recognized that more sophisticated gas thermometry would yield new thermodynamic values, but the suggestion alternate to change, that $IPTS_{48}$ be retained and that values of difference from the TKTS be published periodically as better values emerged, was not accepted.

Guildner's exquisite technique says that this was a mistake. They show that where $IPTS_{68}$ did not change a value, that value is wrong, and that where values were changed, the value on $IPTS_{48}$ was closer to thermodynamic truth (see table below).

Fixed point temperatures

	$IPTS_{48}$	$IPTS_{68}$	Guildner, TKTS
Steam	100°C	100°C	99.975°C
Tin	231.913	231.9681	231.924
Zinc	419.505	419.58	419.514

Before we charge off again into change for the sake of a valueless correspondence, let's reconsider the virtues of a mathematically simple and elegant scale, a *practical* practical temperature scale, as one of my colleagues puts it, such as $IPTS_{48}$ was; and standing beside it, and modified from time to time as better values emerge from experiment, a table of difference between it and the TKTS.

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12/28/76

Axons and axioms

In the October issue (pages 33–39) Gerald Ehrenstein gave a lucid and readable description of the present status of the observational knowledge of the ion channels in nerve membranes. Besides providing information the paper could make one curious to learn how much of this information can be related to axiomatic physics. I use the term "axiomatic" here in the sense that Tisza uses it; not to describe a system formalized to satisfy the standards of logicians, but physics in a form that clearly distinguishes input and output, the axioms and the derived concepts, and that spells out any tacit assumptions.

There was a large input to this subject of physics at an axiomatic level at the end of the 19th century and the beginning of the 20th century. This work was done particularly by Nernst, Planck and Henderson on analyses of the liquid junction potential, and by Bernstein who hypothesized the voltage variable membrane potential and carried out some virtuoso experimental studies. The observational aspects of the problem of the nerve action potential dominated the interest of biologists in the following decades. The input from physics came in the form of improved technology to carry out these observations. It might be said that this work was finally focussed in the work of Hodgkin, Huxley and Katz. Their observations made quantitative the empirical understanding of the action potential in the nerve axon, and in particular in the giant axon of the squid. These experimental findings Hodgkin and Huxley remapped into mathematical expressions for the transient sodium and potassium ion currents that are observed when the nerve transmembrane potential is varied in a step-function manner. This remapping was made in terms of mathematical variables, n, m, h, α_n, β_n, α_m, β_m, α_h, β_h. Only one of the equations has a physical basis, this one being the equation of conservation of membrane current. The other three equations are only mathematical constructs that are designed to fit the data. These equations provide a reasonable description of the experimental results, and hence they form a satisfactory mathematical model for the action potential. But a satisfactory physical model was not forthcoming. In justice to biologists I must say that I have yet to find a biologist, or, for that matter a physicist familiar with the Hodgkin–Huxley equations, who does not protest that they and Hodgkin and Huxley are well aware that the Hodgkin–Huxley equations have no physical meaning.

Because the dominating interest of neurophysiologists since Hodgkin–Huxley has been focussed on gaining an understanding of the central nervous system, the development of a physical model for the action potential is a low-priority concern for biologists. The nerve action potential thus provides a fascinating opportunity for ingenious physicists to ply their trade without much competition, albeit probably without financial support for their research or audiences in either the world of biologists or physicists.

Some of the typical questions that remain to be answered are as follows:

1. If the stationary states of the permeability "system" vary with applied electric field, then the system free energy must vary with electric field. Hence a polarization of the "system" that is the canonical conjugate of the electric field exists.
2. A "system" consisting of a molecule with tens of thousands of atoms must have a very large number of configurational eigen-states available to it, instead of only the two or three that biologists assume. An observable of the "system" must be determined by the Gibbsian distribution functions as a statistical average over all the available states.
3. The description of the time dependence of the observables of the "system" must be given by the appropriate solutions of the master equation of the system,

says Ed Kluth, outspoken Managing Director of Ortec-Brookdeal.

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a Fokker–Planck equation, and certainly not by a simple exponential survival equation that the Hodgkin–Huxley formalism attempts to use. Intellectually speaking, the difficulty is that the step-function response function that is assumed for the "system" will determine the apparent relaxation time deduced for the "system." This relaxation time may thus have little relevance to theoretical transition probabilities if the wrong response function is chosen.

4. In any case, the observed relaxation time is long, the order of milliseconds. The passage of the action potential down the axon causes the polarization of the "system" to be carried through an irreversible cycle. Is the calculated time dependence of the entropy so generated and the net entropy generated for the cycle that which is observed?

5. From the foregoing points one sees that the polarization and the relaxation time of the "system" seem to be the significant parameters of the "system." Is the displacement current produced by the polarization observable?

6. Is the observed voltage-dependent optical birefringence of the membrane consistent with the necessary properties of the polarization?

7. Toxins and pharmaceuticals are known that selectively block ion transport. Tetrodotoxin, TTX, blocks sodium ion transport. Does it do this by changing the "system" polarization, or by interfering with the permeability channels, or by changing the "system" configuration transition probabilities?

