THE LUNG AND ITS DISORDERS IN THE NEWBORN INFANT

Fourth Edition

Avery
Fletcher
Williams

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by

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Foreword to the Fourth Edition

The foreword to the first edition of this remarkable book contains almost all the important data about the principal author, Mary Ellen Avery. Since the publication of that volume, Dr. Avery has moved from The Johns Hopkins University School of Medicine, where she was the Eudowood Associate Professor of Pulmonary Diseases of Children and Pediatrician-in-Charge of the Newborn Nurseries at Johns Hopkins Hospital, to McGill University School of Medicine and finally to Children's Hospital Medical Center of Boston, where she is Physician-in-Charge and Thomas Morgan Rotch Professor in Pediatrics of Harvard Medical School.

In this fourth edition, as in the third, Dr. Avery has recruited Dr. Barry Fletcher to bring his expertise in pediatric radiology to this presentation. Dr. Fletcher, who is now Professor of Radiology and Director of the Division of Pediatric Radiology of the University Hospital of Cleveland, has meticulously rewritten, expanded, and updated the sections of the text dealing with the radiologic detection of lung disorders in the newborn.

New to this edition is Dr. Roberta Williams. Dr. Williams, Senior Associate in Cardiology at Children's Hospital Medical Center in Boston, and Assistant Professor of Pediatrics, Harvard Medical School, was added to the team to cover the explosive growth of the group of diagnostic techniques known by the overall term of noninvasive techniques. Dr. Williams is considered by her colleagues in pediatric cardiology to be one of the leading experts in diagnostic ultrasound in evaluation of heart disease in infants. She has revised the sections on the pulmonary vascular bed and pulmonary edema that were written by Dr. Robert Williams in the last edition.

In this fourth edition Dr. Avery, with the assistance of her two coauthors, has completely rewritten this very successful initial volume of the Major Problems in Clinical Pediatrics series.

ALEXANDER J. SCHAFFER, M.D.

Foreword to the First Edition

Everyone who has any interest in neonatology is acquainted with Dr. Mary Ellen Avery's *The Lung and Its Disorders in the Newborn Infant.* This was the original volume in our series entitled *Major Problems in Clinical Pediatrics.* Published in 1964, its excellence was of a quality all our subsequent contributors have tried hard to attain. By 1968 Dr. Avery deemed it outdated, so rapidly had new knowledge in the field accrued, and her second edition became available. Now, five years later, she feels constrained to update it and revise it once more, for the same good reasons.

This time she has enlisted the help of Dr. Barry D. Fletcher. Dr. Fletcher is an Assistant Professor of Radiology at McGill University and Radiologist at the Montreal Children's Hospital. He received his earlier training in the Radiology Department of the Johns Hopkins Hospital, focusing his interest largely upon infants and children. With his expert assistance, the radiographic illustrations, so very important a part of a work of this nature, have been augmented in number, selected with even greater care, and reproduced with more precision.

Again the authors have come up with "the last word" on this subject.

ALEXANDER J. SCHAFFER, M.D.

Preface to the Fourth Edition

A preface allows an author to acknowledge the events that have led to a new edition, to reflect on changing times, to thank the associates who have stimulated thought and made apparent the need for a revision, and to be grateful that a publisher is ready for another gamble.

Who needs a fourth edition? We hope that those who care for newborn infants, those who want to learn more about their many pulmonary problems, and the innately curious will find in these pages a distillate of the literature on this subject that has appeared in journals of many countries and of many specialties in medicine.

We are struck by the phenomenal improvements in diagnosis and treatment of small infants with respiratory insufficiency. Our neonatal intensive care centers are bustling with activity, with ever smaller patients and ever more equipment. This "fine tuning" of care has led to gratifying results, including a 50 per cent reduction in mortality among low birth weight infants in the last decade and even better results on follow-up with respect to reducing morbidity. In some instances, problems can be prevented, such as individualizing the indications for delivery to decrease morbidity among infants of diabetic mothers. In other instances, postnatal maladaptations can be blunted by prenatal interventions such as the administration of glucocorticoids to accelerate lung maturation. Sometimes it is the appropriate use of muscle relaxants to allow more effective mechanical ventilation, of prostaglandin infusions to keep the ductus open, or of prostaglandin inhibitors to accelerate its closure. We are witnessing a new pharmacologic, technologic, diagnostic, and therapeutic milieu that saves lives. In a more sobering vein, we have also seen new problems emerge, such as bronchopulmonary dysplasia (which required a whole new chapter in this edition). And we ponder and try to understand the impact on the psyche of both parent and child as a result of the new environment we have created.

