Dr. MacKinnon:

Cell physiological research, on which both you and I have spent much of our lives, is like solving a gigantic crossword puzzle. Like the crossword puzzle, cell physiology also has just one unique solution. But to reach out to that unique solution, cell physiologists of the past faced an insurmountable obstacle.

That is, the physico-chemical concepts needed to construct the correct unifying theory were not yet available when the study of cell physiology began. An incorrect guiding theory was introduced (see below) and as time wore on, taught more and more as unqualified truth. Meanwhile, the study of cell physiology broke up into smaller and smaller fragments or specialties. In time each specialty spawned its own lingo, its own methodology and its own subspecialties; the contact of each specialty with other specialties become less and less frequent and more and more perfunctory. The cumulative result is as Durant described: "We suffocated with uncoordinated facts, our minds are overwhelmed with science breeding and multiplying into speculative chaos for want of synthesis and a unifying philosophy." ("The Story of Philosophy", Durant.)

Now, Durant's complaint addressed the lack of a valid unifying theory, which alone can bind together the scattered fragments and offer pathways out of this chaos toward deeper understanding. However, the obstacle to produce a valid unifying theory gradually evaporated when physics and chemistry matured in the late 19th and early 20th century. Therefore, it was not entirely surprising that some forty years ago a unifying theory of cell physiology built upon mature physics and chemistry made its debut. It bears the name, the *association-induction* (AI) *hypothesis*. (See Book #1 listed under "Books" in enclosed Document #1.) Worldwide experimental testing and confirmation of its essence followed rapidly — as chronicled in three additional full-sized monographs published respectively in 1984, 1992 and 2001 (Books #2, #3 and #4 in Document #1) as well as many scientific papers, including those listed under "Articles" in Document #1.

It would seem that the day would soon arrive when swift progress would light up another new age in science (of the living) like the one (of the dead) in the 17th–early 20th century.

The sad truth is forty years later, that day is yet to come. Long after the verification of the essence of the AI Hypothesis, few biomedical researchers, teachers or students here and abroad have ever heard of all these, let alone understanding or teaching them. But why? After all, we live in an age of unprecedented personal freedom and enjoy means of virtually instant communication far and near. What has gone wrong to reproduce this gargantuan backward movement toward the Dark Ages? Who will be the ultimate victims? Ultimately the victim is the entire Mankind. But some are affected more immediately.

To demonstrate that the harm is being inflicted right now on countless innocent scientists, teachers and students across the world by this global information embargo, I focus on your own outstanding scientific work — for which you are awarded the 2003 Nobel Prize. I begin by asking you two questions: First question: do you know that your work is built on the foundation of the membrane pump theory (which was disproved forty years ago) and thus doomed to collapse sooner or later? Second question: do you know that years ago I introduced for the first time a variety of the basic concepts now found (unacknowledged) in your Nobel-Prize winning work on potassium channel? Put differently, do you know that you might be at risk of committing plagiarism? I fully expect that you would answer no to both questions; you really did not know. And accordingly, I shall begin briefing you on some of the critical information that has been withheld from you, beginning with the subject matter of my first question.

If you did not know that the membrane pump theory has been disproved some forty years ago, one legitimate reason could be that this disproof itself has been disproved. If true, one should find that out by consulting the Citation Index or another abstracting publication. However, a thorough search through these media revealed no disproof of the disproof.

In other words, then (or now), no *bona fide* scientific rebuttal, let alone disproof of my disproof of the membrane-pump hypothesis existed. Instead, two bits of gossips have been circulating around on the grapevine. Possibly, they might have created the impression on you that the membrane pump hypothesis is still alive and kicking.

One of these grapevine messages was the offspring of the union of a fact and a popular belief. The *fact* is that Peter Mitchell and Jens Skou have each been awarded a Nobel Prizes for their work on (the postulated) membrane pumps (see below.) And the *popular belief* is that Nobel Prizes are never given to scientific works that have not been proven beyond doubt and are in veracity and originality on equal footing with History's greatest like those of Planck and of Einstein, for example

The other gossip centers on a scientist by the name of Christopher Miller. He, along with several of my other former graduate and postgraduate students, left my laboratory *en masse* in the seventies. The grapevine story reads something like this. When young and trusting, Miller and the others made the mistake of volunteering to study under me, and to participate in research for varying number of years — until they suddenly saw the light and courageously returned to their new-found faith in the membrane pump hypothesis. Since nobody could have known my work better than my students who shared their day-to-day lives with me for years, their *en masse* departure suggests that there must be something seriously wrong with what I taught: the AI Hypothesis or my disproof of the membrane pump theory or both.

In the following I will examine with you the truth behind the gossip. My first contention is that Nobel Prize Committee members and their favorite advisors were not Gods; as human mortals, they make mistakes. And from a careful analysis of the proven mistakes they have made, I found that they were a part of the network of victims-(unknowing) perpetrators of the information embargo. My second contention is that the real cause of the mass exodus of my students was that in a state of panic, they felt that a clean break from my scientific work and me was the only way they could secure jobs after graduation. Details follow.

Peter Mitchell received the Nobel Prize of Chemistry (1978) for his Chemiosmotic Hypothesis. This was astonishing because I have never heard of anyone else being thus honored for merely introducing a hypothesis — a hypothesis that has not been experimentally confirmed then or later. To save space here, I enclose as Document #2, the first 15 pages of a critical review of Mitchell's Chemiosmotic Hypothesis that I wrote in 1981. It shows that the hypothesis itself and its supportive arguments are seriously contradicted by facts.

