PHOTOTHERAPY FOR NEONATAL HYPERBILIRUBINEMIA

LONG-TERM IMPLICATIONS

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Phototherapy for Neonatal Hyperbilirubinemia

Long-Term Implications

Editors

Audrey K. Brown, M.D.
Department of Pediatrics
State University of
New York, Downstate
Medical Center

Jane Showacre, Ph.D.
Pregnancy and Infancy
Branch
National Institute of Child Health
and Human Development

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Foreword

Since phototherapy was introduced in the 1950's it has been used in reducing serum bilirubin levels in the newborn infant with hyperbilirubinemia. Currently, the therapy, in various modifications, is widely used in hospitals throughout the Nation. Research has focused largely on serum bilirubin and short-term effects of the treatment. A number of unresolved questions remain about the physiologic mechanisms invoked by light and the sequelae to phototherapy, both acute and long-term in the human infant. The National Institute of Child Health and Human Development has sought to further stimulate the interest of investigators in these questions. This conference, convened April 24–26, 1974, at the National Institutes of Health, Bethesda, Md., is part of the effort. The contributions of diverse fields to the problem are evident in the presentations of the distinguished clinical and basic scientists who attended. It is our hope that these proceedings will further the concerted studies of the pediatrician, biochemist, physicist, and photobiologist and bring us closer to an optimal treatment of jaundice in the newborn.

EILEEN G. HASSELMEYER, Ph.D.
Program Director
Pregnancy and Infancy Branch
National Institute of Child Health and Human Development

Preface

Hyperbilirubinemia of the neonate and the attendant risk of kernicterus remains a major problem in nurseries throughout the world. In recent years there has been growing appreciation of the risk of development of bilirubin encephalopathy at relatively low levels of bilirubin in infants who have associated clinical factors that augment the potential for development of kernicterus, such as hypoxia, acidosis, hypoproteinemia, and hemolysis. Estimates of the number of infants at actual risk of kernicterus are difficult to arrive at, but it is known that about 17 percent of white infants weighing less than 2,500 grams at birth develop serum bilirubin levels in excess of 15 milligrams percent, while 9 percent of black infants of the same weight develop hyperbilirubinemia of this degree. Further, about 3 percent of full-term infants weighing more than 2,500 grams are likely to have serum bilirubin levels in this range, both in the black and the white populations. It has also recently been appreciated that among Mexican Americans and Chinese populations there may be exaggeration of hyperbilirubinemia as compared with black and white populations.

This degree of hyperbilirubinemia has been associated with significant alterations in motor development, and in many instances, particularly in those small infants at greatest risk, bilirubin encephalopathy can, and does, occur at serum bilirubin levels less than 15 milligrams percent. Because the specific risk to an individual infant, at any degree of hyperbilirubinemia, is difficult to assess clinically, there has been a growing tendency to prevent it altogether or to limit its degree. Because of this tendency, the advent of phototherapy for hyperbilirubinemia has been widely accepted as both simple and effective, and only recently has there been appreciation that phototherapy is indeed a "pharmaceutical" agent that should be appraised both for its immediate safety and efficacy and for its possible long-term implications.

Photobiological data from other species indicate that light can be both beneficial and detrimental to many biological processes. The time has come to evaluate the risk-benefit ratio of this modality of therapy for hyperbilirubinemia of the neonate.

There has been little, thus far, to indicate immediate hazards from this form of therapy, but long-term sequelae have not been adequately assessed. A review of the experience of the past 15–17 years with this agent was thought to be useful. In April 1974, the Pregnancy and Infancy Branch

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of the National Institute of Child Health and Human Development sponsored a conference to assess the photobiological processes involved in phototherapy, as well as to document the long-term clinical experience of clinicians from all parts of the world who have used light in the treatment of hyperbilirubinemia since 1958.

The papers and discussions presented in this book by distinguished investigators from the clinical and basic sciences illustrate not only the breadth of the problem, but also the value of an interdisciplinary approach to its resolution.

We thank the participants, as well as our fellow moderators, Dr. Richard Behrman, Dr. Rudi Schmid, and Dr. Jerold Lucey, for their direct contributions to this volume.

