J. Steroid Biochem. Molec. Biol. Vol. 43, No. 8, pp. 745–749, 1992
Printed in Great Britain.

0960-0760/92 $5.00 + 0.00

CURRENT RESEARCH ON STEROID METABOLISM: TRANSITION FROM BIOCHEMISTRY TO MOLECULAR-CELL BIOLOGY

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INTRODUCTION

The steroid structure forms the nucleus of a large number of natural compounds including cholesterol, steroid hormones, (androgens, estrogens, progestogens, glucocorticoids, mineralocorticoids), vitamin D and bile acids. The levels of these compounds fluctuate in the body to regulate diverse physiological processes including, reproduction, development, tissue growth and differentiation, immune responses, digestion, glucose and mineral metabolism, and behavior.

Current biochemical research on steroids has two distinct facets: (A) study of steroid metabolism—answering the questions of where and how steroids are synthesized, modified and inactivated and (B) study of steroid mechanism of action—answering the questions of how steroids exert their effects in different cells. The *First International Symposium on A Molecular View of Steroid Biosynthesis and Metabolism* was convened on 14–17 October 1991 at Kibbutz Ramat Rachel (Jerusalem, Israel) as a forum for recent research on steroid metabolism (Fig. 1). This special issue includes reviews and research reports presented in this symposium. The papers were written following the discussions at the meeting. All the papers were reviewed, revised and updated to Spring 1992. In this introductory article I shall summarize the recent achievements in this field and the reasons for convening this special forum.

HISTORICAL PERSPECTIVE

In historical perspective the study of steroid hormone metabolism can be viewed in four stages:

1. Endocrine physiology: identification of the tissues and cells that are involved in steroid metabolism and the hormonal factors that regulate their function.
2. Biochemistry: identification and measurement of steroid metabolites by increasingly sensitive assays, and the characterization of the enzymes that synthesize these metabolites.
3. Molecular biology: isolation of the cDNAs and genes encoding the enzymes, and study of the structure and regulation of expression of these genes and the corresponding enzymes.
4. Molecular-cell biology: study of the interrelationship of the structural, enzymatic and regulatory molecules in the steroidogenic cells.

These stages proceeded with some overlap but had peak research activities in successive periods. The transition from one stage to the next was dependent on the achievements of the previous stage and the emergence of new techniques. Current research is at the peak of stage 3 and the beginning of stage 4.

RECENT RESEARCH ACHIEVEMENTS

During the past several years we have seen phenomenal advances in our understanding of the structure, function and regulation of the enzymes that metabolize steroids. The enzymes and/or

Proceedings of the First International Symposium on A Molecular View of Steroid Biosynthesis and Metabolism, Jerusalem, Israel, 14–17 October 1991.