Thus according to the Chemiosmotic Hypothesis, the energy used in the synthesis of ATP in mitochondria comes from dissipating what he calls a "Protomotive Force," a composite of a H^+-ion gradient and an electric potential gradient across the inner membrane of mitochondria. However, it turned out that the H^+ ion gradient is negligible if in existence at all. And the electric potential gradient, instead of being maintained at the theoretically required inside-negative voltage of 200–300 mV, turns out to be only 10–20 mV and in the wrong direction (for a simple account of this disproof, see p. 510 of Book #2 in Document #1.) It is hard to believe that Mitchell did not know these incisive experimental contradictions. Yet to the best of my knowledge, he did not publicly abandon this theory or make drastic changes in it or subscribe to the association-induction hypothesis, which has no trouble explaining most if not all known facts with few additional ad hoc assumptions. This inactivity seems to confirm a saying attributed to a Nobel Prize winner in the biomedical field that once you have won a Nobel Prize you are not allowed to correct your mistakes. True or not, you will soon find out.

Jens C. Skou of the University of Aarhus of Denmark also won the Nobel Prize for Chemistry (1997) — specifically for his work on the hypothetical **sodium pump**. His work is, therefore, not just resting on the foundation of the membrane pump theory but is in fact the centerpiece of that membrane pump hypothesis. To gain a better understanding of Skou's work, I read all his publications I could lay my hands on, including the following.

In 1990 Skou gave the Fourth Datta Lecture. Its printed version bears the title: "The Energy Coupled Exchange of Na^+ for K^+ across the Cell Membrane: The Na^+, K^+ -pump" (FEBS 268, 314, 1990.) In the opening section of this paper, he wrote "that the energy from metabolism of the muscle was not high enough to account for the sodium flux.... The answer to the problem was given by (Hans) Ussing (of the University of Copenhagen) namely, that beside the active transport (or pumping) of sodium, there is a sodium-for-sodium exchange, an exchange diffusion, which energetically is neutral." (p. 314)

To the best of my knowledge, this statement is the first and the last Skou wrote on the problem of energy shortage. What is puzzling is that he made no mention of an (expected subsequent successful) verification of this exchange diffusion hypothesis. Yet as he himself made clear, the validity of his life's work on the sodium pump depends on the validity of this hypothesis.

Thus, unbelievable as it is, we find Nobel Laureate Skou also in the role of victim-(unknowing) perpetrator of this global information embargo. For the truth is that not only is there not a single piece of supportive evidence for the exchange diffusion hypothesis, those who studied it in depth arrived at the opposite conclusion.

Thus, between 1955 and 1970, four independent laboratories have tested this hypothesis on four different kinds of living cells. They unanimously reached the same verdict: Ussing's exchanged diffusion hypothesis has no validity (Hodgkin and Keynes, J. Physiol. 128: 61, 1955; Hoffman and Kregenow, Ann. NY Acad. Sci. 137: 566, 1966; Buck and Goodford, J. Physiol. 83:551, 1966; Ling and Ferguson, Physiol. Chem. Phys. 2: 516, 1970).

Thus, Skou continued to believe that the energy shortage problem had been successfully resolved by Ussing's exchange diffusion hypothesis — long after that hypothesis had been thoroughly disproved. Without the help of the hypothetical exchange diffusion mechanism, the energy shortage persists and as such invalidates the sodium pump hypothesis as well as the broader membrane pump hypothesis. Nonetheless, the Nobel Prize Committee for Chemistry of 1997 saw fit to award the Nobel Prize for his work on the sodium pump anyway. This mindless decision on something given so much public trust, is one instance that suggests what I mentioned earlier: the Nobel Committee members and their favorite advisors are themselves part of the victim-(unknowing) perpetrator network.

However, other than verifying my contention that Nobel Committees are not infallible, Skou's failure to deal with the excessive energy need of the postulated sodium pump was really no more than a minor footnote, if that, in history. To prove or disprove the sodium pump (and the larger membrane pump hypothesis) requires something far weightier. And in essence that was what I tried to achieve — a long time ago.

From 1951 till the middle 1956, I carried out all told some seventy (70) sets of complete and incomplete experiments all giving essential similar results but with increasing reproducibility. The last three sets of complete experiments conducted in 1956 were what I believe to be the most accurate. I then made two simplifying assumptions. First, frog muscle cells use all their available energy exclusively for just one purpose, i.e., pumping Na^+. Second, that all involved processes operate at 100% efficiency. Based on these assumptions, I showed that the minimum energy need for the sodium pump would still be at least 1500% to 3000% of the maximum energy available under the condition.

Within the following ten years, none have disputed my conclusion or the methods used to reach that conclusion. In contrast, the essence of my finding has been twice confirmed. (However, for a bizzare later event involving my former students Jeff Friedman and Chris Miller, see below.)

My conclusion, that the sodium pump hypothesis in specific and the membrane pump hypothesis in general are disproved, should also be viewed from the perspective of the total picture. That is, the sodium pump is but only one of an ever-lengthening list of more and more pumps. Each one of these postulated pumps must derive its energy need from the same source, now shown to be inadequate to cope with just one (sodium) pump alone. For an admittedly incomplete list of the names of pumps already proposed by 1968, see Table 2 (in Document #3 enclosed), — which was collected by Chris Miller from the literature in 1968.

The details of my work on the energy balance of the hypothetical sodium pump were presented in 1962 as a chapter (8) in my first book, "A Physical Theory of the Living State." (Book #1 listed in Document #1) But since this book is no longer in print, I have reproduced *verbatim* this entire chapter as Appendix 1 in enclosed Document #4.

