RESPIRATORY DISTRESS SYNDROME

Edited by
CLAUDE A. VILLEE
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ACADEMIC PRESS, INC.
New York and London 1973
A Subsidiary of Harcourt Brace Jovanovich, Publishers

ACADEMIC PRESS, INC.
111 Fifth Avenue, New York, New York 10003

United Kingdom Edition published by
ACADEMIC PRESS, INC. (LONDON) LTD.
24/28 Oval Road, London NW1

Library of Congress Cataloging in Publication Data
Main entry under title:

Respiratory distress syndrome.

Proceedings of a conference held at Endicott House, Massachusetts Institute of Technology, May 4–6, 1973.
1. Respiratory distress syndrome–Congresses. I. Villee, Claude A., ed. II. Villee, Dorothy B., ed. III. Zuckerman, James, ed. [DNLM: 1. Respiratory distress syndrome–Congresses. WS420 S993r 1973]
RC732.R47 618.9'2011 73-807
ISBN 0–12–722350–9

PRINTED IN THE UNITED STATES OF AMERICA

LIST OF PARTICIPANTS

Mary Ellen Avery, M.D., Department of Pediatrics, McGill University, Montreal 108, P.Q., Canada

Will R. Blackburn, M.D., Department of Pathology, College of Medicine, The Pennsylvania State University, The Milton S. Hershey Medical Center, Hershey, Pennsylvania 17033

Konrad E. Bloch, Ph.D., Department of Biochemistry, Harvard University, Cambridge, Massachusetts 02138

David Charles, M.D., Department of Obstetrics and Gynecology, Boston University School of Medicine, Boston University Medical Center, Boston, Massachusetts 02118

John A. Clements, M.D., School of Medicine, Cardiovascular Research Institute, University of California, San Francisco, California 94122

William D. Cochran, M.D., Department of Pediatrics, Harvard Medical School, Boston, Massachusetts 02115

Shirley G. Driscoll, M.D., Department of Pathology, Harvard Medical School, Boston, Massachusetts 02115

Philip M. Farrell, M.D., Ph.D., Pediatric Metabolism Branch, National Institute of Arthritis, Metabolism, and Digestive Diseases, National Institutes of Health, Bethesda, Maryland 20014

Louis Gluck, M.D., Department of Pediatrics, Division of Perinatal Medicine, School of Medicine, University of California, San Diego, La Jolla, California 92037

Ross N. Howie, M.B., M.R.A.C.P., Department of Pediatrics, University of Auckland, Auckland, New Zealand

John B. Josimovich, M.D., Department of Obstetrics and Gynecology, The University of Pittsburgh, Pittsburgh, Pennsylvania 15213

Manfred L. Karnovsky, Dr. Phil., Department of Biological Chemistry, Harvard Medical School, Boston, Massachusetts 02115

George R. Kerr, M.D., Department of Nutrition, Harvard University, School of Public Health, Boston, Massachusetts 02115

Brian Little, M.D., Department of Obstetrics and Gynecology, Case Western Reserve University, Cleveland, Ohio 44106

Jerold F. Lucey, M.D., Department of Pediatrics, College of Medicine, The University of Vermont, Burlington, Vermont 05401

Ines Mandl, Ph.D., Department of Obstetrics and Gynecology, College of Physicians and Surgeons, Columbia University, New York, New York 10032

Edward J. Masoro, Ph.D., Department of Physiology and Biophysics, The Medical College of Pennsylvania, Philadelphia, Pennsylvania 19129

Matthew S. Meselson, Ph.D., Department of Biology, Harvard University, Cambridge, Massachusetts 02138

Alfred P. Morgan, M.D., Department of Surgery, Harvard Medical School, Boston, Massachusetts 02115

Thomas E. Morgan, M.D., School of Medicine, Office of the Dean, University of Washington, Seattle, Washington 98195

Richard L. Naeye, M.D., Department of Pathology, College of Medicine, The Pennsylvania State University, The Milton S. Hershey Medical Center, Hershey, Pennsylvania 17033

