Meetings

Mechanism of Energy Transduction in Biological Systems: New York Academy of Sciences Conference

Some 60 participants drawn from all parts of the world and representing all facets of bioenergetics gathered in New York during 7 to 9 February 1973 to engage in a dialogue directed to the theme of the principles which can unify bioenergetics. The organizer, D. Green (University of Wisconsin), attempted to achieve the right blend of experimentalists and theorists and of the different disciplines (biology, chemistry, and physics) so that no one point of view would dominate the proceedings.

The conference revolved around three basic questions: Is there a crisis in bioenergetics?; What is the nature of the postulated crisis?; and How can the crisis be resolved? The traditionalists, drawn largely from the ranks of the experimentalists, took the position that within the present conceptual framework of bioenergetics, the solution of the outstanding problems was inevitable given the necessary time and intensity of effort. H. Huxley and B. Hartley (both of the Medical Research Council Laboratory of Molecular Biology, Cambridge University) and F. Harold (National Jewish Hospital, Denver), in their outstanding presentations, implicitly supported this thesis of the inevitability of progress along classical lines. Perhaps it would be more precise to say that the traditionalists, while open to persuasion, were unaware of compelling reasons for any drastic change in the conceptual framework. C. McClare (Kings College, London) was the spearhead of the group of both experimentalists and theorists who challenged the adequacy of the present approach to bioenergetics. This challenge was directed to the mechanism of muscular contraction [McClare and S. Ji (University of Wisconsin)], to the mechanism of enzymic catalysis (R. Lumry, University of Minnesota; Green; and Ji), to the mechanism of electron transfer (M. E. Winfield, Commonwealth Scientific and Industrial Research Organisation, Melbourne), to the mechanism of nerve transmission (L. Wei, University of Waterloo, Ontario; and D. Nachmansohn, Columbia University), and finally to the mechanism of energy transduction (McClare; Green; Ji; G. Weber, University of Illinois; R. Williams, Oxford University; F. Cope, Naval Air Development Center, Warminster, Pennsylvania; and A. Bennun, Rutgers University). While there was by no means agreement within this group as to the nature of the crisis and the corrective measures required to resolve the crisis, the group were convinced that unless new dimensions were added to the conceptual framework, progress would grind to a halt.

McClare developed the thesis that there was a fundamental misconception about energy transduction in biological systems. In all of the classical mechanisms, the notion of macroscopic constrained equilibrium machines has been invoked, but this notion is inapplicable to biological transducing machines that operate at the molecular level. According to McClare, biological transducing machines are molecular machines, and only molecular machines can achieve the observed high efficiency of biological energy transductions. Intrinsic to molecular machines are the concepts of the generation of a vibrationally excited state by one of the reactants in the exergonic reaction, the transfer of energy by resonance, and the relaxation of the energized state by a work performance. Since energization of molecular machines depends upon resonance phenomena, the efficiency of energization can be theoretical.

Green and Ji have systematically developed the concept of molecular machines in their electromechanochemical model of energy transduction and have extended this model to enzymic catalysis, oxidative phosphorylation, active transport, and muscular contraction. In their thesis there is a set of fundamental laws that underlies the performance of all biological energy-transducing systems, and from these laws the mechanistic principles of the transducing systems can be deduced. The laws of bioenergetics, like the laws of thermodynamics, can only be deduced by the a priori method although their validity has to be established by experiment.

The conference was marked by debates that swirled around each of several central issues. Weber challenged the viability of the notion of vibrationally excited states crucial to the molecular machine concept, contending that the lifetime of such states (about 10^{-12} second) would be too short to be useful in biological energy-transducing systems. McClare emphasized that under appropriate conditions, the lifetime of vibrationally excited states, such as that of carbon monoxide, can extend into the second range. L. Shohet (University of Wisconsin), from the analysis of computer models of the alpha helix, concluded that by the appropriate selection of resonance conditions, transfer of vibrational energy through the helix can take place with minimal energy loss at the speed of sound. Ji developed the notion that protein structure could play a key role in stabilizing and extending the lifetime of vibrationally excited states generated in supermolecules. K. D. Straub (University of Arkansas Medical School), the first to propose energy transfer in biological systems by means of phonons, made some incisive comments about the stability question.

The chemiosmotic model of P. Mitchell (Glynn Research Laboratories, Bodmin, England) was the focus of greatest attention and most extended debate in the conference. The model was defended in masterly presentations by Harold and by V. P. Skulachev (State University, Moscow). Williams was the principal protagonist of the view that a transmembrane proton gradient could not be a driving force in energy coupling; only an intramembrane charge separation or potential would meet the energetic requirements. Two dramatic experimental developments which supported Williams' position were revealed at the conference. First, H. T. Witt (Technische Universitet, Berlin) showed

that the intrinsic membrane potential in chloroplasts, but not the *p*H gradient, could be correlated with the capacity for photosynthetic phosphorylation. Second, mention was made of evidence obtained in several different laboratories that coupling could be achieved in nonmembranous suspensions of macromolecules (reported by M. I. H. Aleem, University of Kentucky; and T. Ozawa, Nagoya University; and published by D. R. Sanadi, Retina Foundation, Boston). If there was one issue on which a consensus was reached at the conference, it was that the Mitchell model could only be viable with an intrinsic membrane potential as the driving force. In that revised form, the Mitchell model shares common ground with the electromechanochemical model.

