Cell Biology International 2002, Vol. 26, No. 4, 305–308
doi:10.1006/cbir.2002.0870, available online at http://www.idealibrary.com on IDEAL®

COMMENTARY (AND BOOK REVIEW)

REVOLUTION AND COUNTER REVOLUTION IN CELL PHYSIOLOGY

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Received 17 December 2001; accepted 7 January 2002

Pollack's recently published book (Pollack, 2001) cannot be correctly understood if it is taken out of the context from the scientific ideas first introduced by Gilbert Ling in his Association-Induction Hypothesis (AI hypothesis: Ling, 1962, 1984, 1992, 2001) and other closely-related writings (Nasonov, 1962; Ernst, 1963; Troshin, 1966), because not only does it deal largely with AI hypothesis, but it is presented as a relatively random collection of fragments. Both the uniqueness of the AI hypothesis as the first unifying physicochemical theory of life, and the fact that it has stood 40 years of world-wide criticism are not even briefly mentioned. As a result, one could easily be misled into believing that it is Pollack rather than Ling who had introduced this unifying theory of cell function. The possibility of doing harm by an unbalanced presentation of the material is going to be greatly exacerbated by the lack of familiarity of most biologists with the AI hypothesis.

For nearly a century, two opposing approaches to an understanding of the physiological properties of the living cell have co-existed. They are the 'conventional' membrane theory and the 'heretical' bulk phase theories. Depending on which one of these approaches you adopt, your view of the life of a cell will differ profoundly. Following the first approach, many major attributes of a living cell reflect properties of a specialized submicroscopically thin cell membrane and its attached appendages. Following the second approach, as for example spelt out in detail in Ling's AI Hypothesis (Ling, 2001), the same fundamental features of a cell reflect the properties and behaviour of a water-ion-protein complex maintained at a high (negative) energy and low entropy state, irrespective of where this complex is located. It can be on the surface of a cell or in the depth of cytoplasm. Pollack presents a thesis built on the second approach, and broadly speaking reiterates Ling's fundamental concepts explicitly or implicitly in a cool and superficial way.

Let us consider from several different angles whether the ideas presented in Pollack's book are truly his own and new, and ask how they compare in soundness and veracity with the corresponding original ideas in the AI hypothesis, which are not specifically mentioned.

1. Phase transitions

These are at the basis of a unifying theory of cell function. Pollack seems unaware of two relevant facts. First, 'phase transitions are essentially co-operative phenomena . . .' (Domb and Green, 1972). Thus phase and cooperative transitions are essentially the same thing. Second, Ling's AI hypothesis includes the unifying notion that cell functions in general involve *cooperative transitions* between resting and active state. Regrettably, Pollack makes no mention of these prior deliberations, which suggests that his phase transition theory is just another name for the idea that Ling introduced decades ago (Ling, 1962).

2. The polarized multilayer (PM) theory of cell water

The PM theory of cell water and what it stands for are not mentioned in Pollack's book, an omission that will create confusion. Troshin, in the latest (English) version of his book 'Problems of Cell Permeability' (1966), wrote: 'in my opinion . . . all the water in the protoplasm is somehow organized ("bound").' However, neither Troshin nor anyone else had offered a molecular mechanism of cell

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1065–6995/02/$-see front matter

water organization until Ling (1965) proffered the first molecular theory of cell water referred to as the polarized multilayer theory of cell water. By not mentioning Ling's prior theory by name and what it stands for, and by filling the pages with picture after picture of water existing in polarized multilayers, Pollack risks misleading us into the false belief that it was Troshin, Szent-Györgi, or even Pollack himself, that first introduced the PM theory and what it stands for.

Furthermore, the PM theory is not just a theory of long-range water ordering. It is that, and *much more*. The PM theory represents also the first mechanistic theory of how cells can keep Na^+ and sucrose levels low without the postulating a sodium and other pumps.

Ling (1993) further developed his theory of solute exclusion to such a level of sophistication that, from solute distribution data, one can determine precisely what is the excess water-to-water interaction in frog muscle cell water (i.e. 126 cal/mole). By not mentioning the PM theory by name, and what it stands for, that part of the PM theory which is so important to cell physiology is placed outside the reach for no good reason.