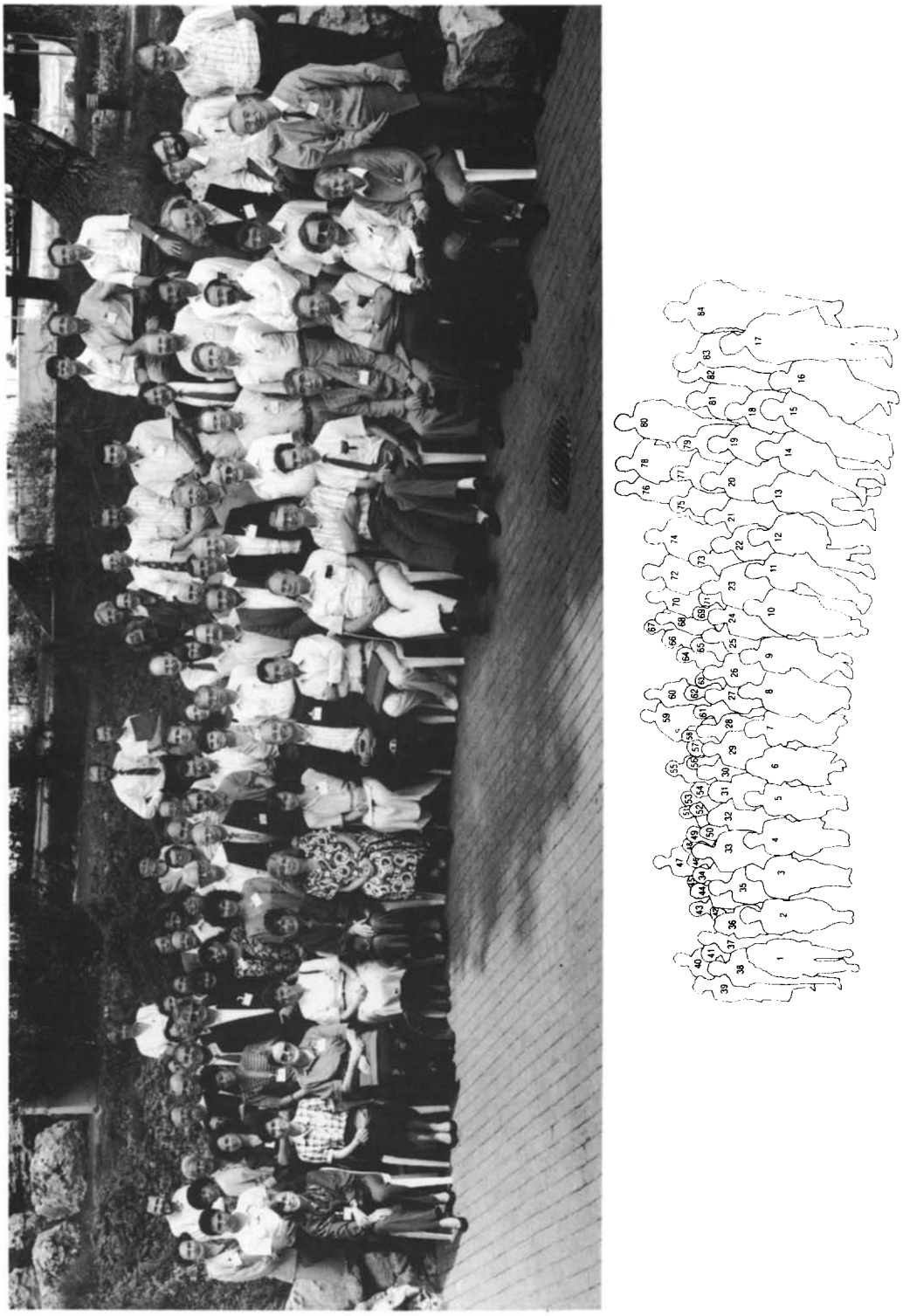

Fig. 1—*legend opposite.*

the corresponding cDNAs for nearly all the major steroidogenic reactions have been isolated. These enzymes can be grouped in three categories:

(A) *P*450 type enzymes and their ancillary electron transfer proteins.
(B) Steroid dehydrogenases.
(C) Steroid conjugating enzymes.

The isolation of these enzymes and/or their cDNAs provided molecular tools, e.g. antibodies and cDNA probes, to pave the way for the following breakthroughs in current research:

- Determination of the number of the genes coding for the different enzymes and the chromosomal location of the genes.
- Analysis of the tissue specificity of expression of the genes.
- Determination of the gene, mRNA and amino acid sequences of the enzymes.
- Expression of cDNAs in cells that do not normally express these enzymes and the study of their enzymatic properties in the absence of other steroidogenic enzymes.
- Analysis of the structure of the enzymes by mutagenesis of cloned cDNAs and engineering of new enzymes with altered substrate and product specificities.
- Demonstration that the capacity for steroid synthesis is determined by major developmental and hormonal regulation of the enzymes at the level of gene transcription.
- Identification of the intracellular mediators of peptide hormone action that affect enzyme gene transcription.
- Isolation of the transcription factors responsible for tissue specific expression and hormonal regulation of the genes.
- Identification of mutations in enzyme genes that cause genetic disorders of steroid metabolism.

Many of these discoveries have broad significance beyond the field of steroids. The determination of the gene sequences revealed new families of enzymes with a multitude of members and increased our understanding of their structure and function. The study of intracellular mediators of hormone action and gene transcription factors are opening new vistas in cell and molecular biology.

(Fig. 1 Opposite)

