CHEMISTRY AND BIOLOGY OF PTERIDINES AND FOLATES

Proceedings of the 12th International Symposium on Pteridines and Folates, National Institutes of Health, Bethesda, Maryland, June 17-22, 2001

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Preface

It is fitting that in this first year of the new millennium, the International Symposium on Chemistry and Biology of Pteridines and Folates was held for the first time in the nearly 50 year history of this Symposium at the National Institutes of Health in Bethesda. Much of the pioneering work on pteridines and folates was originally carried out at NIH and one of the editors (SM) has spent the last 25 years on tetrahydrobiopterin research there. The new Natcher Center provided an excellent setting for the lectures and poster sessions where for the first time, nearly all presentations were made electronically. The 12th International Symposium was opened by a welcoming address from the Dr. Michael Gottesman, the Deputy Director for Intramural Research at NIH, whose own research is focused on a related area.

Over the next four and one half days, there were approximately 75 lectures and 80 posters presented covering an extremely wide range of research on folates and pteridines from chemistry to medically related issues. The many outstanding chapters in this volume reflect the progress and exciting new findings made in these areas since the 11th International Symposium that was held in Berchtesgarden, Germany.

The tradition of recognizing outstanding contributions to pteridine research was continued at this symposium with the selection of Professor Rowena Matthews to present the 2001 Gowland Hopkins Lecture. As introduced by Barry Shane in the following pages, this was an especially appropriate selection, not only because of her well-known scientific and mentoring contributions, but also because of her personal connections to Cambridge and Gowland Hopkins. Rowena's father, the noted biochemist David Green, actually did his dissertation research in Gowland Hopkins lab.

We would like to thank the members of the Advisory Committee for their assistance. Of course, we are especially indebted to the sponsors who helped make the meeting possible and enabled us to provide travel grants to nearly every student and postdoctoral fellow in attendance. We are most grateful to Gilbert Reibnegger and Dietmar Fuchs who arranged for the abstracts to be printed by the International Society of Pteridonology. Finally, we thank the Foundation for Advanced Education in Science (FAES) and especially Adrian Martinez and Carline Coote who handled most of the details.

The 13th International Symposium will be held in Amsterdam in 2005 hosted by Gerrit Jansen and G.J. Peters. We hope to meet our old colleagues once again as well as many newcomers to pteridine research.

Sheldon Milstien
Gregory Kapatos
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Barry Shane

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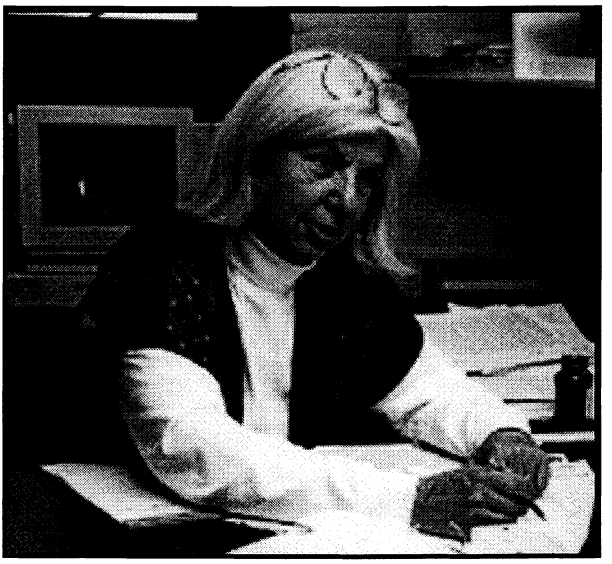
THE GOWLAND HOPKINS LECTURER

Professor Rowena Matthews



It is a pleasure to provide an introduction to Rowena Matthews, the Gowland Hopkins Lecturer of this International Symposium. Rowena's exquisite studies on the enzymes of the methionine cycle over the last twenty years have been responsible for much of our current understanding of the regulation of this cycle and I was delighted that the Symposium Advisory Committee has recognized the contributions of this extremely gifted scientist.

If pedigrees matter in science, which they probably don't, Rowena life got off to a good start in Cambridge, England, where her father, David Green, was doing sabbatical research at the University. Some years later, she received her B.A. in biology (summa cum laude) from Radcliffe College, where she conducted research at Harvard with George Wald on meta-rhodopsin. She received her Ph.D. in biophysics from Michigan where she worked on flavoproteins with Vince Massey. She remained at Michigan for family reasons and is currently Chair of the Biophysics Research Division and holds The G. Robert Greenberg Distinguished University Professorship of Biological Chemistry.