3. The seat of multilayer water polarization-orientation

Pollack claimed that the seats of water polarization in living cells are the side-chains carrying net electric charges on the surfaces of cell proteins. In doing so, he ignores the vast amount of experimental evidence collected over many years by Ling and his coworkers, pointing to the fact that it is the exposed backbone –NH-CO- which is the primary seat of polarization and orientation of cell water. Parenthetically, Figure 5.2 in Pollack has been redrawn from an original figure of Ling's, which contains, in addition to what is reproduced in Figure 5.2 two highly informative insets. The graphs presented in these omitted insets demonstrate that it is the exposed backbone –NH-CO- grouping and *not* charged groups on the surface of native proteins that polarize and orient water in multilayers.

4. Gels in lieu *of protoplasm*

Pollack wrote: 'the concept of a gel-like cytoplasm turned out to be replete with power. It accounts for the characteristic partitioning of ions between the inside and outside of the call . . . It also explains the cell's electric potential . . Thus the gel-like character of the cytoplasm account for the basic feature of cell biophysics.' This is an astonishingly sweeping statement from a scientist whose expertise lies in muscle contraction and not in ion partitioning and cell electric potentials. But Pollack is apparently so convinced of the critical role of gel that he even includes the word in the title of his book.

Equally astonishing is the fact that throughout the book, the word *protoplasm* is not mentioned once. Thus Pollack is implicitly, if not explicitly, suggesting that all living matter is not made of protoplasm but of gels. But there is no reason given for this casual dismissal of such an age-old concept that all the bulk phase cell physiologists almost to a person believes in. And they include Ling, but apparently not Pollack.

However, contrary to Pollack's protestation, *gel* is not difficult to define. A gel is a pliable solid and like all other solids, it does not flow. A sol is a liquid, and like all other liquids, a sol flows. With this basic distinction in mind, one sees clearly that gel cannot be a substitute for protoplasm—because protoplasm can exist both in the gel form and in the sol form. Thus, whereas myoplasm and axoplasm are gels, the protoplasm (endoplasm) of *Nitella* cells can be poured out of a cut end of the cell (Kuroda, 1964). Protoplasm in the pseudopodium of an *Amoeba* even goes through cycles of sol-gel transformation as the organism migrates (Taylor and Condeelis, 1979).

Nor does the existence in a gel state endow a substance with what Pollack calls 'characteristic partitioning' of ions. In an extensive study of model systems, Ling and his coworkers (Ling *et al.*, 1980; Ling and Ochsenfeld, 1983) have shown that solid gels may show little or no exclusion proprieties of Na^+ salts and sucrose. In contrast, solutions (or sols) containing various oxygen carrying linear polymers like polyvinylpyrrolidone strongly exclude Na^+ salts and sucrose. The next paragraph presents evidence that being a gel has little to do with the basic mechanism underlying the creation of a resting potential, as Pollack contends.

5. Seat of the generation of the resting potential

Generation of a resting potential is attributed by Pollack to surplus electric charges inside the bulk of a gel. There are good reasons for rejecting this notion; first, such a theory violates the basic law of the macroscopic electroneutrality. Second, Inoue *et al.*, (1973) and Ueda *et al.* (1974) have shown that if a microelectrode is inserted into an isolated droplet of *Nitella* protoplasm, an internal negative resting potential of 70–90 mV can be measured

across the droplet surface. Furthermore, an action potential can be elicited by the application of an electric pulse (Inoue *et al.*, 1973). This protoplasmic droplet is not a gel, but decidedly a sol.

Pollack suggests in his book that excess electric charges of one sign or the other inside the gels give rise to what is known as the resting potential of living cells. Again, this statement is made by ignoring an enormous volume of work by many investigators, including Ling, whose PhD thesis was on this very same subject. The results of their extensive studies showed that the seat of the resting potential is a microscopically thin surface layer of the cell carrying negatively charged beta- and gamma-carboxyl groups and the ions they preferentially adsorb.