AUDREY K. BROWN, M.D.
State University of New York Downstate Medical Center

JANE SHOWACRE, Ph.D.
Pregnancy and Infancy Branch
National Institute of Child Health and Human Development

Participants

Duane Alexander, M.D.
Special Assistant to the Scientific Director
National Institute of Child Health and Human Development
Bethesda, Maryland

Robert J. Anderson, Ph.D.
Senior Scientist
Corporate Research Department
Beckman Instruments, Inc.
Fullerton, California

David W. Bailey, M.D.
Chief, Pediatric Service
National Naval Medical Center
Bethesda, Maryland

Richard E. Behrman, M.D.
Professor and Chairman, Department of Pediatrics
College of Physicians and Surgeons
Columbia University
New York, New York

Paul D. Berk, M.D.
Chief, Section on Diseases of the Liver
Digestive Diseases Branch
National Institute of Arthritis, Metabolism, and Digestive Diseases
Bethesda, Maryland

David R. Bickers, M.D.
Assistant Professor
Department of Dermatology
College of Physicians and Surgeons
Columbia University
New York, New York

Audrey K. Brown, M.D.
Professor, Department of Pediatrics
State University of New York
Downstate Medical Center
Brooklyn, New York

Richard A. Cahill, M.D.
Chief, Pediatric Hematology
National Naval Medical Center
Bethesda, Maryland

Friedrich Karl Friederiszick, M.D.
Direktor der stadtischen Kinderklinik
Krankenstalten Dortmund
Professor, Department of Pediatrics
University of Munster-Westfalia
Dortmund, Germany

Lawrence M. Gartner, M.D.
Associate Professor, Department of Pediatrics
Director, Division of Neonatology
Albert Einstein College of Medicine
Bronx, New York

Leonard C. Harber, M.D.
Professor and Chairman, Department of Dermatology
College of Physicians and Surgeons
Columbia University
New York, New York

Eileen G. Hasselmeyer, R.N., Ph.D.
Program Director, Pregnancy and Infancy Branch
National Institute of Child Health and Human Development
Bethesda, Maryland

J. Woodland Hastings, Ph.D.
Professor, Department of Biology
Harvard University
Cambridge, Massachusetts

Jean Hewitt
Research Associate, College of Medicine
University of Vermont
Burlington, Vermont

Joan E. Hodgman, M.D.
Professor, Department of Pediatrics
Director, Newborn Service
Los Angeles County-University of Southern California Medical Center
Los Angeles, California

Leonard Indyk, Ph.D.
Assistant Professor, Department of Pediatrics
College of Physicians and Surgeons
Columbia University
New York, New York

Barbara Jackson
Biologist, Program Statistics and Analysis Branch
National Institute of Child Health and Human Development
Bethesda, Maryland

L. Stanley James, M.D.
Professor, Department of Pediatrics
College of Physicians and Surgeons
Columbia University
New York, New York

John D. Johnson, M.D.
Assistant Professor, Department of Pediatrics
Stanford University Medical Center
Stanford, California

Lois Johnson, M.D.
Associate Pediatrician, Neonatal Research Section on New Born Pediatrics
Pennsylvania Hospital
University of Pennsylvania
Philadelphia, Pennsylvania

Jaime Kapitulnik, Ph.D.
Research Biochemist, Metabolic Laboratory
Hadassah University Hospital
Jerusalem, Israel

Cyril D. Karabus, M.D., M.R.C.P., F.R.C.P.E.
Senior Lecturer and Pediatrician-Hematologist
Department of Pediatrics
University of Cape Town
Rondebosch, Cape Province
South Africa

Norman Kretchmer, M.D.
Harold K. Faber Professor of Pediatrics
Stanford University
Consultant, National Institute of Child Health and Human Development
Bethesda, Maryland

Emanuel Landau, Ph.D.
Chief, Epidemiologic Studies Branch
Division of Biological Effects
Bureau of Radiological Health
Food and Drug Administration
Rockville, Maryland

Richard D. Landes, M.D.
Chief, Newborn Service
Walter Reed Medical Center
Silver Spring, Maryland

Charles U. Lowe, M.D.
Scientific Director
National Institute of Child Health and Human Development
Bethesda, Maryland

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

Antony F. McDonagh, Ph.D.
Assistant Professor, Department of Pharmaceutical Chemistry
University of California
San Francisco, California

T. Allen Merritt, M.D.
Pediatric Medical Officer, Pregnancy and Infancy Branch
National Institute of Child Health and Human Development
Bethesda, Maryland

Robert W. Miller, M.D.
Chief, Epidemiology Branch
National Cancer Institute
Bethesda, Maryland

José Obes-Polleri, M.D.
Director, Newborn and Premature Center
Ministry of Public Health
Montevideo, Uruguay

Gerald B. Odell, M.D.
Professor, Department of Pediatrics
School of Medicine
Johns Hopkins University
Baltimore, Maryland

Jiro Ogawa, M.D.
Professor and Chairman, Department of Pediatrics
Nagoya City University
Nagoya, Japan

Yunosuke Ogawa, M.D.
Professor, Department of Pediatrics
Nagoya City University
Nagoya, Japan