8. The observed relaxation time is long for relaxation in a solid, so the change in stationary state with free energy must involve tunneling transitions. Is the temperature dependence of the relaxation time appropriate for such a process?

9. Is the effect of other intensive parameters on which the "system" free energy depends, such as pressure, observed to have the expected effect on the relaxation time?

10. Meyer in 1899 and Overton in 1901 hypothesized that the efficacy of inert gases in producing narcosis in the nerve is proportional to the solubility of the inert gas in olive oil. Is this hypothesis consistent with the expected change in tunneling probability or polarization of the "system" when its environment absorbs an inert gas?

I have made a beginning of an effort to formulate the properties of the ion conductance system in the nerve membrane in my own conception of how a physicist would like to see these points discussed. Some of this material has been published in the Journal of Theoretical Physics **58**, 33 (1976). The main point of this letter can be summarized by saying that, though Ehrenstein calls the Hodgkin–Huxley equations phenomenological, they are certainly not so in the sense that thermodynamical equations are phenomenological, or that the functional form of the equations is derived from axiomatic physics. The Hodgkin–Huxley equations predict nothing beyond the data from which they were formed, except for the frequency domain behavior of the membrane which is determinable from the time domain behavior. They describe the "system" in terms of non-physical parameters, n, m, h and the three α's and three β's. As Ehrenstein points out on page 39, this leads, for example, to the unsatisfactory and unphysical situation in which one must decide whether the observed polarization currents, which biologists call gating currents, depend on m or h or m^3h, or some other ad hoc postulated function.

"Science" as a word conveys the impression of a discipline monolithic in imperatives. However, it is not difficult to prove the generality of the statement, using examples from other fields of life science, that what is excellent and elegant biological naturalism can, at the same time, be poor physics. Failure to understand this truth and to act upon it can be dangerous to any living being, and disastrous to the future of "Science."

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THE AUTHOR COMMENTS: Most of Malcolm Strandberg's scientific comments about understanding the action potential are quite reasonable. The only scientific point I disagree with is his statement that the Hodgkin–Huxley equations predict nothing beyond the data from which they were formed. They do, in fact, predict the shape and conduction velocity of an action potential.

On the other hand, I strongly disagree with some of Strandberg's comments about the role of physicists and biologists in studying biological problems. For example, he states that "the nerve action potential thus provides a fascinating opportunity for ingenious physicists to ply their trade without much competition." Although there are indeed opportunities for physicists in these areas, there is also considerable competition in developing physical models. Furthermore, Strandberg's statement implies much more of a division between physicists and biologists than actually exists. In fact, one frequently cannot tell the physicists from the biologists without a score card. The scientist who is generally considered to have set the stage for Hodgkin and Huxley is Kenneth Cole, whose training was in physics and included the tutelage of Peter Debye.

Strandberg objects to the lack of concern with physical, as opposed to empirical, models. In my opinion, there has

continued on page 76

letters

continued from page 15

been considerable effort in the direction of obtaining physical models, and the main problem is the paucity of physical information about the behavior of the ionic channels. The thermodynamic approach suggested in Strandberg's 1976[1] paper is very reasonable, and has been pursued by a number of biophysicists. Examples are the use of a Boltzmann distribution of states to explain the behavior of ionic channels in lipid bilayers[2] and a probabilistic model of the sodium channel.[3]

Most of the ten questions listed by Strandberg are quite interesting. His statement that they all remain to be answered, however, is incorrect. For example, question 5 asks whether the displacement current produced by polarization is observable. Armstrong and Bezanilla have, in fact, observed such a current.[4] This displacement current is usually called "gating current" because it probably affects the gating of ionic channels. Question 7 asks about the mechanism of blockage by TTX. This question was also answered by Bezanilla and Armstrong.[5] They found that TTX does not interfere with gating current, and concluded that it acts by blocking the sodium channel, rather than by affecting the gating mechanism. There are other questions Strandberg raises whose answers are not yet known. A number of physicists and biologists have been addressing these questions, and Strandberg is certainly welcome to join us.

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4/4/77

Emotional experiences

I am in the process of compiling examples of scientists experiencing an ecstatic or mystical feeling from arriving at a scientific insight into the workings of nature. Such experiences are usually characterized by feelings of awe, wholeness, and profound significance. If your readers know of accounts already published, I would appreciate knowing the references; or your readers may be able to relate instances from their own experience or the experience of colleagues.

There is a widespread notion that scientists are coldly rational and insensitive to the sublime emotions. Perhaps your readers can help me gather some data on the other side of this question.

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2/18/77

Nuclear R&D

I respond to your editorial in February (page 88). You are of course entirely free to be in favor of nuclear energy and to say so. But it is disingenuous for the magazine editorial to baldly state that safety fears of nuclear power are not legitimate reasons for slowing nuclear R&D. Those of us who view nuclear power as an unwise and unnecessary danger often feel that one of our main opponents is, in fact, nuclear R&D. The momentum developed by nuclear research billions has become