
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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Maryland, June 17-22, 2001*

edited by

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CONTENTS

PREFACE xvii

GOWLAND HOPKINS LECTURE

Making Methionine: A Love Affair with Folate

Rowena G. Matthews 1

1. Novel Chemistry of Pteridines

Structure Elucidations of Dimeric Pteridines

W. Pfeleiderer 9

A Selective Procedure for 6-Substituted Pterin Derivatives: Synthesis and Substitution of Pterin 6-Triflate

S. Murata, M. Kujime, and K. Kudoh 19

Solution and Solid Phase Synthesis of Pteridines, Purines and Related Compounds

S. La Rosa, P.H. Boyle, C.L. Gibson, D. Guiney and C.J. Suckling 25

Synthesis of Pteridines with C-2 and C-6 Functional Group Diversity

D. Guiney, P.H. Boyle, C.L. Gibson, S. La Rosa, and C.J. Suckling 31

Stereospecific Synthesis of 2-Desamino-Tetrahydropterins as Probes of Hydroxylase Cofactor Recognition

S. Vasudevan, S.W. Bailey, S.B. Dillard, and J.E. Ayling 37

New Pyranopterins Chemistry Related to Molybdenum and Tungsten Enzymes

D. Guschin, W. Belliston, I.M. Müller and B. Fischer 43

Application of FDCCD Spectroscopy for Determination of Chiralities of Biologically Important Pteridines

N. Chen, K. Ikemoto, T. Sugimoto, S. Murata, H. Ichinose, and T. Nagatsu 49

Photo-Oxidation of Sepiapterin Produces Pterin-6-Carboxylic Acid and H₂O₂ *In Vitro*

H. Rokos and K.U. Schallreuter 55

2. Pteridine-Dependent Enzymes: Structure, Function and Regulation

Regulation of Tyrosine Hydroxylase by S-Glutathiolation: Relevance to

Conditions Associated with Dopamine Neuronal Damage D.M. Kuhn	61
The Conformation of Tetrahydro-Biopterin Free and Bound to Aromatic Amino Acid Hydroxylases and NOS K. Teigen, K.K. Dao, N. Åge Frøystein, A.C.F. Gorren, B. Mayer, J. McKinney, J. Haavik and A. Martínez.....	67
Regulatory Properties of the Tetrahydropterin Cofactor in the Reaction Catalyzed by Human Tyrosine Hydroxylase Isoforms 1-4 B.Almás, D. Clement and T. Flatmark	73
Structure and Regulation of Phenylalanine Hydroxylase, and Implications for Related Enzymes B. Kobe, I.G. Jennings and R.G.H. Cotton	79
Interaction of Phosphorylated Tyrosine Hydroxylase with 14-3-3 Proteins: Effects on Phosphorylation Kinetics R. Kleppe, K. Toska, and J. Haavik	85
Mechanistic Studies of Tryptophan Hydroxylase P.F. Fitzpatrick, S.C. Daubner, and G.R. Moran	91
Role of Phe313/Trp326 in Determining Substrate Specificity in Tryptophan and Phenylalanine Hydroxylases J. McKinney, K. Teigen, N. Åge Frøystein, P.M. Knappskog, J. Haavik and A. Martínez	97
Possible Contributions of Labile Asparagine Residues to Differences in Regulatory Properties of Human and Rat Phenylalanine Hydroxylase R.M.N. Carvalho, T. Solstad, N.E. Robinson, A.B. Robinson and T. Flatmark	103
3-(2-Thienyl)-L-Alanine as a Competitive Substrate Analogue and Activator of Human Phenylalanine Hydroxylase A.J. Stokka and T. Flatmark	109
The N-Terminus of Human Tyrosine Hydroxylase is Responsible for its Association with Phospholipid Bilayers M. Thórólfsson, A. Muga and A. Martínez	115
Mechanisms of Tyrosine Hydroxylase Activation by Stress Activated Protein Kinases K. Toska, R. Kleppe and J. Haavik	121