However, other than Chapter 8 and its reprinted version in Document #4, there are other "contacts" which can lead you to the original work. Thus, under the heading "Articles" in the enclosed Document #1 are also the journal names, volume and page numbers of 18 reviews and original articles published in (mostly) easily accessible journals spanning a period of forty years between 1952 and 1992. In the same Document #1, there is also a list of the ISBN, titles, names of publishers etc. of four monographs published respectively in 1962, 1984, 1992 and 2001. In each of these publications, the disproof of the sodium pump hypothesis (and the membrane pump hypothesis in consequence) was discussed at different levels of details.

Beside its primary purpose of providing the information they contain, I have put together this list also to demonstrate that the absence of public awareness of the disproof of the sodium pump (and the membrane pump hypothesis) had nothing to do with difficulty in locating the original publication.

Next I fill in the historical details of the *en masse* exodus of my students. The story really began at a much more honest time in the history of biomedical sciences.

From the late fifties on I had gradually gathered around me a small band of bright and idealistic young students. To a person, each has made substantial contributions to real science.

Then the lion's teeth and claws were suddenly upon us and upon all those who have come to share my scientific view. A coordinated siege began. As an example, NIH program director, Dr. Paul Bowman told me that our NIH support might be terminated *permanently*. As I scrambled to save my laboratory, panic seized my graduate students.

Four of them including Chris Miller went back to Swarthmore College and asked Professor Savage to stop introducing the AI Hypothesis to new students. Bill Negendank, who went along with the group, told me later that the reason given for their request was a concern about not being able to get jobs on account of their prior association with me. Negendank, however, chose to remain with my laboratory. Holding a MD degree, he saw no danger of being unable to earn a living. However, I was not to find out how much more some of my terrified former student(s) had to degrade themselves beyond severing their ties to my scientific work and me to achieve the comfort and security … until another 20 year later.

In 1976 and thus 14 years after my publication of the disproof of the sodium pump hypothesis, a fledgling science reporter for the ***Science*** magazine published an article in that prominent journal entitled "Water Structure and Ion Binding: A Role in Cell Physiology?" (Science: 192: 1220.) In this article she announced that two scientists, Jeffrey Friedman and Chris Miller had produced "crucial experiments and calculations … that provide strong evidence for the existence of pumps." (p. 1220)

I was entirely flabbergasted when a friend told me about this publication and its main message — twenty years later. One reason for my surprise is that twenty years before, the same Gina Kolata had sent to me and several other scientists a manuscript she wrote with the same, or similar title and asked for our comments. We each thanked her for her courtesy and our comments were eventually all published in a later issue of Science. Totally unknown to us, she did not publish the manuscript sent to us, but a new version containing the above-quoted claim of my former graduate students, Jeffry Friedman and Chris Miller. Nor did Kolata tell us of this manuscript switch, nor send us a reprint of the altered manuscript when published.

When questioned twenty years later, she refused to give me a Yes or No answer to this (obvious) switch. In response to my other request for a copy of the report describing the alleged new crucial experiments and calculations, she apologized, claiming that she was so young and inexperienced that she included the statements (apparently from a nameless but influential scientist) without even checking with Friedman or Miller.

When I asked Friedman and Miller for the document presenting the alleged crucial experiments and calculations, Friedman never answered. Miller did answer but claimed that he had never published the material and had in fact destroyed it after circulating it among friends and therefore it no longer exists.

In fact, the circulated material was not completely destroyed. I was able to collect most if not all of it from Miller's Ph.D. thesis, which up to that time I had not seen. Immediately it became clear why he would not want me to discuss it with him. First, *his alleged crucial experiment* — apparently concocted by the unnamed scientist providing the gossip to Gina Kolata — *never existed*. The alleged crucial calculation refers to Miller's claim that the sodium ion efflux rate used in my energy calculation is ten times faster than the values determined by other cell physiologists. On the surface, this seemed like a reasonable cause for questioning the value used. In fact, it was something for which he ought to feel thoroughly ashamed.

For to arrive at his conclusion, he had turned upside down the sequence of time. Thus, what he did was like claiming that Galileo (1564-1842 AD) was wrong in believing that the earth revolves around the sun — because Aristotle (384–322 BC) and Claudius Ptolemy (2nd C. AD.) have shown that the sun revolves around the earth.

To make this clear, I have included the first 21 pages of an attached 1973 review (Document #3,) which gives a summary of our then ***new*** experimental findings on the sodium ion flux rates of frog muscle cells. The data on these pages present what the subsection title says: "Evidence for a Major Error in Assessing the Intra-Extracellular Exchange Rate of Na^+ Ion." In other words, the published Na^+ efflux rate of all cell physiologists up to that point (myself excepted) were too slow by a factor of ten at least and therefore grossly mistaken.

Now, in what Miller circulated around, he turned the time sequence upside down, claiming that my figure was too fast because other cell physiologists have shown figures that were ten times slower. Miller knew perfectly well what happened first and what happened last and what happened in-between. After all, he was a co-author of that very same paper (Document #3), containing the above quoted subsection with its clarifying title.

To make sure that all the misleading innuendoes and half truths circulating around were made known and straightened out, I wrote and published in 1997 a full review of the subject under the title: "Debunking the Alleged Resurrection of the Sodium Pump." A copy is enclosed and labeled Document #4. As already mentioned above, I attached as Appendix 1 to this Document #4, a reproduction of Chapter 8 of my now out-of-print book, "A Physical Theory of the Living State." You recall that it is in this Chapter 8 that the full original report on the energy balance study was presented. And as such, it documents the disproof of the sodium pump hypothesis in specific and the membrane pump theory in general.

