

## OXIDASES AND RELATED OXIDATION-REDUCTION SYSTEMS

**A**N international symposium on oxidases and related oxidation-reduction systems was held at Amherst College, Amherst, Massachusetts, during July 15-19. The organizers of the symposium (T. E. King, H. S. Mason and M. Morrison) made use of the presence of many biochemists in the United States for the sixth International Congress of Biochemistry, which was held in New York at the end of the month, to bring together most of the leading workers in the field. The symposium was restricted to 49 participants, all of whom except two presented papers. The geographical distribution of the speakers was: United States, 28; Japan, 5; United Kingdom, 4; Sweden, 3; Australia, 2; Israel, 1; Switzerland, 1; Germany 1; The Netherlands, 1. The symposium was generously supported by grants from the National Institutes of Health and the Office of Naval Research. The organizers were assisted by an advisory committee consisting of B. Chance, P. George, M. D. Kamen and E. C. Slater.

The first session of the symposium, on fundamental chemistry, was opened by P. George, who took as his theme the "Fitness of Oxygen" (cf. Lawrence J. Henderson's *The Fitness of the Environment*, first edition, Macmillan, New York, 1913; Beacon Paperback, Boston, 1958) as a terminal oxidant. N. Sutin discussed the mechanisms of some electron transfer reactions in solutions. F. W. Cope proposed a new kinetic theory of electron and ion transport, based on electron conduction within semiconductive particulate and membranous solid structures. His claim that the application of solid-state physics to enzyme kinetics is more fruitful than the conventional theories based on the 'law of mass action' was rather strongly attacked both by Sutin and by Chance. In general, it appeared that the biochemist is not ready to abandon the conventional approach for one that does not seem to offer any advantages, and which, according to B. Rosenberg's paper on some problems in the electrical conductivity of proteins, appears at present to have very limited experimental support.

The second session on peroxidase-oxidases, model oxidases, and related systems was opened by a theoretical investigation of the structure of oxygen-metallic ion complexes by L. L. Ingraham. His molecular-orbital calculations supporting a  $\text{Fe}^{3+}\text{O}_2^-$  structure for oxyhaemoglobin were vigorously discussed, especially by Sutin and L. Orgel. Organic chemistry was now brought into the picture by R. O. C. Norman speaking on the mechanisms of aromatic hydroxylation and ring-opening reactions, and by W. S. Caughey on structure and medium effects on the reactions of iron(II) porphyrins with oxygen and carbon monoxide. M. E. Winfield presented a mechanism for the autoxidation of myoglobin and proposed the first of many mechanisms brought forward during the symposium on cytochrome oxidase. I. Yamazaka suggested a mechanism of the reaction in which peroxidase acts as an oxidase. W. E. Knox described his experiments on the activation of tryptophan pyrolase by reduction and by haematin.

The third session was devoted to oxidases containing non-haem iron or copper (with the exception of cytochrome *c* oxidase). D. I. Crandall discussed molecular oxygenation by iron-activated oxygenases. O. Hayaishi confined his attention to comparative investigations on pyrocatechase and metypyrocatechase, reserving the more general aspects of oxygenases for a brilliant exposition at the opening session of the International Congress of Biochemistry later in the month. Investigations on copper

oxidases were opened by Bo G. Malmström, who discussed the two forms of copper which he has shown to be present in these oxidases by determination of the electron-spin resonance spectrum. E. Frieden reported on the catalytic activity of ceruloplasmin and its inhibition, and C. R. Dawson concluded the session, but not the discussion on copper, by his paper on the reaction between copper and the apoenzyme of ascorbate oxidase.