Substrate Specificities of Phenylalanine and Tyrosine Hydroxylase: Role of Aspartate 425 of Tyrosine Hydroxylase S.C. Daubner, J. Melendez, and P.F. Fitzpatrick	127
Mutation of W457 Alters N-Hydroxy-L-Arginine Oxidation by Inducible NO Synthase: A Single Turnover Study Z.-Q. Wang, C.-C. Wei, J. Santolini, and D.J. Stuehr	133
Regulation of Rat Hepatic Phenylalanine Hydroxylating System <i>In Vivo</i> E. Connolly and J. Donlon	139
 3. Mechanism and Regulation of Pteridine Biosynthesis	
Estradiol Modulates GTP Cyclohydrolase I Gene Expression in Brain Catecholaminergic Systems L.I. Serova and E.L. Sabban	145
PKC-Mediated Regulation of GTP Cyclohydrolase I in Mast Cells and Renal Mesangial Cells C. Hesslinger, V. Parravicin, C. Lapize, I. Ziegler, J. Rivera, and J. Pfeilschifter	151
Regulation of GTP Cyclohydrolase I by Estrogen C. Hesslinge, Z. Chen, A. Ahluwalia, D.L. Selwood, P. Vallance, J. Pfeilschifter, and A.D. Hingorani	157
Sexually Dimorphic GTP Cyclohydrolase I Gene Expression is Independent of Sex Hormones M. Shimoji, K. Hirayama, and G. Kapatos	163
Studies on the Reaction Mechanism of GTP Cyclohydrolase I N. Schramek, A. Bracher, G. Bader, M. Fischer, G. Auerbach, M. Gütlich, W. Eisenreich, R. Huber and A. Bacher	169
Site-Directed Mutagenesis of Residues in the Active Site of Sepiapterin Reductase K. Fujimoto, T. Nonaka, M. Sakurai and S. Katoh	175
Determination of Residues Of Sepiapterin Reductase Phosphorylated by Ca²⁺/Calmodulin-Dependent Protein Kinase II K. Fujimoto, M. Sakurai and S. Katoh	181

The Interaction of GTP Cyclohydrolase I and GTP Cyclohydrolase Feedback Regulatory Protein Can be Detected Using the Yeast Two-Hybrid System

L. Swick, K. Hirayama, and G. Kapatos 187

Co-Induction of Tetrahydrobiopterin and Catecholamine Syntheses in V-1-Overexpressing PC12D Cells

T. Suzuki, T. Yamakuni, T. Nagatsu, and H. Ichinose 193

Sepiapterin Administration Raises Tissue BH₄ Levels More Efficiently than BH₄ Supplement in Normal Mice

K. Sawabe, K. Yamamoto, T. Kamata, O.K. Wakasugi and H. Hasegawa ..199

Cells Take up BH₄, Oxidize it, and the Oxidized Biopterin is Preferentially Released

H. Hasegawa, K. Yamamoto, K. Sawabe, Y. Matsushashi, K. Oguro, O.K. Wakasugi and N. Nakanishi 205

4. Pterins in Non-Mammalian Systems

Catecholamines-Up, a Negative Regulator of Tyrosine Hydroxylase and GTP Cyclohydrolase I in *Drosophila Melanogaster*

J.M. O'Donnell, D.G. Stathakis, D. Burton and Z. Chen 211

The Pteridine Pathway in the Zebrafish, *Danio Rerio*: Development in Neural Crest-Derived Cells and its Control by GTP Cyclohydrolase I

I. Pelletier, P. Boyle, T. McDonald, C. Hesslinger, L. Bally-Cuif, and I. Ziegler 217

Pteridine and Nitric Oxide Biosynthesis in *Physarum Polycephalum*

G. Golderer, S. Leitner, C. Wild, P. Gröbner, E.R. Werner, and G. Werner-Felmayer 223

Pteridines and Pigment Granules of Wing Scales Concerned with Sexual Difference in Wing's Capability Reflecting Near-UV Rays in the Japanese Cabbage Butterfly, *Pieris Rapae Crucifora*

M. Nakagoshi, R. Kondo, H. Sawada, S. Takikawa and A. Yoshida 229

Tetrahydrobiopterin, Nitric Oxide Synthesis and cGMP Concentrations in Mutants of *Physarum Polycephalum* with Altered Sporulation Behavior