But the harm was already done. During the 20 years, when I was not aware of Gena Kolata's manuscript switching and therefore could not have rebutted its falseness, she, Friedman and Miller as well as Science magazine have all become a part of the victim-(knowing or unknowing) perpetrator of the network of global deception.

However, before leaving this subject, let me turn you attention to page 161 of the "Debunking" article (attached Document #4). There I said on page 161: "T(t)here is little doubt in my mind that Miller and all my other graduate and postdoctoral students would have behaved altogether differently if they did not see a total hopelessness in front of them following what they once started to do: to lead the life of a real scientist…" I still have some hope for him. Now a Howard Hughes professor, the security of himself and his family is no longer a question. It is high time for Miller to make amends to avert the everlasting fate of being judged very harshly in human history. Next, I share with you what I dug out further: a pair of upstart "big-time" players in the global information embargo.

As you know too well, every scientist is overwhelmed by the plethora of publications coming off the press everyday. There is no way for anyone to read every publication every day and yet a scientist can rarely afford not to keep up with the literature. In response to this need, some review writers, especially those from highly respected scientific and educational institutions, appoint themselves the arbiters of what the scientific community ought to know and, what not to know.

In the early 1970's, two youngish cell physiologists, I. M. Glynn and S.D.J. Karlish, found themselves in what one may call the Mecca of Cell Physiology, the Physiological Laboratory of the Cambridge University in England. Apparently, they were asked by the editor of the *Annual Review of Physiology* to write a review on the sodium pump and they did.

Here is what Professor H. R. Catchpole of the University of Illinois wrote about Glynn and Karlish's review, which appeared in volume 37, pp. 13–55 of the Annual Review of Physiology. ***"The first comprehensive review which mentioned the sodium pump in its title was that of Glynn and Karlish of 1975. Glynn and Karlish listed 245 articles in support of the sodium pump and none opposed. Yet Ling's idea has been around for 25 years, so had ours, so had Troshin's…"*** (Persp. Biol. Med. 24: 164, 1980.)

Among the "opposing" evidence against the sodium pump hypothesis systematically left out are all the experimental evidence against the sodium pump hypothesis as given in Chapter 8 of the 1962 monograph: "A Physical Theory of the Living State: the Association-Induction Hypothesis" and in the embryonic version of the association-induction (AI) hypothesis called Ling's Fixed Charge Hypothesis published in 1952 (Document #5), review articles like Document #3, as well as the supportive evidence for the AI Hypothesis both collected between 1952 and the year of publication of Glynn and Karlish's review, 1975, including 11 of the articles and reviews among the 18 listed under "Articles" in Document #1 and many others.

Glynn and Karlich were not alone. In 1988, I counted no less than five additional reviews and published symposia edited or written by Glynn and other scientists on a similar subject. Each followed unwaveringly the same tactic initiated by Glynn and Karlish in 1975, that is, citing only findings in support of the sodium pump hypothesis and none opposed. Still more of the same kind came in years after 1988.

The latest review dated 2002 is another review written by I. M. Glynn (alone) for the same *Annual Review of Physiology* under the title:"A Hundred Years of Sodium Pumping." Again the review cited ***only references in support of the sodium pump hypothesis and treated opposing evidence as if it had never existed.***

The brief summary of the reviews written in cell physiology shows that for nearly one half of a century, the dishonest style of writing reviews initiated by Glynn and Karlish has been adopted almost universally. By this unethical maneuvering, the reviewers have created a falsified history of science, which glorify the reviewers' own work and those sharing their view and cause not only the names but the work of all those who hold different scientific views to disappear. The key question is has cell physiology been always like this? The answer is a decidedly No. The deception began not much longer than half of a century ago, when a few misguided individuals took over the helm. Soon the absolute power they wielded corrupted them.

And to give you an idea what was once like to be a scientist — I mean, a real scientist, I cite what was seen as the behavioral guideline from Sir William Bayliss's "Principles of General Physiology" (4^{th} edition, 1927) described by Professor A. V. Hill, Nobel Laureate, as " the greatest book of its kind."

"Shake your counter as boldly every whit,
Venture as warily, use the same skill,
Do your best, whether winning or losing it" (Browning)

"But at the same time, there must never be the least hesitation in giving up a position the moment it is shown to be untenable. It is not going too far to say that the greatness of a scientific investigator does not rest on the fact of his having never made a mistake, but rather on his readiness to admit that he has done so, whenever the contrary evidence is cogent enough."

Only five years after writing the Preface for the 4th edition of Sir Bayliss's book, Professor A.V. Hill was to show how true he was to Bayliss's guideline. Having been awarded the Nobel Prize did not prevent Hill from admitting and correcting a mistake he had once made and vigorously defended when the contrary evidence became cogent. Thus in an article he wrote for the Physiological Review under the title: "The Revolution in Muscle Physiology in which he made this final comment: "He laughs best, who laughs last" only it was Hill's scientific opponent, Gustav Embden, who did the last laughing. (PR 12: 56, 1932.)

Now, A.V. Hill was not only a key player in the field of muscle physiology, he was also a strong proponent of the precursor of the membrane pump theory, called simply the "membrane theory." Indeed, he almost single-handedly put to rout the protoplasmic-oriented cell physiologists in the early 1930's (See Chapter 7 of Book #4 in Document #1.).

Thus, the membrane theory was the only theory I was taught when I arrived in the United States and began my Ph.D. study in late 1945. My sponsor was Professor R. W. Gerard at the Department of Physiology in the University of Chicago. Aided by what I call the Gerard-Graham-Ling microelectrode technique, my early study of the electrical potential difference or "membrane potential" cross the surface of single frog muscle cells apparently offered support for the membrane theory.