Nicholas M. Nelson, M.D., Department of Pediatrics, College of Medicine, The Pennsylvania State University, The Milton S. Hershey Medical Center, Hershey, Pennsylvania 17033

Miles J. Novy, M.D., Oregon Regional Primate Research Center, Beaverton, Oregon 97005

Kenneth J. Ryan, M.D., Department of Obstetrics and Gynecology, Harvard Medical School, Boston, Massachusetts 02115

Dinesh O. Shah, Ph.D., Department of Chemical Engineering, College of Engineering, University of Florida, Gainsville, Florida 32601

John C. Sinclair, M.D., Department of Pediatrics, McMaster University, Hamilton, Ontario, Canada

Clement A. Smith, M.D., Editorial Office, Pediatrics, The Children's Hospital Medical Center, Boston, Massachusetts 02115

Samuel Solomon, Ph.D., Royal Victoria Hospital, McGill University, Montreal 112, P.Q., Canada

H. William Taeusch, Jr., M.D., Department of Pediatrics, McGill University, Montreal 108, P.Q., Canada

William H. Tooley, M.D., Department of Pediatrics, School of Medicine, University of California, San Francisco, California 94122

John E. A. Tyson, M.D., Department of Gynecology and Obstetrics, The Johns Hopkins University School of Medicine, Baltimore, Maryland 21205

Claude A. Villee, Ph.D., Department of Biological Chemistry, Harvard Medical School, Boston, Massachusetts 02115

Dorothy B. Villee, M.D., Department of Pediatrics, Harvard Medical School, Boston, Massachusetts 02115

George Weber, M.D., Department of Pharmacology, Indiana University School of Medicine, Indianapolis, Indiana 46202

Paul A. Weinhold, Ph.D., Veterans Administration Hospital, 2215 Fuller Road, Ann Arbor, Michigan 48105

Richard D. Zachman, M.D., Ph.D., Wisconsin Perinatal Center, University of Wisconsin, Madison, Wisconsin 53715

James E. Zuckerman, Jr., M.D., Department of Obstetrics and Gynecology, Harvard Medical School, Boston, Massachusetts 02115

PREFACE

Respiratory Distress Syndrome is an important threat to the prematurely born infant and a major cause of perinatal mortality. In recent years research has turned up a number of clues regarding its etiology, diagnosis, treatment, and prevention. Thus, the time appeared to be ripe to bring together a group of biochemists, biophysicists, physiologists, pathologists, pediatricians, and obstetricians to reassess our understanding of this clinically important disease. An effort was made to review what is known about the biochemical and physiological alterations basic to the disease, to evaluate the possibility that the disease may be caused by the lack of an enzyme or by the failure of an enzyme system to develop at the appropriate time, and to explore the possibility of inducing the deficient enzyme by treating the individual with a glucocorticoid.

Some 35 investigators met at Endicott House, Massachusetts Institute of Technology, Dedham, Massachusetts, on May 4-6, 1973. During these days there was a lively interchange of ideas and a searching examination of the current concepts regarding this condition. This book includes the papers presented at the conference together with the discussion that followed each paper. The papers and discussions ranged over topics such as the biophysical basis of surface phenomena, the enzymatic pathways resulting in the synthesis of phospholipids, especially saturated phosphatidylcholine, the basis of enzyme induction by steroid hormones, the nature and properties of lung surfactant, the determination of L/S ratios and their use in predicting the possibility of RDS in the newborn, the cell type or types involved in the synthesis of surfactant, the nature of the specific protein synthesized by the lung, and the etiology and epidemiology of RDS, together with its treatment by continuous positive airway pressure.