J. Donald Ostrow, M.D.
Medical Investigator, Veterans Administration
Associate Professor, Department of Medicine
University of Pennsylvania
Philadelphia, Pennsylvania

Paul H. Plotz, Ph.D.
Senior Investigator
Arthritis and Rheumatism Branch
National Institute of Arthritis, Metabolism, and Digestive Diseases
Bethesda, Maryland

Jean-Pierre Ploussard, M.D.
Assistant Chef de Clinique
Hospital Bretonneau
University Paris VII
Paris, France

Rudi Schmid, M.D., Ph.D.
Professor, Department of Medicine
University of California
San Francisco, California

Jane Showacre, Ph.D.
Health Scientist Administrator, Pregnancy and Infancy Branch
National Institute of Child Health and Human Development
Bethesda, Maryland

Calvin C. J. Sia, M.D.
Pediatrician
Childrens Medical Clinic
Honolulu, Hawaii

Kim-Leong Tan, M.B., M.R.C.P.E., D.C.H.
Senior Lecturer, Department of Pediatrics
Faculty of Medicine
University of Singapore
Singapore

Thomas P. Vogl, Ph.D.
Adjunct Professor, Radiation Physics
Department of Radiology
College of Physicians and Surgeons
Columbia University
New York, New York

Wolf W. Zuelzer, M.D.
Director, Children's Research Center
Children's Hospital of Michigan
Detroit, Michigan

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PHYSICAL SCIENCE APPROACHES TO PROBLEMS OF PHOTOTHERAPY

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Purpose of the Conference

Audrey K. Brown

Since 1958, when Cremer first described the effect of light on serum bilirubin levels in newborn infants, phototherapy has been widely employed both to prevent neonatal hyperbilirubinemia as well as to control it.

Recognizing the widespread use of phototherapy in nurseries, staff of the National Institute of Child Health and Human Development (NICHD) in 1972 discussed with members of the Perinatal Biology and Infant Mortality Research and Training Committee means by which the NICHD might seek and offer support for solutions to questions arising in the use of phototherapy to control and treat hyperbilirubinemia in the neonatal period. The conference reported in this book is a direct outgrowth of a recommendation from that Committee that an international interdisciplinary conference be organized at which physicians and other scientists, long active in the field of phototherapy or photobiology, would be asked to share their experiences. It was hoped that through this means insight would be gained into the questions arising concerning long-term implications regarding safety. It was recognized that the data available would be based, in most instances, on the use of phototherapy without accurate information concerning the dose of irradiance. Nevertheless, the Committee felt that this large body of experiential data should not be lost.

The recent conferences organized by the National Academy of Sciences in Washington (February 1973) and by the National Foundation in Jerusalem (March 1974) did not attempt to include this particular body of clinical data, which would of necessity also encompass some anecdotal information. Further, it was felt that a vast new body of information was emerging concerning light biology and light physics that ought to be shared further with the medical community that was applying light therapy to infants.

In preparation for this conference, the NICHD sought to identify long-term studies of phototherapy that might have been performed anywhere in the world since the introduction of this modality to treatment for neonatal hyperbilirubinemia in 1958. We endeavored to include in this conference the majority of long-term studies in which the experimental design offers insight into any potentially detrimental effects of phototherapy.

Physicians with such long-term studies of infants receiving phototherapy were given several months in which to organize data in response to specific questions concerning the effects of light. In the efforts to identify studies relating to long-term studies, we gratefully acknowledge the assistance of F. Alison, M.D.; Lenore Ballowitz, M.D.; Johan Gentz, M.D.; Wong Hock Boon, M.D.; H. Cardin, M.D.; E. Croso, M.D.; Pamela A. Davies, M.D.; John A. Davis, M.D.; Peter M. Dunn, M.D.; Mario Ferreiro, M.D.; Peter Franke, M.D.; F. K. Friederiszick, M.D.; Eduardo Jurado Garcia, M.D.; H. De V. Hesse, M.D.; C.D. Karabus, M.D.; Jesus Linares, M.D.; José Obes-Polleri, M.D.; Jiro Ogawa, M.D.; S. Onishi, M.D.; Marcello Orzalesi, M.D.; H. D. Petermann, M.D.; Antonio Priolisi, M.D.; F. F. Rubaltelli, M.D.; José Senna, M.D.; K. L. Tan, M.D.; and T. Valaes, M.D.

In 1973 the NICHD appointed an ad-hoc advisory committee on phototherapy composed of pediatricians and others engaged in research in the field. This committee was charged to advise on the need for additional research and to consider experimental protocols designed to meet these needs. A series of meetings followed and led to the issuance of a request for proposals and the support by contract of current studies that seek to answer a number of questions regarding the safety of phototherapy in the treatment of neonatal hyperbilirubinemia.