It was in the fall of 1948, Professor Alan C. Hodgkin of the famous Physiological Laboratory of Cambridge University in Cambridge, England visited out department in Chicago. I had the pleasure of showing Hodgkin how to make and fill the microelectrodes (See Document #6.) He in turn suggested a little later to the editor of the Physiological Review to invite me to write a review. My review on the membrane potential was to appear at the same time as another review he was writing for the Biological Review. This was a high honor I greatly cherished. After all, I had not even gotten my Ph.D. degree.

But as I was gathering materials to write this review, I was increasingly alarmed by the virtual absence of substantial experimental support for the sodium pump hypothesis. Yet this sodium pump hypothesis is the foundation of my Ph.D. thesis in which the electric potential difference I routinely measured across the surface of muscle cell with the microelectrode were seen as a "membrane potential" — a name that came straight out of Bernstein's Membrane Theory. Eventually I decided to do some simple experiments of my own. I expected that the muscle cell should lose its K^+ on (simultaneous) exposure to pure nitrogen (which blocks respiration), sodium iodoacetate (IAA, which blocks glycolysis) and 0° temperature, [which slows down outward pumping of Na^+ (a process with a higher temperature coefficient) more than it slows down inward diffusion (with a lower temperature coefficient.)]

To my astonishment, the K^+ concentrations remained unchanged after 5 hours of incubation in N_2, IAA and 0°C. (See Table 5 of enclosed Document #5.)

Even though this kind of experiment did not by itself disprove the sodium pump hypothesis (and I was beginning to think of more incisive ones), I began to suspect that the claim I made in my Ph. D. thesis as well as my first four full-length papers (co-authored with Professor Gerard) that cellular electric potential is a membrane potential might be incorrect. After six requests for postponement I decided to give up my dream of glory and declined the invitation to write the review.

I also began to suspect that it was not a pump in the cell membrane that keep the cell Na^+ concentration low and the cell K^+ concentration high. But I had no better mechanism to offer for what caused the asymmetric distribution of this pair of chemically highly similar ions.

So when I left Chicago for my first job as an instructor in the Wilmer Institute at the Johns Hopkins Medical School in Baltimore, I was obsessed with the wish to find a new explanation for the asymmetric K^+/Na^+ distribution. Nonetheless, months and months went by, I got absolutely nowhere.

Then suddenly while sitting in cubicle in the basement of Welsh Library, an idea dawned on me that was to change the direction of my future cell physiological research altogether. It was a new mechanism for the selectivity of K^+ over Na^+ in living as well as non-living systems.

The essence of this idea has two components. The first component is what I later call the "principle of enhanced association through site fixation" (For up-to-date details, see p. 769 of Document #5 and p. 48 of Book #4 in Document #1.) Thus while very little K^+ associates with the negatively charged carboxyl groups of an acetate anion in solution, the association is intense when the carboxyl groups are fixed on the end of side chains of a protein molecule. The second component is fundamental statistical mechanics. That is, the probability of a β- or γ-carboxyl groups associating with the smaller hydrated K^+ is much higher than associating with the larger hydrated Na^+. If one takes into account the phenomenon of dielectric saturation, a K^+/ Na^+ selectivity ratio of about 10 was achieved. The main fixed anionic sites suggested for this role are the β- and γ-carboxyl groups of intracellular proteins, myosin for example.

I don't recall exactly what day or month that was when the new idea came into existence. But it could not be later than 1950, for the first publication I put out on the subject appeared in an abstract that appeared in print in 1951 (see Document #7.) A longer version was sent to Hodgkin, Hill, Katz, Harris and many others. All answered with encouraging comments. It was at about this time that Bill McElroy and Bentley Glass were organizing the second Symposium on Phosphorus Metabolism and I was invited to give a paper.

It was in this paper enclosed as Document #5 that a fuller exposition of my new idea on K^+ selectivity over Na^+ was presented (pp. 767–772.) Elated by this discovery I must have talked to some friends at the Hospital. To support my belief that the kind of global swindling perpetrated by Glynn and Karlish began at a much later date, I tell you a heart-warming story that took place in the big lecture hall of the Johns Hopkins Hospital. One day not too long after I found my new mechanism of selective accumulation, I was heading for the Welsh Library via the board-walk. There was a big overflowing crowd at the entrance of the lecture hall. I poked my head in to find out what was going on. Just as I found out that it was Professor A.B. Hastings from Yale lecturing on his expertise subject, K^+ in living systems, someone yelled from the audience, "Is Dr. Ling in the audience?"

Not sure of what I heard, I hesitated but was eventually hustled all the way down until I was scribbling on the blackboard on the podium, describing my new hypothesis. After I finished, Professor Hastings, the honored guest speaker of the occasion, came to me and shook my hand, saying that all his life he suspected that the K^+ /Na^+ selectivity has something to do with the different hydrated diameters of the two ions. Now you got it.

Long after this totally unexpected encounter and when things looked really bad, I always thought back with gratitude and admiration for having met Professor A.B. Hastings. Like Professor A. V. Hill, he too was a personification of what Sir Bayliss envisioned as a great cell physiologist.

While the mechanism was originally introduced to explain selective accumulation of K^+ over Na^+ in living cells, the mechanism suggested was in fact far more general and easily lends itself to other applications. Thus in 1953, it was extended to account for the s*elective K^+ permeability* of living cells (Document #8.) In 1956 my report at Atlantic City that the cellular resting potentials as well as glass electrode potentials are not membrane potentials but adsorption potentials at the cell or electrode surface was also based on the same basic mechanims of selective adsorption of K^+ over $Na^{+.}$. That report also brought me into contact with George Eisenman and his coworkers in Philadelphia.

