Monoamine oxidase

Monoamine Oxidase and Its Inhibition. (Ciba Foundation Symposium 39 (new series).) (In Honour of Mary L. C. Bernheim.) Pp. xii+415. (Elsevier/Excerpta Medica/North Holland; Amsterdam, Oxford and New York, 1976.) Dfl.78; $29.95.

THE present resurgence of interest in monoamine oxidase (MAO) and its inhibitors (MAOIs) stems directly from the discovery that at least two functionally distinct forms of the enzyme exist in many mammalian tissues, including the human brain. The problem is now to assess the physiological and pharmacological significance of this finding particularly with regard to the use of MAOIs in the treatment of certain affective disorders. This volume is intended to update and assemble some of the more recent findings in the field.

Almost without exception, the papers comprising this book are of a high standard. The first five articles deal with the nature and properties of the multiple enzyme forms together with the mechanism of action of acetylenic MAOIs. The second section catalogues a series of re-investigations into the physiological significance of MAO using MAOIs that more or less specifically inhibit one or other of the enzyme forms. A final group of seven papers deals with the evaluation of these newer MAOIs in the treatment of certain types of depressive illness and with also the possible usefulness of changes in human blood platelet MAO activity as indicators of such disease states as depression, migraine and schizophrenia.

The most interesting and revealing portions of this volume are the 125 pages of discussion. A feeling of bewilderment and uncertainty is constantly surfacing throughout these pages. Is the 'amine hypothesis' of depressive illness the correct model? Against all preconceptions, may antidepressant drugs act by reducing and not increasing the effective concentration of pharmacologically active amines at the receptor site? Perhaps the site of action of MAOIs is not in the brain but in the periphery: the accumulated amines may then penetrate the blood–brain barrier. Are MAOIs effective antidepressants because they inhibit MAO or is it because they inhibit amine synthesis by a feedback mechanism or perhaps block the uptake of amines by cellular elements in the brain? Is the ability of the tricyclic antidepressant drugs to inhibit one of the two forms of MAO with a K_i of about 10^{-5} M a factor in their mood-elevating properties? Is it even possible to make meaningful studies on the role of MAO *in vivo* when that fraction associated with nerve endings is less than 5% of the total? These and many other problems are discussed in this fascinating volume.

It seems absurd that so little is known about the role of an enzyme originally characterised as long ago as 1928 by Mary Bernheim. There is one inescapable conclusion that may be drawn from this book: until the aetiology of depressive illness is understood and the biochemists and clinical psychiatrists achieve some standardisation in their respective disciplines, the treatment of affective disorders with MAOIs will continue to be a 'hit-and-miss' affair. **Godfrey G. S. Collins**

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Mammalian gluconeogenesis

Gluconeogenesis: Its Regulation in Mammalian Species. Edited by Richard W. Hanson and Myron A. Mehlman. Pp. xxvi+592. (Wiley-Interscience: New York and London, 1976) $36.40; £18.60.

THIS volume of 15 essays is dedicated to Professor Henry A. Lardy for his outstanding contributions to biochemistry–impressively listed in the introduction. The editors have sought to compile the most significant information gleaned from 25 years of research on gluconeogenesis, an area in which Professor Lardy has played an important part. The chapters are grouped into four sections: the enzymology of gluconeogenesis; the involvement of the mitochondrion; the experimental approach to gluconeogenesis in liver and kidney; and gluconeogenesis in man. The sections seem to cover the main areas of current interest: the properties and regulation of the enzymes unique to glucose production that do not function in glycolysis; the vital question of the concentration of substrates actually available to these enzymes; the significance of the intracellular location of the enzymes, particularly phosphoenolpyruvate carboxykinase (PEP-CK); transmitochondrial membrane carriage of reducing equivalents; the interaction and competition for energy and substrate between urea synthesis and gluconeogenesis; the different manner of control of gluconeogenesis in liver and kidney; and last but by no means least what it all means for *homo sapiens*.

As the editors point out we now know a great deal about the pathway of gluconeogenesis from various substrates, but considerably less about how the process is controlled. It remains unclear whether for glucose formation from lactate and alanine pyruvate carboxylase or PEP-CK constitutes the pacesetting enzyme. The activity of the former is strongly regulated by acetyl-CoA, but it is pointed out that we can at present only guess at the concentrations of CoA esters available to the enzyme *in vivo*. PEP-CK exists in at least two forms and possesses a varied distribution between mitochondrion and cytoplasm in different species. The level of the cytoplasmic form in particular responds to a number of hormones. Although the varied distribution is described by several authors and the range of activities in different species compared, there seems no suggestion of what the rationale for this diversity may be. The enigma of an apparent K_m for PEP-CK towards oxaloacetate far in excess of available concentrations, resolved for the cytoplasmic enzyme by Ballard (*Biochem. J.* **120**, 809, 1970), remains an acute problem for the mitochondrial enzyme since the overall mitochondrial concentration of oxaloacetate seems so low. It was Lardy himself who pointed out the virtue of a cytoplasmic location of PEP-CK if it led to oxaloacetate transfer from the mitochondrion as malate, since this simultaneously resulted in 2H transfer to the cytoplasm needed at the stage of triose phosphate formation when gluconeogenesis is proceeding from substrate not initially undergoing oxidation. It is interesting to learn that in pigeon liver, where phosphoenolpyruvate synthesis is almost entirely mitochondrial, negligible glucose synthesis from either pyruvate or alanine occurs. Except in relation to man, little consideration seems to be given to the role of glycerol as a gluconeogenic substrate, yet in prolonged fasting it becomes quantitatively important and could also be a source of reducing equivalents for other precursors.

This volume will be indispensable to all workers in the field and is to be recommended to anyone interested in gluconeogenesis. It is a pity that a number of the chapters have no summary section, but, perhaps to compensate, the editors have provided their own synopsis of the contributors' main points and the current state of the art. **K. L. Manchester**

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