Revising this book has consisted mostly of the inclusion of recent information as well as hundreds of new references; however, some deletions were required — not because the information was incorrect, but because it does not seem appropriate to burden today's student with yesterday's observations when improved technology makes current ones more precise. We can probably never do justice to our predecessors who used the tools at hand to probe the problems they encountered. In some instances, we have chosen to focus on the most recent and relevant studies at the expense of historical completeness, and we therefore offer our apologies to those whose observations appeared in the first three editions but not in this one.

As is true for all books, the authors must call on their own experiences, which consequently reflect some personal biases. In our case, these occurred in a number of different settings: For Dr. Avery, first the nurseries of the Johns Hopkins Hospital from 1959 to 1969; then, from 1969 to 1974, at the Montreal Children's Hospital; and since 1974 at the Boston Hospital for Women, Beth Israel Hospital, and Children's Hospital under the aegis of the Joint Program in Neonatology. Since 1976, Dr. Fletcher has been associated with the intensive care nursery of Rainbow Babies' and Children's Hospital in Cleveland in addition to his previous affiliations at Johns Hopkins and McGill University.

In recognition of the need to expand the section on cardiovascular changes at birth, and to add information concerning the diagnosis and management of the evér more prominent problem of patent ductus arteriosus, we have introduced Dr. Roberta Williams, cardiologist at the Children's Hospital in Boston, as a new coauthor, and in so doing underscore the ever-increasing interdependence of students of the heart and lungs.

Colleagues in neonatology who provide continuing stimulation include Dr. H. William Taeusch, Jr., Director of the Joint Program in Neonatology, and Drs. Ivan Frantz, Michael Epstein, and William Cochran, in charge of newborns at Children's Hospital, Boston Hospital for Women, and Beth Israel, respectively. Drs. Elizabeth Brown, Ann Stark, Bradley Thach, Edward Lawson, David Coulter, Ilene Sosenko, Marie Robert, Van Demottaz, Neil Finer, Saul Adler, David Brown, Margo Cox, Heber Neilsen, John Torday, Vallop Kanjanapone, and Eileen Farrell were the fellows in neonatology who, along with the house staff, deserve most of the credit for providing a high level of care and continuing to investigate the needs of our small patients.

We are further indebted to our many colleagues in obstetrics and pediatric surgery, radiology, and pathology at the Harvard and Case Western Reserve University teaching hospitals who consulted on our patients and whose studies have helped transform the state of the art in these disciplines. They are too numerous to name in this preface, but their contributions are referred to throughout this text.

We are continually mindful of the teamwork required among individuals from various disciplines whose common goal is to meet the special needs of the newborn. The field of nursing in particular has been expanding and has taken on major responsibilities in the care of patients. In addition, we have become more dependent on engineers to design and maintain our equipment and on statisticians to keep us honest and to remind us of the necessity to be precise and quantitative.

Finally we also wish to thank those who were so helpful in preparing the manuscript, especially Joseph P. Molter, who photographed most of the new illustrations, and Dora Staneff, who contributed several new drawings. Bess Ficken and Florence Avitabile did much of the secretarial work, and Heather Carswell provided editorial assistance. Their contributions have been essential and significant.

We hope that all of our colleagues will find this volume a useful reflection of their efforts, and to all of them we extend our thanks for making it possible.

January, 1980

MARY ELLEN AVERY
BARRY D. FLETCHER

Preface to the First Edition

A monograph devoted to one organ at one time of life can be written only if innumerable investigators at the bedside and in the laboratory have directed their attention to the problem over many years. This work is a compilation of the experience in many parts of the world. It follows the publication of textbooks devoted to the newborn infant and his illnesses, upon which I have relied in great measure to provide the background and perspective needed to focus upon the lung. Three books in particular, Clement Smith's *Physiology of the Newborn Infant* (Thomas), William Silverman's *Dunham's Premature Infants* (Hoeber), and Alexander Schaffer's *Diseases of the Newborn* (Saunders), have provided much useful information about newborn infants. Potter's *Pathology of the Fetus and Infant* (Year Book) and Spencer's *Pathology of the Lung* (Macmillan) also furnished a wealth of information and references.