Fig. 1. Participants of *The First International Symposium on A Molecular View of Steroid Biosynthesis and Metabolism* at Kibbutz Ramat Rachel. 1. Nava Dekel (Israel), 2. Bon-chu Chung (Taiwan, Rep. of China), 3. Tamara Hudnik-Plevnik (Yugoslavia), 4. Rita Bernhardt (Germany), 5. Anita H. Payne (U.S.A.), 6. Fortune Kohen (Israel), 8. Abraham Amsterdam (Israel), 9. Mordechai Shemesh (Israel), 10. John B. Schenkman (U.S.A.), 11. Michael R. Waterman (U.S.A.), 12. Yves Tremblay (Canada), 13. Yutaka Shizuta (Japan), 14. Fernand Labrie (Canada), 15. Ariel Rosler (Israel), 16. Sybille G. E. Meyer (Germany), 17. Tsuneo Omura (Japan), 18. Van Luu-The (Canada), 19. Perrin C. White (U.S.A.), 20. Peter J. Hornsby (U.S.A.), 21. William E. Rainey (U.S.A.), 22. Alex Tsafriri (Israel), 23. Israel Hanukoglu (Israel), 24. Jaime Kapitulnik (Israel), 25. Gerd-Rudiger Janig (Germany), 26. Kyuichiro Okuda (Japan), 27. Diane S. Keeney (U.S.A.), 28. Jean-Guy Lehoux (Canada), 29. John C. Loper (U.S.A.), 30. Peter W. Jungblut (Germany), 31. Susan Gilman (Israel), 32. Paola Belvedere (Italy), 33. Jan-Ake Gustafsson (Sweden), 34. Yoram Salomon (Israel), 35. Rina Meidan (Israel), 36. Luisa Dalla Valle (Italy), 37. Ronnie J. Barkey (Israel), 38. Mehmet E. Dokucu (Turkey and U.S.A.), 39. Aliza Eshkol (Israel), 40. Eugene Bosmans (Belgium), 41. Michal Lahav (Israel), 42. Muriel Zohar (Israel), 43. Hugo Vanden Bossche (Belgium), 44. Yitshak Koch (Israel), 45. Marit Bakke (Sweden), 46. Toshihiko Yanase (Japan), 47. Tamar Hanoch (Israel), 48. Rachel Catinot (France), 49. Claudia Simontacchi (Italy), 50. Margaret Carey (England), 51. Francois Gasser (France), 52. Lorenzo Colombo (Italy), 53. Peter I. Mackenzie (Australia), 54. Masahiko Negishi (U.S.A.), 55. Revital Rapoport (Israel), 56. Henry J. Barnes (U.S.A.), 57. Bernard P. Schimmer (Canada), 58. David Sklan (Israel), 59. Jerzy Adamski (Germany), 60. Jozef De Boever (Belgium), 61. Keith L. Parker (U.S.A.), 62. Francois Hatey (France), 63. Virginia H. Black (U.S.A.), 64. Colin R. Jefcoate (U.S.A.), 65. Robert C. Tuckey (Australia), 66. Liliane Aflalo (Israel), 67. Peter F. Hall (Australia), 68. Joseph Orly (Israel), 69. James I. Raeside (Canada), 70. Ilan Tur-Kaspa (Israel), 71. Ratimir Klepac (Yugoslavia), 72. Dale B. Hales (U.S.A.), 73. Michael E. Baker (U.S.A.), 74. Antonio Selman (Israel), 75. Walter L. Miller (U.S.A.), 76. Kenneth R. Korzekwa (U.S.A.), 77. J. Ian Mason (U.S.A.), 79. Iruvanti M. Rao (U.S.A.), 80. Evan R. Simpson (U.S.A.), 81. Veli Isomaa (Finland), 82. Kuo-Chi Cheng (U.S.A.), 83. David J. Waxman (U.S.A.), 84. H. James Armbrecht (U.S.A.). (Photo by Joel Fishman.)

A FORUM FOR ENZYMES OF STEROID METABOLISM

The research achievements noted above characterize a mature and rich field of medical and biotechnological importance. Yet, this field is included at most only as a small part in other broader meetings. The broad steroid meetings cover all aspects of steroids and do not concentrate on problems of steroid metabolism. The steroidogenic *P*450s were generally discussed only briefly in *P*450 meetings dominated by the field of drug metabolizing enzymes. There was no specific forum for steroid dehydrogenases, as this area of research only recently started to expand. Although pathways of steroid metabolism include different types of enzymes, these function in concert to produce the steroid output of each tissue. Thus, the division of the field by enzyme type would eliminate discussion of common problems of regulation and integration of steroid metabolism.

In view of the situation described above, this symposium was convened to put enzymes of steroid metabolism at center stage. The symposium was intended to promote exchange of ideas to further research into basic and applied aspects of the structure, function and regulation of the different families of enzymes that metabolize steroids. The symposium was expected to increase understanding of the enzyme families, stimulate characterization and engineering of new enzymes with medical and biotechnological importance, strengthen the integration of the regulatory aspects of steroid biosynthesis and metabolism, and lead to new collaborations among research groups. The logo of the meeting was designed (Fig. 2) to symbolize the major subject of the meeting: steroid structure placed over an ellipsoid projection of the world globe—the globe to signify the international participation at the meeting, and to symbolize the enzymes of steroid metabolism.