From the investigations of these committees and from the work of the National Academy of Sciences Committee on Phototherapy in the Newborn, the following was evident:

1. Surprisingly few prospective studies of the safety of phototherapy have been performed, probably because its safety was assumed and there was little clinical appreciation that light might be detrimental.
2. Most studies to date have evaluated the efficacy of phototherapy in preventing hyperbilirubinemia of the premature. Followup was usually confined to the neonatal period. Relatively few studies have analyzed the use of phototherapy to control, rather than prevent, hyperbilirubinemia, and thus far have given insufficient basis for the development of guidelines for the use of light to control already established hyperbilirubinemia, which is of course, its most common use in practice today.
3. Surprisingly, no major studies of phototherapy could be identified concerning the reduction in the incidence of kernicterus through the use of phototherapy.
4. With regard to basic questions concerning the mechanism of action of light, while major advances had been made with regard to our understanding of how light affects bilirubin in vitro, no definite answer was available concerning its major mode of action in vivo.
5. With regard to the minimum "dose" required in vivo to promote most effective clearance of bilirubin, no data were available because in no study was the actual "dose" of light recorded.

Therefore, the conference was devoted to two aspects of phototherapy. The first sessions served the initial purpose of sharing experiences gleaned from the followup studies of infants who received phototherapy several years ago. For this experience we turned to our colleagues from other continents who have employed phototherapy for many years.

The second day considered areas that were largely overlooked in the early years of the use of light, namely, the chemical, physical, and biologic aspects of the interaction of light and man.

At the conclusion of the conference we addressed specific research needs in relation to the safety and efficacy of phototherapy and the problems of neonatal hyperbilirubinemia.

Pharmaceutical Photons

J. W. Hastings

When discussing phototherapy the following question often arises: Does light—to which we are all exposed all of our lives—really penetrate the body? Anyone who has looked carefully knows very well that it does, and one of the nicest ways to visualize this is to look at the painting of the 17th century French artist Georges de la Tour (figure 1). The newborn is certainly more transparent than the virgin.

Indeed if light does have a beneficial effect in phototherapy, it must

FIGURE 1. "The Education of the Virgin," Georges de La Tour (1593–1652). From the Frick Collection, New York.

penetrate, and the fundamental fact is that this light initiates photochemistry.

Gaining knowledge about the photochemical reaction or reactions is the central matter of concern, and it is precisely this challenge that has drawn the attention of so many of us outside of medicine. For as soon as the photon interacts with a molecule, a new chemistry comes into play. A potential drug action is thereby created in situ, wherever it may be that the photon is absorbed. The positive power and potential of such a technique is obviously enormous, in many respects. One can turn the "drug" on and off, administer it at widely different rates—in fact this represents the timed-release drug par excellence. One can build in specificity both chemically and in terms of physical location. Specific wavelengths of light can be aimed at specific chemical targets, excluding others.

But as with all drugs, light should be accorded appropriate respect. The photon that initiates a helpful reaction can equally well initiate a harmful reaction.

Obviously one reason for this special respect in the case of light is that our basic knowledge of photochemistry is still inadequate. I am not talking about applied photochemistry or about working out the messy details of the photochemistry of the cell, with its diverse substances, membranes, and interactions. The photochemistry of the cell is also an unknown, and we will undoubtedly have to get to work on this problem even without a good knowledge of the basic molecular photochemistry. What I refer to is the need for basic knowledge in the field.

Another reason for special caution in using phototherapy is the fact that because we live in light, we tend to think that we need not consider it as hazardous. This clearly is not the case. Pigmentation and other mechanisms to protect against light are abundant in living organisms. Even trees and plants, while they have elegant systems to capture the energy of the photon to fix carbon and thereby provide the nutritional basis for all life, are at the same time provided with protection against the light—they are in effect waging a constant battle against the concurrent destructive effects of light.

The idea that something could have both good and ill effects is not really foreign to us; certain substances, such as trace metals for example, are nutrients at a low concentration but may be toxic at higher levels. The example of oxygen as a toxic substance, while being essential to life, is well known in medicine. Life is believed to have had its origin and early evolution in an oxygen-free atmosphere. With the appearance of oxygen, new and energetically significant biochemical pathways involving oxygen evolved in the organism. But destructive oxidizing species were inevitably produced from the molecular oxygen, and biochemical systems that function to detoxify these occur in all aerobic forms. Catalase and peroxidase destroy H_2O_2. Just recently (1969) it has been shown that *erythrocuprein*, known for some 30 years as a blue cupro protein from the erythrocyte but having no assigned activity or function, is in fact an enzyme—now called

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