ACKNOWLEDGMENTS

The organizers of the conference would like to express their appreciation to each of the participants for his part in making the conference a success, to Dr. Virginia Apgar and the National Foundation for a grant defraying part of the expenses of the conference, to Dr. Matthew Meselson for a generous gift in support of the conference, to Miss Mimi Pierson and the staff of Endicott House for their excellent service, to the Ross Laboratories, Columbus, Ohio for a grant toward preparation of the manuscripts for publication, and especially to Hazel Cox who cheerfully and beautifully typed the camera-ready copy of the manuscript. We also thank Dr. Will Blackburn, Hershey Medical Center, Pennsylvania State University, for granting permission to use the electron micrograph shown on the jacket.

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RESPIRATORY DISTRESS SYNDROME: STATE OF THE ART

Mary Ellen Avery, M.D.
Department of Pediatrics, McGill University,
Montreal Children's Hospital, Montreal, P.Q.

Were I speaking to any other group about hyaline membrane disease, I would doubtless be quoting the work of many in this audience. Thus, this assignment poses a considerable constraint, one aspect of which is, at least the need to quote you correctly. I shall avoid the temptation of an historical approach, which always provides some comfort because one can state facts without necessarily being a critic. Rather I choose the "high risk" approach, which is to try to assign observations and measurements to be found in the published literature into one of three categories; Certain, Probable, or Possible. Perhaps the only point of absolute certainty is that however I arrange the observations, the result will be controversial. Indeed, over the years I have moved findings from one column to the other, sometimes for reasons of increasing certainty, sometimes for reasons of increasing doubt.

My defense of this approach to an interdisciplinary meeting concerning a disease is to admit that we can now know some things for certain, because we have the tools, and the experimental method with which to use them. Within the limits of our measurements and our comprehension we can assert that some points are now accepted by everyone. An entry into the probable column indicates my own desire for further confirmation, or explanation, or precision, or a larger experience. After all, $p < 0.05$ only indicates that the odds are great that the observations will be reproducible! I have included a category called possible, because occasionally an unusual observation is published that may or may not be reproducible or significant. Changes in the dorsal vagal nuclei, for example, could indicate a central neural basis for some of the pulmonary disturbances; or

evidence of pepsinogen in lungs postmortem could mean aspiration, or alternatively, pepsinogen-like compounds in normal lung.

Surely we have a number of answers to the kinds of questions asked a decade ago about this disorder; we also have a number of new questions that arise in part from some of the previous answers. Now to the construction of the three columns of information (Table I).

If I were to list the critical unanswered questions (in the hope that some of them might be answered by participants in this conference) they would be as follows:

1) Why does the occasional term or even post-term infant have hyaline membrane disease?
2) What spares the occasional 800 gram infant who escapes the problem?
3) What are the conditions that optimize alveolar type II cell function with respect to surfactant synthesis and secretion?
4) What regulates surfactant production and turnover?

In closing, I would like to invite your participation in the game of lateral movement. Some of the evidence you are about to present may make it necessary to reconstruct these columns by the end of the conference. I hope the equilibrium will be tilted to the left rather than right, for the lives of a good many prematurely born infants depend on our ascertaining the truth about their problems. Armed with careful observations and measurements, we shall be in the best position to provide life-saving treatment.