An invited lecture followed in which I apparently convinced Eisenman and others in my audience of the general validity of my theoretical model of selective K^+ adsorption over Na^+. Accepting my model, Eisenman and coworkers further extended it with the new idea that the selectivity for the 5 alkali metal ions could vary with what they described as a change in the field strength of the anionic site. This important new idea, as well as some relevant old idea from colloid chemist Bungenberg de Jong gave me both the impetus and some additional building blocks for a new adventure. That is, to develop my original simple model of selective K^+ accumulation (called Ling's Fixed Charge Hypothesis, see Book #4, Chapter 10) into the unifying theory, the AI Hypothesis (mentioned at the opening of this letter.) That was of course forty years ago when the AI Hypothesis became published in full. Three years later, the Polarized Multilayer Theory of Cell Water was added, completing the AI Hypothesis.

Recently a physicist friend who had some familiarity with my work sent me an email. In this, he told me that in his opinion I should be happy about your ion channel work being awarded the Nobel Prize for chemistry — because it is "very close" to my work. After spending some time in the library I realized that he was not wrong.

Indeed, it seems that the more I read of your work, the more I realized how correct my friend was. All except his opinion that I should be happy about all these. I am not. No one else would. Thus, would you jump with joy when someone else got the Nobel Prize for ideas that you introduced for the first time many years ago but was not acknowledged? Would you not cry "plagiarism" loud and clear so everyone would hear it and force the offender to restore to you what is rightly yours? To be more specific, I shall make one direct comparison and a few loose pointers on ideas you might have presented without the knowledge that I had introduced them earlier.

(1) In enclosed Document #9, Figure 1 shows carboxyl groups carried on a protein(s) lining the wall of a cell membrane pore. Here the carboxyl group serves as a selective

device (what you would call a "K^+ filter") for achieving selective K^+ permeability in and out of living cells. This figure was presented in 1965 in an article entitled: "Physiology and Anatomy of the Cell Membrane…" (Fed. Proc. Symposium 24: S-103, on page S-110.; see also enclosed Document #9 for a later exposition of the AI Hypothesis of ionic permeability; see also Chapter 13 of Book #4 for reason that the lipid bilayer part of this figure is no longer valid.) The pencil-encircled part of this figure is compared with a similar figure (Fig 10) reproduced from an article you published with Chris Miller in the J. Gen. Physiol. 23 years later in 1988. Your reference list does not include my name or my prior publication. I am inclined to think that you are an innocent victim here. But since Miller knew my work well (See pp. 39–40 in Document #3), there was no justification for his not acknowledging me as the original author — without committing plagiarism.

(2) The concept of cooperativity in the adsorpion of K^+ ions means that the adsorption of a K^+ on one carboxyl group increases the change of the nearest neighboring carboxyl group also adsorbing K^+. This is shown in the illustrations on both page 45 and page 47 in the enclosed Document #11. See also Documents #10 and 12 on cooperativity.

(3) The idea that a linear array of carboxyl groups can provide a mechanism for diffusion of K^+ faster than in free water is first shown in 1962 in Documents #13, p. 336. And again in enclosed Document #11, Fig. 22 on page 34. For evidence of C. Miller's familiarity of this accelerated diffusion, see <http://www.gilbertling.org/lp18.htm> and also p. 33 in Document #3.

(4) Adsorption or desorption of Ca^{++} on a nearby *cardinal site* (receptor site) controls the sodium current and a molecular mechanism to explain it. See Document #14, from Ling in "Die Zelle, Structur und Funktion (H. Metzner ed.) 3rd Ed. Wissenschftlich Verlag, Stuttgart, 1981; Section 15-6 in Book #4.

So you see, you are already a very active member of this global information embargo network. You have already done me a great deal of harm in taking as yours a good part of my life's work. And your being awarded the Nobel Prize would make many people of the world listen to and believe you rather than me. But wouldn't you like to be awarded for what are truly yours and not somebody else's? I am sure of that.

By recording only publications in favor of the membrane pump hypothesis and ignoring all opposed, Glynn and followers have done away with the search for truth as the goal of science and have installed in its place the perpetration and glorification of the *status quo* right or wrong. And over the long run, the sin/crime of the deception is going to be paid in the lives and suffering of countless innocent men, women and children. Just take one incurable disease, cancer as an example

In America alone, 1990 innocent men, women and children died of cancer everyday in the year 2000. Put differently, cancer kills more innocent Americans on any two ordinary days (3980) than on that single calamitous day, 9–11, 2001 at the World Trade Center (2801.)

As a cell physiologist yourself, I do not need to tell you that the chance of curing cancer (and of many other incurable and even more threatening disease(s) would be greatly improved if the theory of the living cell is heading in the right direction. From all the above, it is obvious that the membrane pump theory is not heading in the right direction, nor does it provide the barest minimum of a molecular mechanism for the control of the living machines by drugs and other "cardinal adsorbents". In contrast, the AI Hypothesis is heading in the right direction. And the AI Hypothesis does offer the foundation of drug control (See Chapter 14 of Book #4.) Yet since 1988, all support from government agencies like NIH, NSF, ONR and private foundation like the Howard Hughes Medical Foundation have been lavishly and exclusively supporting workers subscribing to the membrane pump theory. Meanwhile all governmental financial support has been taken away from me and all others who have been pursuing science by the rule — abandoning the theory that has been unequivocally disproved (MPT) and following the affirmed one (AIH). But what has this unilateral support produced? For answer, let us return to Glynn and Karlish.