The symposium program was strictly focused on studies of steroid metabolism using molecular biological approaches. The initial response to the announcement of the meeting program and to the invitations was very positive (only one of the invited speakers could not accept the invitation). Representatives of the great majority of the laboratories that have contributed to the recent advances noted above attended the symposium. Abstracts originated from 18 different countries (Fig. 3). In addition to the papers included in this issue, many abstracts reported the isolation, characterization, and regulation of new enzymes from various eukaryotic sources, bacteria, and plants.

The success of the symposium lay in the quality and the quantity of new information revealed by the participants. The focused program of the meeting fulfilled a real need in this field. The participants exchanged ideas and research probes and established new collaborations. An indication of the success of the meeting was the decision to convene this symposium every 3 years. Organizational efforts are currently underway to convene the second symposium in the U.S.A.

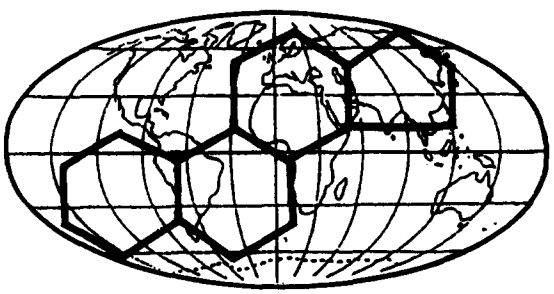

Fig. 2. The logo of *The First International Symposium on A Molecular View of Steroid Biosynthesis and Metabolism.*

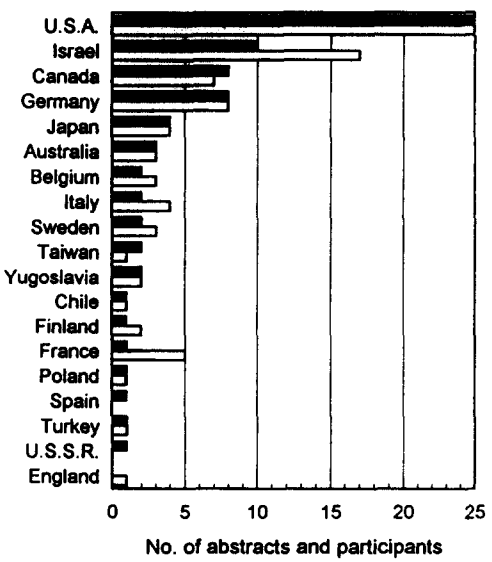

Fig. 3. The countries of origin of the abstracts (closed bars) and the participants (open bars).

Looking to the future, while stage 3 (see above), characterization of the "molecules" of steroid metabolism, continues, the challenge ahead becomes the elucidation of the "dynamics" of regulation and interactions of the molecules in the steroidogenic cell. We currently understand only some of the links in the chain of events that lead from hormone action on the cell surface to changes in gene expression and steroid secretion. This knowledge is still far from being able to describe in molecular detail many fundamental processes, e.g. cholesterol transfer to mitochondria, transfer of cell surface signals to nucleus and other organelles in the cell, and specific activation of gene transcription. The study of these processes will continue to illuminate the workings of steroidogenic as well as eukaryotic cells in general.

Acknowledgements—As the organizers and participants we owe the greatest debt of gratitude to Serono Symposia in Rome, Italy, under the directorship of Dr Sergio Rossetti, without whose prompt and strong support this symposium would not have been possible. We are also grateful to The Maurice and Gabriela Goldschleger Conference Foundation of the Weizmann Institute of Science, Rehovot, Israel, and the Janssen Research Foundation, Beerse, Belgium for providing support that enabled participation of many young scientists in the symposium. The members of the organizing committee, Drs Fortune Kohen, John B. Schenkman, and Michael R. Waterman, and Dr Alvin M. Kaye provided most valuable advice and help in the organization of the symposium. We are grateful to Ms Simonetta Carbonetti and Ms Sarah Wolfeiler for the technical aspects of symposium organization, and to Mr Hillel Fine for the hospitality and the service at Mitzpeh Rachel Guest House of Kibbutz Ramat Rachel. We also thank the reviewers of the manuscripts, whose names are listed on a preceding page, and Ms A. Lane of Pergamon Press for their contribution in the preparation and publication of this symposium.