So we might ask, are there any completely good and accurate aspects in Pollack's book? The answer is yes; indeed many. Pollack's lampooning the big sodium channel and small potassium channel is one. His effort at demolishing the so-called single channel currents is another. Not the least is his strong recommendation as 'a compelling read' Ling's '*Debunking the Alleged Resurrection of the Sodium Pump Hypothesis*' (1997). For this article alone shows, purely on energy grounds, how the membrane pump theory ought to have been retired 40 years ago. But there are still other reasons for retiring the membrane pumps including the following:

(1) Closed sacs of perfectly healthy giant squid axon membrane furnished with ATP and other requisite components do not pump Na^+/K^+ against concentration gradients. Thus, this preparation, ideal for verifying the central postulates of the membrane theory, has not justified the hopes assigned to it.
(2) Cells without functional cell membranes and (postulated) pumps continue to selectively accumulate K^+ and exclude Na^+.

The crucial question arises as to why the majority of life-scientists have so utterly failed to come to grip with one incisive fact after another against the membrane pump theory for so long? The answer is very complex. But one of them is the fragmentation of cell physiology. The big picture is not in the focus of more and more scientists engaged in the pursuit of smaller and smaller subjects, with all the inevitable shortcomings of fragmentation.

In support of this fragmentation idea is the striking difference between the number of major books on cell physiology published by the subscribers to the bulk phase theories compared with subscribers to the membrane pump theory. From the supporters of the bulk phase theories, one can count the first book by Nasonov (founder of the then Leningrad Institute of Cytology), called 'Local Reactions of Protoplasm and Gradual Excitation' (1962), another book by Nasonov's pupil and successor, Troshin, a former director of the Institute of Cytology, which dealt with the 'Problems of Cell Permeability' (1966), four books by Ling (1962, 1984, 1992 and 2001), and finally Pollack (2001), which is a total of seven. And now what of the number of books from the supporters of the membrane theory? The result of a similar search gives a figure of zero.

It seems that the supporters of the membrane theory cannot write books covering the broad overall subject of cell physiology—perhaps because the fragmented pieces of cell physiology seen from that perspective are hard to be put together as a coherent piece. Anyone attempting to do this will inescapably have to confront the list of devastating evidence against the basic membrane pump theory including those cited above.

SUMMARY

In my best judgement, Pollack (2001) does not add much valid knowledge beyond or different from Ling's AI Hypothesis. If anything, it might even detract from it. That said, I must also add that its shortcomings notwithstanding, I can still recommend Pollack's book for several reasons. In a world of the education and research of basic biology stacked from floor to ceiling with the membrane pumps and phospholipid bilayers, any book from the camp of the bulk phase theories of cell physiology is like water in a scorched desert, even if this water is not pure water, but water contaminated by errors of omission and commission. This is my major reason for recommending Pollack's book. Then there are some lesser reasons for my recommending Pollack's book.

Ling has spent his entire life single-mindedly testing and developing his unifying physicochemical theory of life. By this time, few of his once large entourage of students have survived the persecution (real or threatened) for their dissenting views. The publication of Pollack's book shows that it is still possible for those with courage and dedication to continue the life of a dissenting scientist from received wisdom, and which still make a very real contribution to Science.

Then there is a third reason for recommending Pollack's book. As years pass, Ling's own adventure into the inner working of the living cell

has taken him deeper and deeper, and inevitably farther and farther away from the younger generation of scientists who will eventually inherit one day all that is truthful and valid, which is plentiful in Ling's work. For them, correct or incorrect, Pollack's more light-hearted four-colored approach may serve the role of a chocolate-coated introduction to Ling's more serious book, from which the more seriously minded must seek and glean more definitive answers. However, I need to state my conditions for recommending Pollack approach.

To begin with, if you have only casual interest in cell physiology and look for some relatively light-hearted entertaining reading to begin with, by all means buy a copy of the book, read it and take what you will from it. For the more serious-minded cell physiologists, the condition for my recommendation is that you must get hold of a copy of Ling's latest book (2001): '*Life at the Cell and Below-Cell Level. The Hidden History of a Fundamental Revolution in Biology*' which offers the most effective antidotes to some of the more serious errors in Pollack's expose. Thus armed, you will be protected from the lasting harm of the errors of commission and omission I mentioned in Pollack treatise.

We ought to be reminded at this stage of the words of Max Planck: 'New theories do not necessarily prevail; they simply survive as old ideas fade away.'

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