But interest in a subject and desire to assemble information about it could never have come from textbooks alone. Much came from opportunities for clinical and laboratory experience at The Johns Hopkins and Boston Lying-In Hospitals, and in the Department of Physiology, Harvard School of Public Health. But even more came from the stimulation of my teachers. I cannot possibly acknowledge everyone who has helped make this work possible. I cite for special mention Dr. George Anderson, who reminded me that the newborn infant has special and puzzling problems; Drs. Harry Gordon, Alexander Schaffer, and Janet Hardy, who by their stimulating rounds in the nurseries of The Johns Hopkins Hospital interested me in devoting special attention to newborn infants; Drs. Jere Mead, James Whittenberger, and Charles D. Cook at Harvard, who communicated much of their enthusiasm and knowledge about the physiology of the lung; and especially Dr. Clement Smith, whose own great interest in, and knowledge of, the newborn infant was shared through both his writings and his teaching to me as his research fellow for two years at the Boston Lying-In Hospital, and more recently in the preparation of this work. I gratefully acknowledge the encouragement of my present chief, Dr. Robert Cooke, Professor of Pediatrics at Johns Hopkins, who has turned me loose in the newborn nurseries at Hopkins, and Drs. Richard Riley and Richard Shepard, who provide constant stimulation and advice on respiratory physiology. What is useful in this book is in large measure due to the observations and teachings of these people. What is missing or erroneous is in no measure their responsibility. I have tried to put together the pieces of a puzzle. Portions of a picture emerge. Probably some pieces are wrong, others are

missing. If this work serves to stimulate others to help complete the picture, I shall be justly rewarded.

It is appropriate to acknowledge as well the changing status of medical investigation in this country. My predecessors for the most part accumulated their experience and wrote their works in the midst of the pressures of pediatric practice or large routine laboratory and teaching responsibilities. I have been relatively free to pursue investigations as they seemed appropriate, and to read at length, with only as many clinical and teaching responsibilities as were important to stimulate the investigative ones. This has been possible in large measure because of the generosity of the National Institutes of Health. A special traineeship provided support for the first three years after a pediatric residency, and subsequently research grants have made possible much of the work that is presented in this book. I am also indebted to The Maryland Heart Association and The American Thoracic Society for financial support, and to The John and Mary R. Markle Foundation for its great generosity in encouraging me to devote the largest portion of my time to teaching and research.

I am indebted to my many colleagues at The Johns Hopkins Hospital and elsewhere who endured endless questioning about some of the conditions discussed in these pages, and especially Dr. Alexander Schaffer, who reviewed the entire text. Dr. Olga Baghdassarian of the Department of Radiology not only collected most of the films, but wrote some of the descriptions of them, and wrote the section on "Roentgenographic Evaluation of the Chest."

The text could not have appeared in its present form without the assistance of Miss Carol Hoffman, who helped with the drawings and literature survey, Mrs. Joan Holthus, who typed the manuscript, and Mrs. Dorothy Lyne, who assisted with the manuscript.

I wish to thank Dr. Robert R. Wright and Mr. Charles Stuart of The University of California Medical Center for their courtesy in allowing me to reproduce on the end sheets their beautiful photomicrographs of lung tissue which were originally published in Science, Vol. 137, August 24, 1962.

And finally I wish to acknowledge the great assistance and advice of the staff of W. B. Saunders Company.

MARY ELLEN AVERY

Contents

PART I

Normal Development and Physiology of the Fetal and Neonatal Lung

Chapter One

LUNG DEVELOPMENT

The pediatrician has a special interest in the problem of lung growth, since he is called upon to care for immature infants. Organ maturation must evolve to a degree capable of function before extrauterine life is possible; not infrequently it appears that viability of the prematurely born infant is limited by the lung. It is not until approximately 26 to 28 weeks of gestation that the potential airway and capillary proliferation around the airway are sufficient for gas exchange.

DEVELOPMENT OF THE AIRWAYS

Before the period of viability, the lung is essentially a glandular organ, with closed airspaces. In a 24-day embryo, there is an outpouching of the gut; at 26 to 28 days, two primary branches appear, which are the major bronchi; for the next three months, growth consists of branching of the endodermal tube into the surrounding mesenchyme. The mesenchyme itself is of two types, a relatively cellular one, which surrounds the endodermal tree, and a less cellular one, which fills the remaining space. Ham and Baldwin (1941) suggest that the more cellular mesenchyme is the source of the nonepithelial elements in the alveolar walls, and the noncellular type gives rise to pleura, subpleural connective tissue, interlobular septa, and cartilage of the bronchial tree.

Cartilage deposition begins at about 10 weeks. By 16 weeks, antenatal formation of new bronchi is nearly complete, but cartilage continues to appear until the 24th week, when it reaches the same extent as is found at term (Fig. 1–1).

By 12 weeks the lobes of the lung are well demarcated. Elastic fiber bundles are present in the walls of the trachea and main bronchi, as well as the pulmonary artery and pleura (Loosli and Potter, 1959). Septa can first be recognized between the 18th and 20th weeks of fetal life. They consist of sheets of areolar tissue, which pass for varying distances from their pleural attachments into the lung. They have the same distribution in the fetus as in the adult, most numerous at the sharp edges of the lung and sparse over the lateral aspects (Reid and Rubino, 1959).