E. N. Moudrianakis (Johns Hopkins University) has opened wide the door to a reevaluation of the first acceptor for activated phosphate in photosynthetic phosphorylation. He presented unequivocal evidence that the first acceptor was adenosine monophosphate and that formation of adenosine triphosphate (ATP) depended on a myokinase-like transfer of a phosphoryl group between two molecules of bound adenosine diphosphate (ADP). A similar interpretation, based on results obtained with submitochondrial particles, was first proposed by Ozawa several years ago, but eventually came in for severe criticism published by P. Boyer (University of California, Los Angeles) and M. E. Pullman (Public Health Research Institute, New York). What this demonstration by Moudrianakis probably means is that the hydrolysis of ATP to ADP and inorganic phosphate is not the microscopic reversal of oxidative or photosynthetic phosphorylation.

The sticky problem of how electrons from reduced complex III can find their way into the heme group in a crevice in the interior of cytochrome c was considered by R. Dickerson (California Institute of Technology), B. Chance (University of Pennsylvania), and Winfield. Despite the elegant x-ray studies of Dickerson and the exhaustive spectroscopic studies of Chance, there was no consensus about the mechanism of electron transfer, although the cloud of conjecture was thick. Winfield, in one of the most penetrating presentations of the conference, laid bare the sorry state of our present ignorance of this crucial problem. If evidence were needed for the crisis in bioenergetics, the problem posed by the mechanism of electron transfer involving the components of the mitochondrial electron transfer chain can provide food for thought.

The generation of accurate structural information about energy-transducing systems is undoubtedly the crowning achievement of contemporary bioenergetics. The surveys of progress in muscle (Huxley; M. Morales, University of California School of Medicine, San Francisco; and J. Gergely, Retina Foundation), the mitochondrion (Y. Hatefi, Scripps Clinic and Research Foundation, La Jolla, California; L. Packer, University of California, Berkeley; and A. Tzagoloff, Public Health Research Institute), the sarcoplasmic reticulum (D. MacLennan, University of Toronto; and A. Martonosi, St. Louis University), and the chloroplast (Moudrianakis; L. Vernon, Brigham Young University; and R. Park, University of California, Berkeley) were among the high points of the conference. The x-ray crystallographic studies of chymotrypsin (Hartley) and of cytochrome c (Dickerson) pointed up the stark contrast between the precision and beauty of the accumulated structural information about these two macromolecules and the pitifully limited understanding of the mechanisms of both catalysis and electron transfer. Clearly, knowledge of the structural information is a necessary but not sufficient condition for adumbrating the functional principles.

The number of new concepts presented at the conference was high. These included enzymes as transducers of thermal to electromechanochemical potential energy (Green and Ji), force-generating mechanisms for muscular contraction (R. Dowben, Southwestern University Medical School, Dallas; McClare; and Ji), thermodynamic models for oxidative phosphorylation (Bennun and Weber), and molecular models for nerve transmission (R. Keynes, Agricultural Research Council Institute of Animal Physiology, Babrahan, Cambridge, England; Wei; I. Tasaki, National Institute of Mental Health, Bethesda, Maryland; and Nachmansohn). Cope developed a solid-state model for mitochondrial function.

A gap of at least 100 years separates parallel developments in physics and biology. The cooperative and symbiotic relation between theory and experiment has by now a long tradition in physics, but this relation is only in its formative stage in biology. If this conference has helped to convey the message to workers in bioenergetics that experiment without theory is as sterile as theory without experiment, it will have served a useful and historic purpose.

H. Baum (Chelsea College, London), played the role of Solomon in a brilliant summary of the conference. He pointed up the close analogies between the prolonged debate over atomism that raged in the late 19th century and the present dilemma in bioenergetics.

Mitchell, the cosponsor of the conference, was unfortunately unable to be present, but, nonetheless, the power of his approach and insights dominated the proceedings. The notion of vectorial electron flow and vectorial coupling, which he has championed, would now appear to be one of the greatest achievements in bioenergetics.

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Forthcoming Events

September

9–12. American Soc. of **Mechanical Engineers** (Plant Engineering and Maintenance Div.), 16th annual, Cincinnati, Ohio. (M. Jones, ASME, United Engineering Center, 345 E. 47 St., New York 10017)

10–11. National Conf. on **Cancer Nursing,** American Cancer Soc., Chicago, Ill. (ACS, 219 E. 42 St., New York 10017)

10–13. **Carbonisation and Graphitisation,** Inst. of Physics, Newcastle upon Tyne, England. (H. Marsh, Northern Coke Research Labs., Univ. of Newcastle upon Tyne, Newcastle upon Tyne, NE1 7RU)

10–14. **Structural Mechanics and Reactor Technology**, 2nd intern. conf., American Nuclear Soc., Berlin, Germany. (T. A. Jagger, c/o BAM, Unter den Eichen 87, 1 Berlin W. 45)

12–14. American **Ceramic** Soc. (Electronics Div.), Atlanta, Ga. (F. P. Reid, ACS, 4055 North High St., Columbus, Ohio 43214)

12–14. **Physics of Semimetals and Narrow-Gap Semiconductors**, Univ. of Wales and Inst. of Science and Technology, Cardiff, Wales. (J. E. Aubrey, Dept. of Applied Physics, UW and IST, King Edward VII Ave., Cardiff CF1 3NU)

12–15. **Organ Transplantation** Soc., 6th congr., Varese–Villa Ponti, Italy. (G. R. Pedroni, Studio MGR, Via Lanzone 40, 1 20123 Milan, Italy)

12–17. American **Medical Writers** Assoc., Bethesda, Md. (E. Stahl, Ayerst Labs., Montreal, P.Q., Canada)

13–14. Society for **Management Information Systems,** 5th annual conf., Chicago, Ill. (A. Suter, SMIS, 221 North La Salle St., Chicago 60601)

13–15. International Congr. on the **Knee Joint**, 75th, Dutch Orthopaedic