S. Leitner, G. Golderer, P. Gröbner, G. Werner-Felmayer, and E.R. Werner 235

- BH₄ and NOS are Involved in Light Controlled Development of Sporangiohores in the Fungus *Phycomyces Blakesleeanus***
J. Maier, R. Hecker, P. Rockel, J. Wildt and H. Ninnemann 241

- Determination of Tetrahydropterins as Native Pteridines in Two Microorganisms, *Tetrahymena Pyriformis* and *E. coli***
K. Ikemoto, T. Sugimoto, S. Murata, M. Tazawa, T. Nomura, H. Ichinose, and T. Nagatsu 247

- Identification of the Sulfurtransfer Pathway for the Generation of the Dithiolene Moiety of Molybdopterin in *Escherichia Coli***
S. Leimkühle and K.V. Rajagopalan 253

5. Tetrahydrobiopterin and Endothelial Function

- Tetrahydrobiopterin and Vascular Endothelial Function**
Z.S. Katusic 259

- L-Ascorbic Acid Increases Intracellular Tetrahydrobiopterin Via a Chemical Stabilization and Potentiates Nitric Oxide Synthesis in Endothelial Cells**
R. Heller, A. Unbehaun, B. Schellenberg, B. Mayer, G. Werner-Felmayer, and E.R. Werner 265

- The Redox Status of Bound Pterin Cofactor Determines Whether eNOS Produces NO or Superoxide Anion: [³H]-BH₄ Binding Studies Provide Insights into Vascular Pathophysiology**
C.L. Jones, J. Vásquez-Vivar, B. Kalyanaraman, J.M. Griscavage-Ennis and S.S. Gross 271

6. Clinical Aspects of Pteridines

- Sepiapterin Reductase Deficiency: Molecular Analysis in a New Case Presenting with Neurotransmitter Deficiency Without Hyperphenylalaninemia**
L. Elzaouk, H. Osmani, W. Leimbacher, A. Romstad, J. Friedman, M. Maccollin, B. Thöny, and N. Blau 277

- Molecular Basis of DOPA-Responsive Dystonia**
C. Sumi-Ichinose, F. Urano, M. Kojima, R. Kuroda, H. Shiraishi, Y. Hagino, T. Nagatsu, T. Nomura, H. Ichinose 285

Human Nigrostriatal Dopamine Neurons Express Low Levels of GTP Cyclohydrolase I mRNA K. Hirayama and G. Kapatos	291
Immunosuppressive Effects of the 4-Amino Analogue of Tetrahydrobiopterin E.R. Werner, G. Werner-Felmayer, S. Bahrami, W. Strohmaier, G. Brandacher and R. Margreiter	297
Tetrahydrobiopterin Responsive Hyperphenylalaninemia Without Biopterin Deficiency H. Shintaku, M. Asada, Y. Sawada, and T. Yamano	301
The Fate of Intravenously Administered Tetrahydrobiopterin and its Implications for Heterologous Gene Therapy of Phenylketonuria C.O. Harding, M. Neff, K. Wild, and S. Milstien	305
Influence of Hydrogen Peroxide (H₂O₂) on Pterin Homeostasis in the Depigmentation Disorder Vitiligo K.U. Schallreuter	309
Catechol-O-Methyltransferase Inhibition in the Treatment of Tetrahydrobiopterin Deficiency S. Ponzzone, G. Baglieri, A. Battistoni, C. Peduto, M. Giovannozzi, S. Valenzise, A. Ferraris, A. Martini, and M. Spada	319
Changes in Dihydropteridine Reductase (DHPR) Activity of the Occupationally Lead Exposed Workers A.B.Engin, D.Tuzun, and G.Sahin	329
Clinical Utility of Pteridine Measurement in Cerebrospinal Fluid K. Hyland and L.A. Arnold	335
Effect of Ascorbic Acid in Measurement of Serum Pteridine Concentration T. Kajita, H. Shintaku, Y. Sawada, M. Asada, D. Tachibana, and T. Yamano	341
The Effect of Tetrahydrobiopterin (BH₄) on Sperm Motility H. Shintaku, Y. Sawada, Y. Nakamura, A. Muso, and T. Yamano	345
Tetrahydrobiopterin Deficiency in Diabetic Rats C.J. Meininger, K. Hatakeyama, T.E. Haynes, K.A. Kelley, and G. Wu ...	349

