centre formation. Alternatively, the coloration may arise from the formation of stable lipid peroxides, although in this case, we do not know why the nucleus is favoured discriminatingly for the production of lipid peroxide radicals.

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1 Steen, H. B., *Photochem. Photobiol.*, 9, 479 (1969).

Reversibility and biological machines

GRAY[1], in discussing reversibility and biological machines, applied a formula derived by Brillouin[2], describing the energy required to determine the positional limits of a microscopic system, to the muscle cross bridge. A result of his analysis is that the cross bridge is too small to be controlled directly by any internal system which matches the tension to the external load, and that control must extend over greater distances; I doubt if anyone would contest this. Gray then, however, extends the concept of 'profitable controlability' from this restricted example to all machines of molecular dimensions which operate cyclically and argues that their mode of operation involves an irreversible, unidirectional step; if this is not so, then the efficiency of energy conversion must be very low indeed. This idea is identical to that of McClare[3], who has argued that muscle contraction is an irreversible quantum-mechanical process whereby the free energy from ATP is converted to mechanical work. In fact, perfectly workable, self consistent models of muscular contraction can be made without any recourse to quantum mechanics, by general methods applicable to any energy conversion process[4], but Gray claims to advance a definite proof that this is impossible and that biological molecular machinery cannot be considered as an energy converter in the classical thermodynamic sense.

This does not follow, however, from Gray's idea of 'profitable controlability' which only has meaning when the rate of working of a molecular machine is geared to the prevailing force-field (thermodynamic gradients or whatever) by some cybernetic process, to achieve a thermodynamically reversible operation. If this criterion does not apply the 'controlability' of the system is meaningless, or rather irrelevant. There is no evidence that molecular machines must be controlled in this way, and so Gray has only produced a proof for one highly restricted set of conditions. It is perhaps worth considering the case of such molecular machines as ion pumps in the cell membrane, which can be driven backwards and which seem to function with high efficiency[5]. It is not possible to argue that there is no direct energy conversion occurring (as in a system involving mechanical work) because a substantial part of the work performed is that of moving a charge through an electric field gradient; that is, free energy from ATP is being used directly, by way of a conformational change, to achieve translation in a force-field. This must be taken to be a direct experimental disproof of Gray's thesis.

In summary, although the rate of energy conversion by a biological machine of molecular dimensions is subject to microscopic variation within the statistical limits imposed by the Second Law, there is no proof that size alone has any direct connection with the overall efficiency of the energy conversion process, or its potential reversibliity.

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1 Gray, B. F., *Nature*, 253, 436 (1975).
2 Brillouin, L., *Science and Information Theory* (Academic, New York, 1962).
3 McClare, C. W. F., *Nature*, 240, 88 (1972).
4 Hill, T. L., *Prog. Biophys. molec. Biol.*, 28 (1975).
5 Garrahan, P. J., and Glynn, I. M., *J. Physiol., Lond.*, 192, 217 (1967).

GRAY REPLIES—In the first few lines of his comment Hill[1] incorrectly paraphrases the contents of my letter, then identifies his version with a theory of McClare[2] (to which I did not even refer) which has been published for some time. He attributes to me claims which I do not make, for example, to advance a definite proof that "perfectly workable self-consistent models of muscular contraction cannot be made without recourse to quantum mechanics". Perfect workability, however, depends on how much or how little detail one is satisfied with in a theory. Hydrogen and oxygen will react explosively to form water and the statement $\Delta G < 0$ and its implications may be a 'perfectly workable self-consistent model' to some people who are interested only in distinguishing potential explosives from inert material. To the man interested in why the reaction is explosive, at one temperature and almost immeasurably slow at a temperature one degree lower, however, this 'perfectly workable' model is completely useless! He needs the macroscopic theory of chain reactions, and a third man with an even greater sense of curiosity needs quantum mechanics to understand the magnitudes of the reaction cross sections involved in this theory.

The first part of Hill's second paragraph reveals a misunderstanding of my main thesis, which is that very small (molecular) machines cannot be individually controlled if they are to work efficiently, not the reverse. He argues that there is no evidence that biological molecular machines are controlled "by gearing to some prevailing force field to achieve a thermodynamically reversible operation". He is here reiterating the view expressed by McClare[2], and my letter shows this is necessarily true, from a consideration of quantum theory and the observed sizes and efficiencies of molecular machines. We seem to agree that the independent working units, such as a crossbridge or a pump site, cycle autonomously in normal conditions in their forward direction, that is, using ATP. Clearly they cannot be made to go in reverse without the intervention of control, by definition, thus giving a concomitant drop in efficiency for units of this size. Experimental results on the reversal of ion pumps[3] do not conflict with this conclusion, since the reversal of the ion pump obtained in human red cells was achieved in highly abnormal conditions, not the normal environment of these cells and the energy expended in producing this abnormal environment must not be ignored in any discussion of efficiency and reversibility. Obviously any cyclic machine can be run backwards if one goes to sufficient lengths to push it, but there will be a drastic loss in efficiency except in the classical limit, where one can operate reversibly without energy cost. My brief statement about the reversal of muscle should be understood in this sense.

Hill's last statement does not seem to make sense, as the Second Law imposes no limits, statistical or otherwise, on the rate of energy conversion of any machines from molecular biological to macroscopic steam engines. It gives a criterion for distinguishing processes in which work can potentially be extracted from others in which it cannot.

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1 Hill, A. E., *Nature*, 257, 72 (1975).
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3 Glynn, I. M., Lew, V. L., and Luithi, U., *J. Physiol., Lond.*, 207, 371 (1970).

Matters arising

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