It is difficult to do justice to what has been, and continues to be, an extremely productive research career, so I will concentrate on a few areas that represent my personal list of Rowena highlights. A hallmark of Rowena's research is that she has a knack of picking key regulatory enzymes to investigate. Rowena backed into the folate field by serendipity. To start her independent research studies, she chose to investigate methylenetetrahydrofolate reductase, because it seemed like an interesting flavoprotein, a prescient choice. At that time, Carl Kutzbach and Bob Stokstad

had recently described the inhibition of the reductase by adenosylmethionine, and had suggested that the methionine cycle was regulated by adenosylmethionine inhibition of this enzyme. Rowena's initial studies on the catalytic mechanism of the reductase led to a number of major findings. She showed that the reaction proceeds via a dihydrofolate intermediate, leading to an understanding of the catalytic mechanism as well as new concepts on flavoprotein mechanisms, and that this enzyme functions as a dihydropterin reductase, and may play a role in neurotransmitter metabolism. The mechanism by which adenosylmethionine regulates this enzyme and the essential irreversibility of the reaction catalyzed *in vivo* were established. This had important implications for B_{12}/folate interrelationships as it demonstrated two important postulates of the methyl trap hypothesis, namely that the reductase is an irreversible, committed step in methionine biosynthesis and that methionine can alleviate the methyl trap via adenosylmethionine inhibition of the reductase. During this period, Rowena conducted a detailed analysis of the role of folylpolyglutamates as enzyme substrates and inhibitors of a variety enzymes involved in one carbon metabolism. She showed that dihydrofolate polyglutamates are potent inhibitors of the reductase. Mechanistically, this tight affinity was explained by the affinity of the enzyme for dihydrofolate reaction intermediates. Studies with other enzymes such as thymidylate synthase demonstrated differential effects of glutamate chain length on the substrate and inhibitory effect of these compounds, which suggested a mechanism by which one carbon metabolism could be directed away from amino acid metabolism and towards nucleotide synthesis.

Some of her most exciting studies have been on the B_{12}-dependent methionine synthase. The gene for the *E coli* methionine synthase was cloned by her postdoctoral fellow Ruma Banerjee and the availability of large amounts of enzyme made possible detailed mechanistic and structural studies. In what was the start of a highly productive and ongoing collaboration with her colleague Martha Ludwig, the structure of the cofactor domain of the synthase was solved, our first look at one of nature's most beautiful structures. This was followed by the structure of the activation domain of the synthase, as well as the auxiliary protein flavodoxin reductase, which interacts with this domain, and a description of the protein-protein interactions involved. Over the last few years, we have been treated to an ongoing series of classic studies on the mechanism of the synthase, including the role of Zn in the protein, and a detailed description of how the oxidation state of the cofactor influences its coordination with the protein and elicits conformation changes that position the cofactor for catalysis or reductive methylation.

Rowena provided the sequence information that allowed Rima Rozen to clone the human methylenetetrahydrofolate reductase cDNA and, with the accumulating interest in the 677C->T polymorphism in this gene, it seemed natural that Rowena would be the one to explain to us why a valine substitution in the protein could cause so much excitement. Her beautiful studies with Martha Ludwig demonstrated how this substitution influences

flavin binding and leads to protein instability, and also explained how this adverse phenotype can be ameliorated by improved folate status. With the exponential increase of SNPs in folate genes being associated with practically every disease of aging as well as development, Rowena and Martha are going to have their hands full over the next few years.

The best way of describing the high regard Rowena is held in by her peers is that her presentations at scientific meetings, which are usually of the keynote speech or state of the art presentation variety, are eagerly awaited for their new insights. The quality of her science, and the careful approach she uses, is so highly respected that Rowena's comments carry a weight that her peers would give to few other investigators. Her presentations are thoughtful, thorough and concise and are presented with great elegance and style. Her multimedia presentations, involving Quicktime movies and Rowena gyrating on the stage, are a joy to behold. For those of us not well versed in the intricacies of enzyme mechanisms, her lucid descriptions make for what some of us is an incomprehensible subject suddenly crystal clear. We walk out of the room as experts on conformational changes in B_{12} cofactors and methionine synthase – I just wish we could remember it all the next day.

Rowena is an excellent teacher and mentor of graduate students, and her past students think extremely highly of her, both as a teacher and as a person. I have often observed her at meetings go out of her way to discuss research and to encourage graduate students and she always finds time for students. She is a very thoughtful and considerate person in the best tradition of the teacher. I consider her a role model for what a scientist should be.

On a personal note, Rowena and I started our independent research careers about the same time, and we first met shortly after at the International Symposium in La Jolla in 1978. I recall some interesting discussions we had together with Bob Stokstad about the reductase. Bob and I were both charmed by Rowena and I recall how delighted Bob was that Rowena was going to continue studies on the enzyme, as he thought this was an important enzyme in one carbon metabolism. We both followed Rowena's scientific career closely after that. I have had the pleasure of interacting with her at many scientific meetings and have called her on many occasions for advice when my laboratory encounters stumbling blocks in unraveling enzyme mechanisms. She has always been very generous with her time and her insightful ideas, and has always freely discussed her ongoing studies with me. I was delighted when Rowena agreed to give the keynote address at a celebration of Bob Stokstad's life held in Berkeley a few years ago.

It has been a privilege for me to have this opportunity to introduce this Symposium's Gowland Hopkins lecturer, a truly impressive scientist and an even more impressive lady.

Barry Shane
University of California at Berkeley