In their 1975 review, Glynn and Karlish cited 245 papers, exclusively favorable to the sodium pump hypothesis. In contrast, their 2002 review counts only 95 papers (also exclusively favorable). Of these 95, 64 are repeats of what was already reviewed in the 1975 review. This leaves only a total of 31 (favorable) papers that have accumulated worldwide in the 27 years since 1975. Thus despite lavish support by public institutions like NIH, NSF, ONR and private foundations like the Howard Hughes Medical Institution in the US alone, the average world-wide productivity is only *1.15* papers per year.

In contrast, during the same 27 year period, guided by the AI Hypothesis, my laboratory alone has produced ninety-five (95) original papers in addition to three major books (Books #2, #3 and #4 in Document #1). All came after the exodus of my former students and during the last 15 years entirely without governmental or private foundation support. It was Raymond Damadian and his tiny struggling Fonar Corporation that has permitted my little group to live on scientifically — in the form of salaries, shelter and facilities. For the first ten years, most of our miniscule laboratory operating expenses of about a thousand dollars per year came from my own pocket (i.e., my salary.) In the last few years, we also received a few thousand dollars from my son Tim and daughter-in-law, Kimberly to pay for additional expenses publishing my new book, “Life at the Cell and Below-Cell Level.”

It is self-evident that so far humanity as a whole has failed to find a cure for cancer (and for many other incurable and even more threatening diseases.) One reason for this man-made tardiness is unquestionably that the verified and productive guiding theory has been blacklisted. As a result, promising young scientists no longer have the freedom to follow their conscience, their best judgements, the results of their experiments and the one and only ethical guideline eloquently expressed by Sir William Bayliss. Meanwhile, government science supporting agencies like NIH and NSF, and major priate funding agencies like the Howard Hughes Medical Foundation, have been exclusively supporting in the last fifteen years work based explicitly or implicitly on the long-defunct membrane pump theory.

In closing, I ask you another question. At this very moment, 19 year olds are asked to give up their most precious possession, their lives to protect American citizens. Shouldn’t you and other intelligent and caring scientists like you, who have now the visibility and public trusts that come with the Nobel Prize, join me in righting the wrongs in basic cell physiological science, wherever they are?

As a token of good will, I am sending you (by separate mail) a gift. It takes the form of my latest book, “Life at the Cell and Below-Cell Level” listed as Book #4 in Document #1. You will find that it contains the first and only account of the history of cell physiology from its very inception to 2001. It tells not only the story of the AIH; it tells also the full story of the MPT as well. The over 500 single and multiple references in the book will lead to most of the information that might have been withheld from you in your past.

But it would be wrong to say that the job ahead for you would be easy. It is going to be a very challenging one. But that was the way, perhaps the only way of keeping alive and growing what the West has discovered in the 17th to 19th century that we call Science.

Sincerely yours,

Gilbert Ling
c/o Fonar Corporation
110 Marcus Drive
Melville, NY 11747

Document #1

ARTICLES

1. Ling, G.N. (1952) The role of phosphate in the maintenance of the resting potential and selective ionic accumulation in frog muscle cells. *Phosphorus Metabolism,* Vol. II, pp. 748–795 (W.D. McElroy and B. Glass eds.) The Johns Hopkins University Press, Baltimore.
2. Ling, G.N. (1955) Muscle electrolytes. *Amer. J. Phys. Med.* 24: 89–101.
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4. Ling, G.N. and Ochsenfeld, M.M. (1965) Studies on the ionic permeability of muscle cells and teir models. *Biophys. J.* 5: 777–807.
5. Ling, G.N. and Ochsenfeld, M.M. (1965) Studies on the ionic accumulation in muscle cells. *J. Gen. Physiol.* 49: 810–843.
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7. Ling, G.N. (1969) A new model for the living cell: a summary of the theory and recent experimenta evidence for its support. *Intern. Rev. Cytology* 26: 1–61.
8. Ling, G.N. (1970) The physical state of water in living cells and its physiological significance. *Intern. J. Neurosci. 1:* 129–152.
9. Ling, G.N. (1973) What component of the living cell is responsible for its semipermeable properties? Polarized water or lipids? *Biophys. J.* 13: 807–816.
10. Ling, G.N. and Ochsenfeld, M.M. (1973) Mobility of potassium ion in frog mscle cells, both living and dead. *Science* 181: 78–81.
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13. Ling, G.N. and Negendank, W. (1980) Do isolated membranes and purified vesicles pump sodium? A critical review and reinterpretation. *Persp. Biol. Med.* 23: 215–239.
14. Ling, G.N. (1980–1981) Water and the living cell as seen from the viewpoint of a new paradigm. *Intern. Cell Biol.* 1980–1981: 904–919.
15. Ling, G.N. (1988) A physical theory of the living state: application to water and solute distribution. *Scanning Microscopy Intern.* 2: 899–913.
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17. Ling, G.N. (1992) Can we see living structure in a cell?. *Scanning Microscopy Intern* 6: 405–450.
18. Ling, G.N. (1997) Debunking the alleged resurrectrion of the sodium pump hypothesis. *Physiol. Chem. Phys. & Med. NMR* 29: 123–198.

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1. Ling, G.N. (1962) *A Physical Theory of the Living State: the Association-Inducuton Hypothesis.* Blaisdell Publ. Co., Waltham, Mass. (Book out of print but can be obtained at Amazon. com
2. Ling, G.N. (1984) *In Search of the Physical Basis of Life*. Plenum-Kluwer Publ. ISBN 0-306-41409-0
3. Ling, G.N. (1992) *A Revolution in the Physiology of the Living Cell*. Krieger Publ. Co., Malabar, Fl. ISBN 0-89464-309-3.
4. Ling, G.N. (2001) *Life at the Cell and Below-Cell Level: the Hidden History of a Fundamental Revolution in Biology.* Pacific Press, 110 Marcus Drive, Melville, NY 11747. ISBN 0-970-7322-0-1.