The Effect of Tetrahydrobiopterin (BH₄) on Diabetic Nephropathy in Streptozotocin (Stz) Induced Diabetic Rats

H. Shintaku, M. Imanishi, M. Okumura, S. Fujii, E. Kawai, S. Genba, K. Takahashi, Y. Sawada and T. Yamano 355

Determination of Sepiapterin and Sepiapterin Reductase in Human Skin

H. Rokos, W. Beazley, and K.U. Schallreuter 359

7. Neopterin

Neopterin, an Immunodiagnostic and Oxidative Stress Indicator

G. Neurauter, A. Laich, C. Enzinger, B. Widner, B. Wirleitner, and D. Fuchs 365

Role of Neopterin in Immune Monitoring in Transplant Medicine

T.F. Mueller, S.O. Grebe, and G. Reibnegger 371

Neopterin and 7,8-Dihydroneopterin-Induced Signal Transduction Cascades in Cell Lines

C. Enzinger, B. Wirleitner, C. Lutz, H. Niederegger, G. Böck, G. Baier-Bitterlich and D. Fuchs 377

Determination of Neopterin Levels in Gingival Crevicular Fluid (GCF)

A.B. Engin, T. Baydar, N. Ozmeric, A. Bodur, A. Uraz, K. Eren, and G. Sahin 383

Neopterin and Biopterin Levels in Pregnancy

D. Tachibana, H. Shinataku, H. Fukumasu, S. Yamamasu, Y. Fukumasu, N. Iwanaga, O. Ishiko, Y. Sawada, M. Masada, S. Katoh, K. Yamano, and S. Ogita 387

8. Tetrahydrobiopterin and Cell Death

Tetrahydrobiopterin (BH₄)-Mediated Neuronal Death Following Intrastratial Kainic Acid: Implications for Parkinson's Disease

J.A. Foster and R.A. Levine 393

Inhibition of Oxidative Stress During Developmental Cell Death: Cellular and Behavioral Effects

L. Groc, L. Bezin, H. Jiang, T.J. Hunter, J.A. Foster, and R.A. Levine 399

The Role of Tetrahydrobiopterin (BH₄) in Trophic Factor Withdrawal-Induced Apoptosis in PC12 Cells

H. Jiang, D. Koubi, L. Groc, T.J. Hunter, P.Z. Anastasisdis, A.I. Rodriguez, G.B. Corcoran and R.A. Levine 405

Apoptotic Death of PC12 Cells Induced by Ischemia-Like Conditions is Mediated by Tetrahydrobiopterin (BH₄) Metabolism

D. Koubi, H. Jiang, T.J. Hunter, P.Z. Anastasisdis, A.I. Rodriguez, G.B. Corcoran and R.A. Levine 409

9. Folate and Antifolate Chemistry

New Approaches Towards Inhibitors of Folate-Dependent Enzymes: Rapid Synthesis of 5-Deazapterins from Uracil Derivatives

M.C. Bagley, D.D. Hughes, R. Lloyd, and V.E.C. Powers 415

Solid and Solution Phase Strategies for the Synthesis of Potential Inhibitors of Folate Biosynthesis

C.L. Gibson, P.H. Boyle, D. Guiney, C.R. Hemmer, K. Ohta, S. La Rosa and C.J. Suckling 421

Progress Towards the Synthesis of Pyrimidodiazepine-Based Folates as Potential Inhibitors of Glycinamide Ribonucleotide Formyltransferase

D.L. Parker, D.P. Parker, A.L. Kimball, B.K. Ayida, and P.S. Ray 427

10. Antifolates

Role of P53 Status on Sensitivity to Thymidylate Synthase Inhibitors and Induction of Apoptosis

H.H.J. Backus, H.M. Pinedo, D. Wouters, M.C. Koudijs, C.G. Ferreira, and G.J. Peters 433