TABLE I

CERTAIN	PROBABLE	POSSIBLE
-- worldwide (1)	-- males > females (1)	-- maternal diabetes predisposes (1)
-- prematurity predisposes (1, 2)	-- 2nd born twin at greater risk (3)	-- maternal hemorrhage predisposes (1)
CLINICAL		
-- onset near time of birth (1)	-- Sparing effect (4, 5)	-- familial predisposition (6)
-- 3-5 day course to death or recovery (1)	maternal toxemia	
-- retractions, tachypnea	small-for-date	-- late pulmonary sequelae in survivors (7)
-- cyanosis (1)	premature rupture of membranes	
-- C. Section without labor predisposes (2)		
PATHOPHYSIOLOGY		
-- Right-to-left shunts (8)	-- Total serum proteins ↓ (14)	
-- Reduced lung compliance (9)	-- α, antitrypsin ↓ (15, 16)	-- Lung hypoperfusion (12)
-- Reduced FRC (9, 10)	-- Fibrinolysins ↓ (17, 18)	
-- Reduced effective pulm. blood flow (12)	-- Peripheral edema (19, 21)	-- Pulmonary edema (22)
-- Low systemic blood pressure (8, 11)	-- Poor renal perfusion (20)	
-- Metabolic acidosis (13)		
PATHOLOGY		
-- Poor lung distensibility (9)	-- osmiophilic bodies reduced early, increased later (25, 26, 38)	-- pepsinogen found in lung (27)
-- Poor stability (atelectasis) (9)		
-- Decr. saturated phospholipids (23)		
-- Membrane contains fibrins and cellular products (24)		
-- Injury to epithelial cells (24)		
ETIOLOGY		
-- Surfactant deficiency during disease	-- Surfactant deficiency primary (in utero)	-- Surfactant synthesis impaired or destruction ↑
-- Evidence - effectiveness of continuous distending airway pressure (28, 29)	Evidence	
	1. Predictability of L/S ratio (30, 31)	
	2. Low corticoids in cord blood of infants at risk (32)	-- Autonomic dysfunction (35)
	3. Maternal corticoid administration protects the infant (36)	
	4. Animal studies. Longer survival rabbits after corticoids (37)	

REFERENCES

1. M.E. Avery, The Lung and Its Disorders in the Newborn Infant, W.B. Saunders Company, Philadelphia, 2nd Ed., (1968).
2. J. Fedrick and N.R. Butler, Lancet II, 768, (1972).
3. J. Rokos, O. Vaeusorn, R. Nachman, and M.E. Avery, Pediatrics 42, 204, (1968).
4. E.R. Alden, T. Mandelkorn, D.E. Woodrum, et al., Pediatrics 50, 40, (1972).
5. L. Gluck, M.V. Kulovich, and J.B. Gould, Pediatric Research 6, 409, (1972) (abst.).
6. S.N. Graven and H.R. Misenheimer, Am. J. Dis. Child. 109, 489, (1965).
7. F.M. Shepard, R.B. Johnston, E.C. Klatte, H. Burko, and M. Stahlman, New Eng. J. Med. 279, 1063, (1968).
8. M. Stahlman, W.J. Blankenship, F.M. Shepard, J. Gray, W.C. Young, and A.F. Malan, Biol. Neonate 20, 300, (1972).
9. I. Gribetz, N.R. Frank, and M.E. Avery, J. Clin. Invest. 38, 2168, (1959).
10. E. Bancalari, O.L. Garcia, and M.J. Jesse, Pediatrics 51, 485, (1973).
11. G. Wallgren, J.S. Hanson, B.S. Tabakin, N. Raiha, and E. Vapaavuori, Acta Pediat. Scand. (Suppl.) 179, 69, (1967).
12. J. Chu, J.A. Clements, E.K. Cotton, M.H. Klaus, A.Y. Sweet, and W.H. Tooley, Pediatrics (Suppl.) 40, 709, (1967).
13. R. Usher, Pediatrics 32, 966, (1963).
14. R.D. Bland, New Eng. J. Med. 287, 9, (1972).
15. R.K. Mathis, E.F. Freier, C.E. Hunt, W. Krivit, and H.L. Sharp, New Eng. J. Med. 288, 59, (1973).
16. R.V. Kotas, L.E. Fazen, and T.E. Moore, J. Pediat. 81, 593, (1972).
17. E.A. Samartzis, C.D. Cook, and A.J. Rudolph, Acta Pediat. 49, 727, (1960).