The chemists had the first word in the fourth session on flavin-containing oxidases. P. Hemmerich discussed the chemistry of flavin-metal interaction, dealing in particular with metal-ligand charge transfer, and A. Ehrenborg, the nature of flavin-free radicals. The biochemists continued with discussions by T. P. Singer on the comparative biochemistry of succinate dehydrogenase, by Y. Ogura on the action of mechanism of several flavin enzymes, by V. Massey on D-amino-acid oxidase, by R. C. Bray on xanthine oxidase, and by P. Handler on several metalloflavoproteins. The controversy which has raged for several years on whether the iron atom in iron-containing flavoproteins undergoes oxidoreduction in the course of the enzymatic reaction was not settled, even after an extra evening session. H. Beinert produced new and convincing evidence that iron is concerned in the  $g = 1.94$  signal in the electron-spin resonance spectrum which appears on reduction of these flavoproteins. This does not, however, prove that the iron atom is reduced, since the signal probably involves another atom, possibly a sulphur. V. Massey made a plea that his data, which show that the rate of reduction of the iron atom, as measured chemically, is several orders of magnitude slower than the overall reaction catalysed by the enzyme, should not be ignored.

M. D. Kamen opened the fifth session with a discussion on the status of the *Rhodospirillum* haemoprotein and other atypical haemoproteins as bacterial oxidases. I. C. Gunsalus considered the generation of active oxygen for mixed function oxidation, dealing in particular with investigations arising out of his discovery that this reaction is involved in the lactonization of camphor. Microsomal oxidases were discussed in four papers: by H. Staudinger on the mechanism of microsomal hydroxylation, R. W. Estabrook on spectral and kinetic investigations of microsomal pigments involved in this reaction, R. Sato on the CO-binding haemoprotein and NADPH-specific flavoprotein in liver microsomes and their roles in microsomal electron transfer, and H. S. Mason on the structure and oxidase function of liver microsomes.

A 'free' afternoon was devoted to a discussion of the controversial question of the separate identity of cytochrome *a* and *a<sub>3</sub>*. Most workers in the field appear now to accept the postulate of Keilin and Hartree, which they made in 1939, that cytochrome *c* oxidase contains two differently bound haem *a* molecules, one of which combines with oxygen and respiratory inhibitors, while the other does not. However, the so-called 'unitary' hypothesis is still supported by Onunuki and Wainio. Most workers assume that a single protein contains both types of haem *a* prosthetic groups (Siamese twins according to T. King)—a concept which can be formulated cytochrome *aa<sub>3</sub>*. There is at present no compelling evidence in favour of two separate proteins—cytochrome *a* and cytochrome *a<sub>3</sub>*—although this cannot yet be excluded.

Ten papers on cytochrome *c* oxidase were presented in the next two sessions, by K. Okunuki (presented by S. Takemori) on the reaction with trinitrophenylated cytochrome *c*, Q. H. Gibson on the reaction with cytochrome *c*,

H. Beinert on the function and disposition of the copper, W. W. Wainio on some anomalous reactions of the oxidase, M. Morrison on its components and their reactions, E. C. Slater on its composition and oxidation-reduction potential, T. E. King on a cytochrome *c*-cytochrome oxidase complex, L. Smith on the reaction of the oxidase with cytochrome *c*, P. Nicholls on its mechanism and E. E. Jacobs on its reaction with high-potential electron donors. Comments from R. Lomberg and K. Okunuki, who were unable to be present, were submitted by E. C. Slater and S. Takemori. There is now general agreement that copper forms part of the enzyme, although its exact role remains to be determined. Q. H. Gibson agrees with B. F. van Gelder and E. C. Slater that equal amounts of the *a* and *a<sub>3</sub>* components are present in active cytochrome *c* oxidase. Gibson's discovery that cytochrome *c* oxidase preparations contain non-reducible cytochrome *a<sub>3</sub>* explains the higher ratios of *a*:*a<sub>3</sub>* reported by M. Morrison. P. Handler brought forward the coupling of sulphite oxidation with the cytochrome *c* oxidase reaction as evidence in favour of an iron-O<sub>2</sub><sup>-</sup> radical as an intermediate in the enzymo reaction.