Synthesis of N-[4-[(2-Amino-6-Methyl-3,4-Dihydro-4-Oxo-7*h*-Pyrrolo[2,3-*D*]-Pyrimidin-5-*Y*l)Methyl]Benzoyl]-*L*-Glutamic Acid as an Antifolate

A. Gangjee, Y. Zeng, J.J. Mcguire, R.L. Kisliuk, and E. Chu 439

Effect of Bridge Truncation of Classical 2,4-Diamino-5-Substituted Furo [2,3-*D*]Pyrimidine and 2-Amino-4-Oxo-6-Substituted Pyrrolo[2,3-*D*]Pyrimidine on Antifolate Activity

A. Gangjee, Y. Zeng, J.J. Mcguire, and R.L. Kisliuk 445

Selection of Methotrexate-Resistant *Lactobacillus Casei* in the Presence of Folate or 5-Formyl-Tetrahydrofolate Affects the Resistance Mechanism

F. Mandelbaum-Shavit 451

**Molecular Mechanisms of Resistance to Antimalarial Antifolate Drug
Pyrimethamine-Sulfadoxine**

M.A. Nzila 457

**5-Fluorouracil Induction of Fas and Apoptosis in Colon Cancer Patients:
Relation of Clinical Outcome with Thymidylate Synthase, Mcl-1 and Rb**
G.J. Peters, H.H.J. Backus, D.F. Dukers, C.J. Van Groenigen, W. Vos, E
Bloemena, D. Wouters, J.M.G.H. Van Riel, K. Smid, and H.M. Pinedo ... 461

**Synthesis of 2- or 4-Seleno Analogues of dUMP and FdUMP, and the
Corresponding Nucleosides. Interactions with Mammalian Tumor
Thymidylate Synthase of the Selenonucleotides and Inhibition of Tumor
Cell Growth by the Selenonucleosides**

A. Miazga, B. Golos, Z. Zielinski, J. Ciesla, W. Rode, K. Felczak, K.
Wyszynska, and T. Kulikowski 467

**Induction of Resistance to the Multi-Targeted antifolate MTA (Ly231514)
in Widr Human Colon Cancer Cells**

J. Sigmoid, H.H.J. Backus, D. Wouters, G. Jansen, and G.J. Peters 473

11. Folate: One Carbon Metabolism Enzymes

**Mutational Studies of an Essential Glutamate Residue in *Escherichia coli*
Folypolyglutamate Synthetase with a Role in ATP Binding**

Y. Sheng, Y. Shen, and A.L. Bognar 479

**Rapid Purification of the T-Protein of the Glycine Cleavage System from
Rabbit Liver**

M.C. Anguera and P.J. Stover 485

Effects of Cellular Glycine on Cell Proliferation

A.K. Herbig, S. Girgis, and P.J. Stover 491

**Microarray Analysis of Genes Induced by Methionine Starvation
and Growth on Different Sulfur Sources in Yeast**

A. Bognar, P. Jorgensen, and M. Tyers 495

12. Folate Enzymes: Dihydrofolate Reductase and Thymidylate Synthase

**Gene Structure and Expression of *Trichinella spiralis* Thymidylate
Synthase**

M. Dabrowska, E. Jagielska, A. Plucienniczak, J. Kwiatowski, and W. Rode	501
Lack of Mutation of L1210 Thymidylate Synthase with Altered Sensitivity to FdUMP Inhibition	
J. Ciesla, Z. Zielinski, E. Jagielska, A. Plucienniczak, J.R. Bertino, and W. Rode	507
Enzymes of Thymidylate Biosynthesis in <i>Trichinella pseudospiralis</i> Muscle Larvae and <i>Caenorhabditis elegans</i> Dauer Larvae	
M. Dabrowska, Z. Zielinski, B. Golos, M. Wranicz, and W. Rode	513
Thymidylate Synthase Heterogeneity Assessed by Monoclonal Antibodies	
B. Golos, E. Walajtys-Rode, A. Porebska, J. Ciesla, M. Dabrowska, Z. Zielinski, and W. Rode	519
Structure-Based Modeling of Reversed N9-C10 Bridge Antifols with Human, Pc and Tg DHFR	
V. Cody	525
13. Folate: Methionine Cycle Enzymes	
Regulation of Mammalian Methionine Synthase by B₁₂	
S. Oltean and R. Banerjee	531
Biochemical Studies of Human Methionine Synthase Reductase	
H. Olteanu and R. Banerjee	537
14. Methyltransferases and Methylation Reactions	
Model Studies for the B₁₂ Dependent Methyltransferases	
T. Darbre	543
Betaine-Homocysteine S-Methyl-Transferase (BHMT) Transcription is Inhibited by S-Adenosylmethionine (AdoMet)	
C. Castro, A.P. Breksa, E.M. Salisbury, and T.A. Garrow	549
Can Elevated Plasma Homocysteine Levels Result in the Inhibition of Intracellular Methyltransferases?	
S. Clarke and K. Banfield	557
The Neuropathy of Disturbed Brain Methylation Reactions.	
D.G. Weir, A.M. Molloy, and J.M. Scott	563