18. C.M. Ambrus, D.H. Weintraub, D. Dunphy, J.E. Dowd, J.W. Pickren, K.R. Niswander, and J.L. Ambrus, Pediatrics 32, 10, (1963).
19. O. Celander, in J.H.P. Jonxis, H.K.A. Visser, and J.A. Troelstra (eds.), The Nutricia Symposium on the Adaptation of the Newborn Infant to Extrauterine Life, Chas. C. Thomas, Springfield, (1964).
20. A.C. Allen and R. Usher, Pediat. Res. 5, 345, (1971).
21. J.M. Sutherland, T.E. Oppe, J.F. Lucey, and C.A. Smith, Am. J. Dis. Child. 98, 24, (1959).
22. J.M. Lauweryns, Human Pathology 1, 175, (1970).
23. G.W. Brumley, W.A. Hodson, and M.E. Avery, Pediatrics 40, 13, (1967).
24. R.A. Barter and T.G. Maddison, Arch. Dis. Child. 35, 460, (1960).
25. M. Campiche, M. Jaccottet, and E. Juillard, Ann. Pediat. 199, 74, (1962).
26. J.U. Balis and P.E. Conen, Lab. Invest. 13, 1215, (1964).
27. A.J. McAdams, R. Coen, L.I. Kleinman, R. Tsang, and J. Sutherland, Am. J. Path. 70, 277, (1973).
28. G.A. Gregory, J.A. Kitterman, R.H. Phibbs, et al., New Eng. J. Med. 284, 1333, (1971).
29. V. Chernick and D. Vidyasagar, Pediatrics 49, 753, (1972).
30. L. Gluck, M.V. Kulovich, R.C. Borer, P.H. Brenner, G.G. Anderson, and W.N. Spellacy, Am. J. Obstet. Gynec. 440, (1971).
31. J.A. Clements, A.C.G. Platzker, D.F. Tierney, C.J. Hobel, R.K. Creasy, A.J. Margolis, D.W. Thibeault, W.H. Tooley, and William Oh, New Eng. J. Med. 286, 1077, (1972).
32. B.E.P. Murphy and Robert C. Diez d'Aux, J. Clin. Endocrin. & Metab. 35, 678, (1972).
33. J.A. Lemons and R.B. Jaffe, Am. J. Obst. Gynec. 115, 233, (1973).
34. W.N. Spellacy, W.C. Buhi, F.C. Riggatt, and R.N. Holsinger, Am. J. Obst. Gynec. 115, 216, (1973).

35. S. Buckingham and S.C. Sommers, Am. J. Dis. Child. 99, 216, (1960).
36. G.C. Liggins and R.N. Howie, Pediatrics 50, 515, (1972).
37. H.W. Taeusch, Jr., M. Heitner, and M.E. Avery, Am. Rev. Resp. Dis. 105, 971, (1972).
38. G.G.W. Jacobson and D. Gairdner, Archives of Dis. in Childh. 45, 289, (1970).

DEVELOPMENT OF THE ENZYMES OF LIPID BIOSYNTHESIS IN THE HUMAN FETUS

Edward J. Masoro, Ph.D.
Department of Physiology and Biophysics,
The Medical College of Pennsylvania,
Philadelphia, Pennsylvania

INTRODUCTION

From my initial communication with Dr. Villee, it was my understanding that my assignment was to review our knowledge of the biosynthesis of the pulmonary surfactant phospholipids by the human fetus. A survey of the currently available literature quickly established that information on the development in the human fetus of the enzyme systems involved in the biosynthesis of surfactant phospholipids is scant. I therefore decided first to review the kind of information that would be needed to define completely this biosynthetic function before reviewing the data currently available. Following these two descriptive discussions, a critical assessment of the state of this field at its current stage of development will be undertaken and possible fruitful areas for future research suggested.

THE BIOSYNTHESIS OF PHOSPHOLIPIDS

Although many phospholipids exhibit surfactant properties, this activity principally resides quantitatively in the lecithin molecules (I), dipalmitoyllecithin and l-palmitoyl, 2-myristoyllecithin depicted in Figure I. Therefore, it is on the biosynthesis of these two compounds that our discussion will focus.

Need these two phospholipid molecules be synthesized by the lung or might they be synthesized elsewhere and delivered to the