LETTERS TO THE EDITOR

Autonomic Energy Conversion

Dear Sir:

Dr. Caplan (1, 2) has developed a theoretical treatment of muscle as an energy converter which we have discussed elsewhere (3). We concluded that his theory predicts (*a*) a variation of the rate of the driving reaction with load on the muscle, widely different from that occurring in fact; (*b*) wide variations in the free energy change of the driving reaction with load, which could not, in practice, occur. In this issue of the *Biophysical Journal* (4, 5) Caplan suggests extensions to his treatment to circumvent these objections. We are grateful to the Editors for giving us the opportunity to comment briefly on the new material. As happens all too often to theories, this one has lost its seductive youthful simplicity and put on weight. Unfortunately the new features that protect the theory from the chill winds of disproof do so only by preventing it from making any exact predictions whatever.

Caplan now suggests that the "regulator" proposed in his original theory not only controls the chemical flux in the "converter" but also contributes a substantial flux of its own. All that can be observed is the sum of the fluxes in the converter and the regulator and since no details are given of the subdivision between them, this suggestion at once removes the theory from the realm of the testable. His new suggestion that the free energy change involved is a "local" one, and can therefore vary widely, is similarly so vague that it is impossible, for us at least, to tell whether it is theoretically feasible, let alone experimentally testable.

For our part we have tried to extend the quantitative treatment that we have already published, and which is not, apparently, disputed by Caplan. Assuming for the moment that it is possible, as Caplan claims, for the "local" free energy change of a particular chemical reaction to differ widely from its ordinary free energy change, nevertheless, *over the whole cycle* of contraction and relaxation in which n moles of chemical reaction have occurred, then the chemical free energy made available to the converter must be $-n\Delta F$, where ΔF is the ordinary free energy change. This follows from the fact that by the end of relaxation, all the contractile machinery is back in its initial state, save that a small quantity of substrate (*PC*) has been consumed. Even less free energy will be available to the converter if part of it has been used by the regulator, as is now claimed by Caplan.

Consider what happens when the muscle contracts against a series of different loads. The variation of the *total* free energy made available in a whole cycle of contraction and relaxation, is known; and is shown by the dotted line in the graph. Now in Caplan's theory, the *rate* at which free energy is made available to the converter is given by $h \times A$ kcal/sec where h is moles/sec and A is the (local) free energy change (in kcal/mole) taken with negative sign. The variation of $h \times A$ with load can be derived from our (3) equations 18 to 21 by methods similar to those described on our p. 25.

The graph (Fig. 1) shows the result of comparing the *rates* and *totals* of free energy change obtained in this way for the case where $\Delta F/\Delta H$ has been taken as 1.0; and clearly the curves are of very different shape. Similar, and often greater, differences in shape are found if other values of $\Delta F/\Delta H$ are assumed, or if a proportion of the free energy made available is held to be consumed in the "regulator" rather than in the "converter."

The only way to reconcile the two curves shown on the graph is to suppose that when the force is small, and the speed great, the converter only operates for a very short time. For example, with a load of 0.15 P_0 the converter would only function for about 0.025 sec in a con-

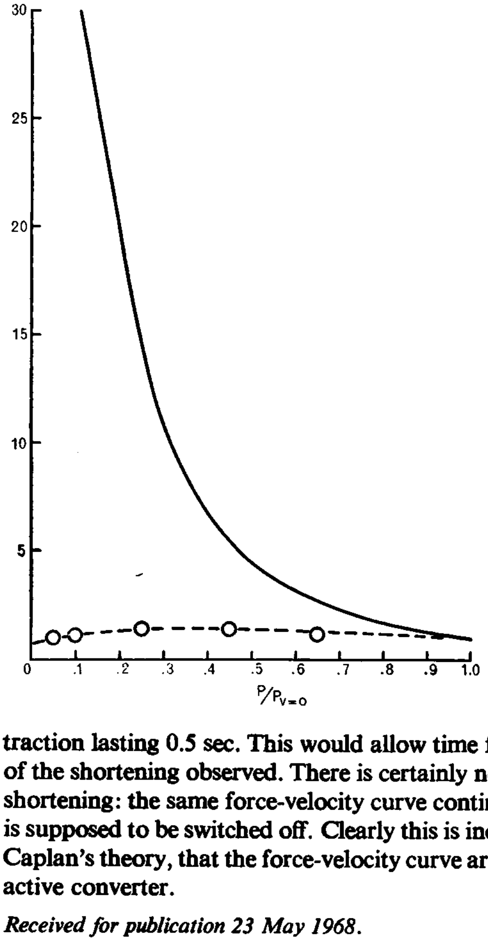

FIGURE 1 Graph shows how free energy made available changes with load, Abscissae. Force, as a fraction of isometric (i.e. $X/P_{v=0}$. Ordinates. Full lines, *rate* at which free energy is made available to the converter, as a multiple of the isometric value. Calculated as explained in the text. Interrupted line, *total* free energy made available in a whole cycle of contraction and relaxation also as a multiple of the isometric value. Experimental values from Carlson, Hardy, and Wilkie (6).

traction lasting 0.5 sec. This would allow time for only 0.5 mm of shortening—about a tenth of the shortening observed. There is certainly no discontinuity at this moment in the curve of shortening: the same force-velocity curve continues to be followed even though the converter is supposed to be switched off. Clearly this is incompatible with the main successful feature of Caplan's theory, that the force-velocity curve arises directly from the intrinsic properties of the active converter.

Received for publication 23 May 1968.

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P.S. We have just seen the Appendix to paper II in which Dr. Caplan objects to our six choices of Y (or ξ_2^l). We feel that he should have gone on from there to show what value of ξ_2^l would actually fit the experimental facts. (D.R.W. and R.C.W.)

[*Received by Editor 4 June 1968*]