The last two sessions were devoted to oxidase systems and oxidative phosphorylation in intact mitochondria. A. W. Linnane reported on the induction by oxygen of the synthesis of mitochondria in anaerobically grown yeast cells. E. R. Redfearn discussed the interaction of electron carriers in the mitochondrial NADH<sub>2</sub> and succinate oxidase systems. Oxidative phosphorylation was dealt with in four papers. L. Ernster described a new method for investigating phosphorylation in the cytochrome *b-c* region, D. E. Griffiths examined possible reaction mechanisms at the pyridine nucleotide level and P. D. Boyer suggested carboxyl activation as a possible common reaction in substrate-level and oxidative phosphorylation, and in muscle contraction. Boyer stated that there is now no clear evidence for a role for phosphohistidine in oxidative phosphorylation, and that all data can be rationalized in terms of the succinyl-CoA synthetase being responsible for the incorporation of inorganic phosphorus-32 into mitochondrial protein-bound phosphohistidine. C. L. Wadkins reported interesting work on the oligomycin-inhibited, dinitrophenol-stimulated interaction between the ADP-ATP exchange enzyme and cytochrome *c*. B. Chance reported data on the reaction-velocity constants for electron transfer and transport reactions. He proposed that three types of reactions are involved in oxidative phosphorylation: (1) a rapid electron-transfer process, limited by the speed with which an electron departs from an iron atom and by the speed of its travel through the haem-linked groups to the periphery of the protein; (2) an electron-transfer process which involves

a thermal reaction in which the adjacent electron-bearing haematin becomes properly orientated; (3) a process involving the formation of high-energy intermediates of the cytochromes.

The last two papers dealt with the mitochondrial morphology as revealed by the electron microscope, with particular reference to the structure with projecting sub-units discovered by Fernandez-Moran. Those features of this structure which have been regarded as essential have gradually undergone a change, summarized colloquially by the sequences 'knobs', 'knobs on sticks' and 'the tripartite knobs-sticks-base plate'. There was general agreement that the morphological structure is not an artefact, but no agreement as to its physical significance. D. E. Green defended his suggestion that the structure represented the 'elementary particle' of electron transport. E. Racker, in a paper with D. F. Parsons, B. Chance and others, discussed the correlations between electron-transport activity, ATPase and the morphology of the submitochondrial particles, which led him and his colleagues to conclude that the projecting sub-units do not contribute an essential component to the electron-transport chain. A possible correlation between the sub-units and ATPase activity (coupling factor I) was suggested. Those attending the symposium were not disappointed in their expectations of a vigorous discussion, which was brought to a close by Racker's revelation that the 'knobs-sticks-base plate' structure shown by electron microscopy had been painted, in appropriate colours, by a Finnish artist in the 'thirties.

The papers presented at the symposium are to be published in due course. Since all but two of them were circulated to participants several weeks before the symposium, only 10 minutes were allowed for each presentation, hence maximum time was made available for discussion. The time-table for the symposium was planned on the hopeful assumption that the participants would have read the preprints (weighing 3.5 kg) before the meeting. Although in this respect most of the participants disappointed the organizers, the discussions were mostly lively, and there can have been few points in the field of oxidases which were left undiscussed.

If I may be permitted to record what struck me most about this symposium—and the identical thought was voiced by one of the most senior and most distinguished of the participants—it was the number, breadth and depth of the contributions made to the discussions by B. Chance, covering everything from theoretical chemistry, through physical chemistry, mechanism of enzyme action, oxidative phosphorylation to the morphology of mitochondria. It was a masterly performance, which contributed much to the high standard of the discussions. E. C. SLATER

## EDUCATIONAL AND SOCIAL FAILURE: SOME FURTHER OBSERVATIONS

By JOHN BRADLEY

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AN earlier report of mine<sup>1</sup> gave an account of a new projection technique which had been used to provide evidence of the development of a concept of a family dominance hierarchy in children of school age.

The projection test was given to primary school children of 8-11 years of both sexes and to a group of 1,600 secondary modern school boys and girls of 11-15 years, and the results showed that the mother is regarded as the salient member of the family in the earlier primary years but that she is increasingly displaced by the father, the process of displacement being complete for the majority of children by the fourteenth year.

Groups of children committed to approved schools and a group of children who had failed to make satisfactory academic and social progress in a grammar school gave a significantly different pattern of test results.

It was shown that social and educational failure, which can be defined as an obvious deviation by the child from the social and educational standards acceptable to those in whose care he finds himself outside the home, have a similar aetiology and that both can be understood only through a study of the family authority relationships and a consideration of the child's response to these relationships. It was further shown that these relationships