Dopamine-Stimulated Solid-State Signaling: A Novel Role for Single-Carbon Folates in Human Attention

R.C. Deth, A. Sharma, and M. Waly 569

15. Folate and Homocysteine and Neural Tube Defects

Is Moderate Hyperhomocysteinemia Due to Folic Acid Depletion Rather than Insufficient Dietary Intake?

C. Enzinger, A. Laich, B. Widner, B. Wirleitner, E. Artner-Dworzak, and D. Fuchs 575

C677t MTHFR Genotype is a Risk Factor for Thromboembolism: Comparison of T Allele Frequency and Homocysteine Level Between Female Thromboembolic and Non-Thromboembolic Vascular Patients, NTD Mothers and Matched NTD Controls

Z Yates and M.D. Lucock 581

Molecular Bases of Hyper-Homocysteinemia Due to Inborn Errors of Folate and Cobalamin Metabolism

D.S. Rosenblatt 587

Vitamin B6 (PLP) and Neural Tube Defects: Is There an Association?

L.A. Afman, N.M.J. Van Der Put, C.M.G. Thomas, F.J.M. Trijbels, and H.J. Blom 593

16. Folate: Analysis and Nutrition

Erythrocyte Folate Levels in Operating Room Personnel

T. Baydar, M. Baydar, and G. Sahin 601

A Human Ileostomy Model to Determine Folate Bioavailability From Food

C.M. Withhöft, L. Johannesson, and M. Jägerstad 609

12 Channel Coulometric Electrochemical Detection for the Identification of Polyglutamate Homology Amongst Cellular Folates

M.D. Lucock, Z. Yates, E. Goodall, and G. Achilli 615

Gastro-Intestinal pH Modulates Facile Interconversion of Native Formylfolates During Absorption

M.D. Lucock, Z. Yates, and A. Cade 619

Control Of Folate Production in Lactic Acid Bacteria by Using Metabolic Engineering

W. Sybesma, M. Starrenburg, I. Mierau, M. Kleerebezem, W.M. De Vos, and J. Hugenholtz 623

17. Folate Transport

Evidence for a Cryptic Gene that Enables *E. coli* to Specifically Transport Folate Analogs

J.M. Green and B.P. Nichols 631

Folate Transport Abnormalities and Congenital Defects

R.H. Finnell, B. Wlodarczyk O. Spiegelstein, A. Triplett, and J. Gelineau-Vanwaes 637

Role of Multidrug Resistance Proteins (MRP) in Resistance to Antifolates and Folate Homeostasis

G. Jansen, Y.G. Assaraf, D.G. Priest, M. Bunni, M. Kool, I. Kathmann, J.H. Hooijberg, R.J. Scheper, B.A.C. Dijkmans, G.J. Kaspers, and G.J. Peters . 643

Kinetics Of Reduced Folate Carrier- and Membrane-Associated Folate Receptor-Mediated Transport of Antifolates

R. Mauritz, G.J. Peters, G.A.M. Kathmann, A. Rosowsky, H.M. Pinedo, and G. Jansen 649

Cell Biology and Regulation of the Intestinal Folate Absorption Process

H.M Said 655

PARTICIPANTS 661

INDEX 673

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
Robert Levine
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 B₁₂/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 of 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 B₁₂-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 B₁₂ 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.

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