It has long been known that the respiratory epithelium is rich in glycogen in embryonic life (Bernard, 1859). It is most abundant in regions of the lung where cell division is most rapid and disappears from mature cells when citric acid cycle activity increases (Sorokin et al., 1959). Sorokin suggested that glycogen is required to support epidermal mitosis in embryonic tissues. He established this dependence on glycolysis by means of tissue explants; growth and differentiation proceeded in like fashion whether the fetal lungs were raised on standard media or media with added malonate or cyanide, or in the absence of air. Only the explants given fluoride, which inhibits glycolysis, failed to differentiate (Sorokin, 1961).

During rapid lung growth, the epithelial mass increases relative to mesenchyme

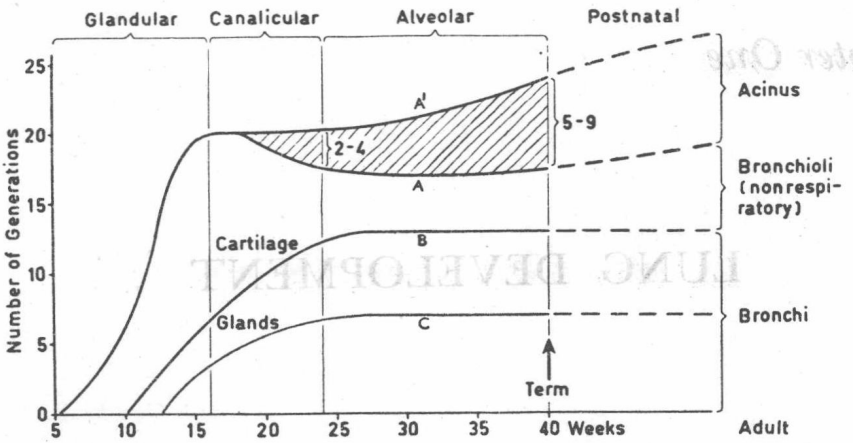

Figure 1–1. Intrauterine development of the bronchial tree. Line A represents the number of bronchial generations, and A' the respiratory bronchioles and alveolar ducts. B is the extension of cartilage along the bronchial tree, and C the extension of mucous glands. (From Bucher, U., and Reid, L.: Thorax *16*:207, 1961.)

(Fauré-Fremiet and Dragoiu, 1923). Mitotic counts show two epithelial divisions per stromal division during early and late organogeny, and a higher ratio in mid-development (Sorokin et al., 1959). With unequal cell division, it would be expected that the more rapidly dividing tissues would branch (Fig. 1–2). Cannulization of the airways occurs at approximately 20 weeks, with the appearance of a cuboidal cell lining (Laumonier, 1952).

Terminal airsacs or alveoli appear as outpouchings of the bronchioles, and after 28 weeks these alveoli increase in number to form multiple pouches of a common chamber known as an alveolar duct. The time of appearance of alveoli in the human lung is not constant but may begin at 28 weeks and progress to term, since frequently some terminal airspaces are lined by cuboidal epithelium near term. This observation has led to confusion about the role of air breathing in "flattening" cuboidal epithelium. Farber and Wilson (1933), and later Whitehead et al. (1942), felt that epithelium was flattened as a result of the introduction of air at birth. The excised lungs of stillborn infants, after artificial respiration, showed less cuboidal epithelium than did the control lung. Potter (1953) based exceptions to this suggestion on extensive observations indicating that the histologic structure of the lungs is essentially the same after birth as before birth. Parmentier (1962) confirmed these findings in human and rat lungs. He saw progressive differentiation of lung structures in utero with attenuation of alveolar epithelium. The strongest evidence that attenuation of epithelium can occur in the absence of air breathing is that of Sorokin (1961), who demonstrated the formation of thin-walled alveoli in tissue explants of embryonic lung. Electron micrographs of fetal lungs likewise show an abrupt attenuation of cuboidal cell cytoplasm extending over adjacent capillaries (Low and Sampaio, 1957).

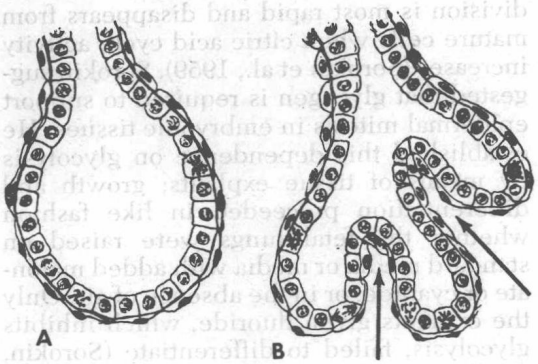

Figure 1–2. Schematic illustration of the role of cell division in branching of the developing lung. (From Sorokin, S., et al.: Develop. Biol. *1*:125, 1959.)