Document #2

Oxidative phosphorylation and mitochondrial physiology: A critical review of chemiosmotic theory and reinterpretation by the association-induction hypothesis. *Physiol. Chem. Phys.* 13: 29 (1981) or go to www.gilbertling.com, choose volume (and article) from drop-down list.

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Debunking the alleged resurrection of the sodium pump hypothesis**.** *Physiol. Chem. Phys. & Med. NMR* 29:123 (1997) or go to www.gilbertling.com, choose volume (and article) from drop-down list.

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The role of phosphate in the maintenance of the resting potential and selective ionic accumulation in frog muscle cells. *Phosphorus Metabolism* (W. D. McElroy and B. Glass, eds) Johns Hopkins University Press, Baltimore, Vol. II p. 150 (1952)

Document #6

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Document #7

Tentative hypothesis for selective ionic accumulation in muscle cells. *Amer. J. Physiol.* 167: 806

Document #8

Selective cellular permeability according to the fixed-charge hypothesis. Proc. 19th Intern. Pysiol. Congress, Montreal, (1953) pp. 566–567

Document #9

Physiology and anatomy of the cell membrane: the physical state of water in the living cell. *Fed. Proc. (Symposium)* 24: S-103, (1965) Figure 1 on p. S110

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The theory of the allosteric control of cooperative adsorption and conformation changes. In *"Co-operative Phenomena in Biology"* (1980) (George Karreman, ed.) Pergamon Press, New York pp. 39–69

Document #11

A new model for the living cell: a summary of the theory and recent experimental evidence in its support. *Intern. Rev. Cytology* 26: 1 (1969.)

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The role of inductive effect in cooperative phenomena of proteins. *Biopolymers Symposium No. 1,* pp. 91–116 (1964)

Document #13

A Physical Theory of the Living State: the association-induction hypothesis. Cited as Book #1 under Document #1.

Document #14

Elektrische Potentiale lebender Zellen. *Die Zelle: Stuktur und Funktion* (H. Metzner) Wissenschaft. Verlag, Stuttgart (1981) p. 385

February 22, 2008

Professor Roderick MacKinnon
Laboratory of Molecular Neurobiology and Biophysics
The Rockefeller University
1230 York Ave, New York, NY 10021

Dear Professor MacKinnon:

Five years have passed since I sent you a registered 17-page letter with various documents and a book — not long after you were awarded one half of the Nobel Prize for Chemistry of 2003.

I wrote the letter because I was truly flabbergasted by what you have (apparently) done. Thus, four major components of your Nobel-Prize winning work on ion channels — as summarized on pages 14-15 of my letter — were first introduced by me as the enclosed documents make irrefutable. Yet, I could not find a shred of evidence that you had acknowledged my priority and given me due credit. For this reason, I mentioned to you that you were at risk of having committed plagiarism. I then invited you to correct my mistake —if any — by telling me where you had in fact given me credit earlier.

Anyone would agree with me that those five full years offer more than enough time to write a short answer to my letter.The fact that you have not done so suggests that you are unable to rebut my accusation but also would not make the effort to set straight the serious harm done to me by plagiarizing a substantial part of my life's work as your own. If that is indeed your position, I would be forced to repeat what I did in 1986 to Prof. Bertil

Hille of the Department of Physiology in the Washington University in Seattle. You can read all the letters exchanged as well as the final verdict at www.gilbertling.org/lp16a.htm. I close this letter with a warning. If you do not respond to this last appeal within the next three weeks, I will make public in print and online the (unanswered) letter I wrote you on November 17, 2003 along with the present one.

Sincerely yours,

Gilbert Ling

Damadian Foundation of Basic and Cancer Research
Fonar Corporation
110 Marcus Drive
Melville, NY 11747

PS This letter will also be sent registered with a return slip so that I will know exactly if and when you get it.

PPS I also enclose a copy of the letter I sent you on November 17, 2003.

April 2, 2008

Professor Roderick MacKinnon
Laboratory of Molecular Neurobiology and Biophysics
The Rockefeller University
1230 York Ave, New York, NY 10021

Dear Professor MacKinnon:

More than a month have gone by since I sent you on February 22 of this year a follow-up letter of another unanswered one I sent you five years ago on Nov. 17, 2003. According to the Post Office, this second letter was delivered to you at 3:13 pm on February 26. Although the Post Office has the signature of the person who accepted the letter, the return slip apparently got lost and never reached me.

Because of the seriousness of the next step I would be forced to take, I decided to offer you one more chance to either refuting or admitting/correcting the suspected plagiarism described in detail on pages 14–15 of my 2003 letter.

All you have to do is to write a short note. In this note, you can either rebut (with indisputable supportive documented evidence) or correct the wrong done to me by your prior failure to give me due credit for ideas I first introduced but have been incorporated into your Nobel-Prize-winning work as your own original work. I will then help you publish it in Physiological Chemistry Physics and Medical NMR, of which I am the current Editor-in-Chief.

Enclosed are copies of both my original Nov 17, 2003 letter and the more recent one dated February 22 of this years

Sincerely yours,

Gilbert Ling

Damadian Foundation of Basic and Cancer Research
Fonar Corporation
110 Marcus Drive
Melville, NY 11747

PS. This letter, like its predecessors, will be sent registered with return slip so that I will know exactly when it is delivered. Only this time it will go by two separate routes: one by next-day registered mail and the other by Fed Ex.

Received April 22, 2008.