A most significant milestone in lung development appears to occur at about 26 to 28 weeks, when the fetus weighs about 1 kg. At this time the capillary network, which arose about the 20th week from vascular structures in the mesenchyme, proliferates close to the developing airway (Potter, 1953). Extrauterine existence is not possible until

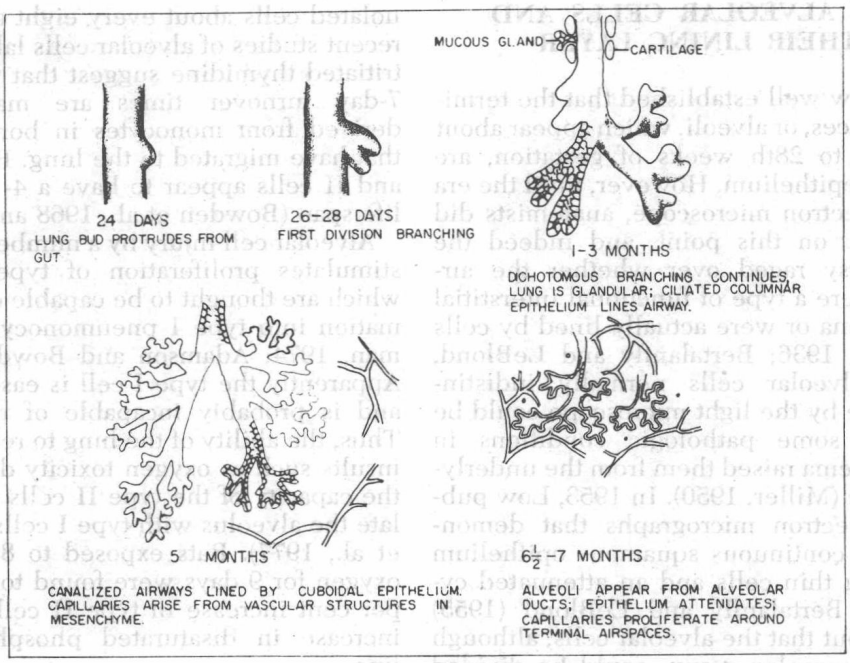

Figure 1–3. Diagrammatic representation of the stages of lung development.

there is a sufficiently extensive surface area of the lung for gas exchange (Fig. 1–3).

Extensive studies of lung growth in tissue culture have clarified a number of questions: for example, it is evident that the lung in organ culture is capable of being a self-developing entity; even after it is separated from the embryo and the mother, rudiments of the lung can develop in vitro. The older the fetal lung fragments are at the time of initiation of culture, the better the prospects of obtaining a differentiated organ. In vitro blood vessels do not develop to the extent that they do in vivo.

Evidence of an inductive capacity of the investing mesenchyme comes from the studies of Rudnick (1933) with the chick lung and Sampaolo and Sampaolo (1958) with the rabbit lung. Removal of the mesenchyme from the lung bud interrupts the process of epithelial branching. Once the mesenchyme is regenerated, growth of the epithelium proceeds. The epithelium alone, isolated in vitro, is incapable of morphogenesis. Alescio and Cassini (1962) have reported that the substitution of bronchial mesenchyme for tracheal mesenchyme promotes the development of a supernumerary bud at the grafting site. These studies indicate that the pulmonary epithelium is capable of budding in a given region for some time after it would normally stop doing so.

DEVELOPMENT OF GLANDS AND CILIA

By eight weeks, long after the trachea is lined by the pulmonary endoderm, a secondary invagination of its epithelium occurs to form the paratracheal mucous glands (Sorokin, 1960). Cilia are evident in the trachea and main bronchi at 10 weeks and in the peripheral airways by 13 weeks (Bucher and Reid, 1961). Goblet cells with PAS-positive material appear in the bronchial epithelium at 13 to 14 weeks. Glands appear first as solid buds from the basal layers of the surface epithelium, at about the 15th to 16th weeks of gestation, and later as tubules that branch and form mucus-containing acini (Thurlbeck et al., 1961; Sorokin, 1960; Bucher and Reid, 1961). Granular acini can be identified by 26 weeks. From their staining characteristics, it appears that the fetal acini contain some acid mucopolysaccharide, which may contribute to the acid pH of tracheal fluid (Reid, 1967).