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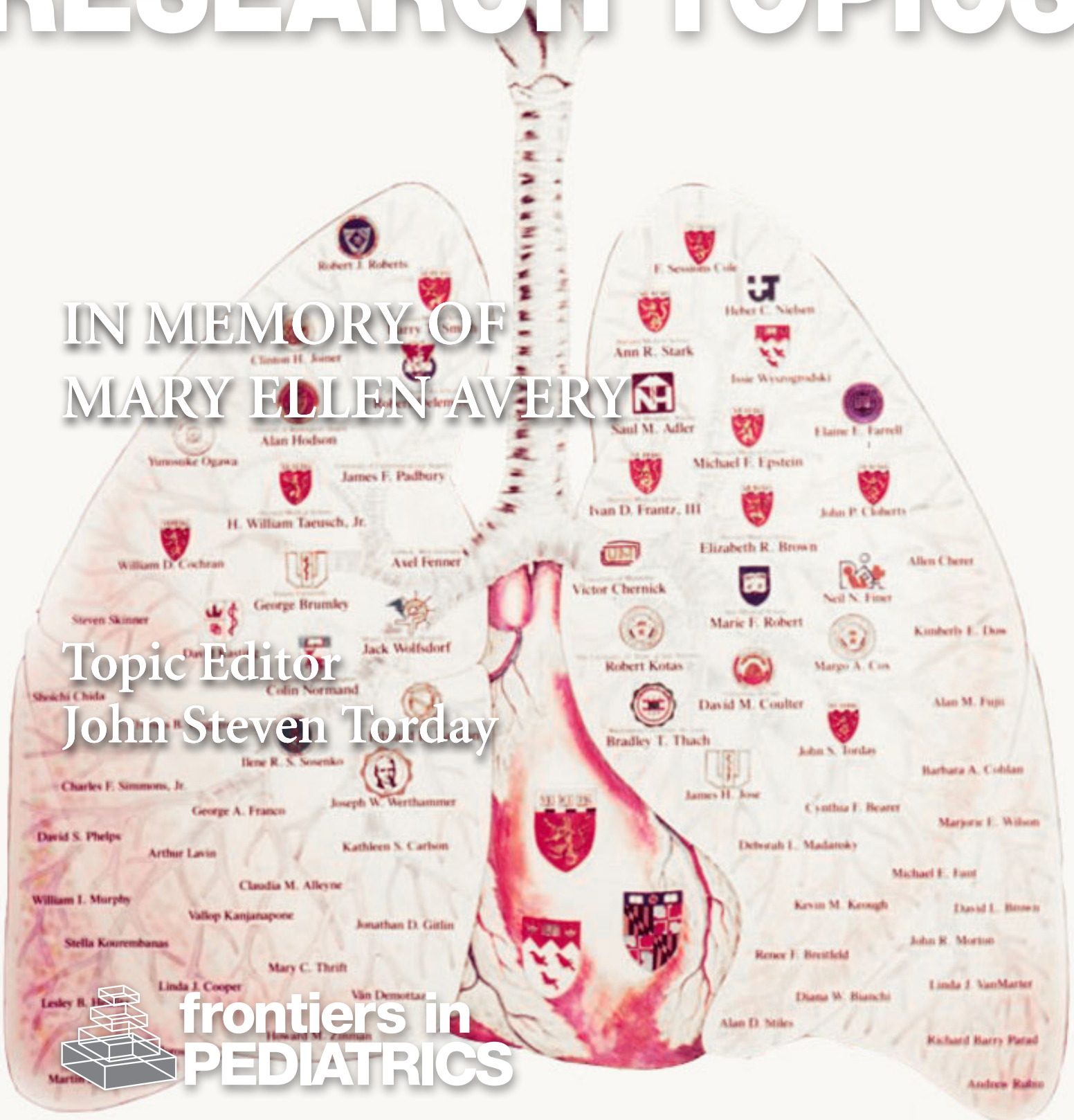

IN MEMORY OF MARY ELLEN AVERY

Topic Editor
John Steven Torday

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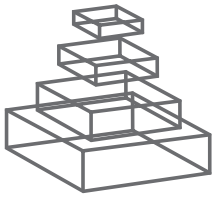

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IN MEMORY OF MARY ELLEN AVERY

Topic Editor:
John Steven Torday, University of California- Los Angeles, USA

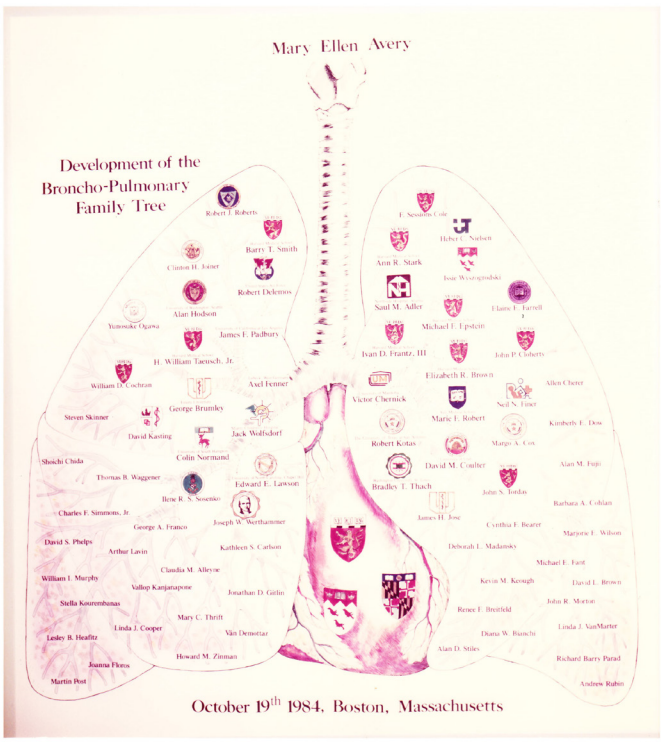

Image taken from Stark, A. R. My tribute to Mary Ellen Avery. Frontiers in Pediatrics (2014) doi: 10.3389/fped.2014.00050.

Mary Ellen Avery was the driving force behind the discipline of Neonatology. She fought against convention when she published her ground-breaking paper in 1959 showing that Hyaline Membrane Disease was caused by lung surfactant deficiency. Up until then it was thought to be an due to amniotic fluid aspiration, as suggested by Hoccheim in 1903. She encouraged her students to think out of the box, as long as we were studying 'something that you couldn't live without'. In addition to being a great clinician-researcher she was a mentor. The article is by her former students writing about their personal experiences under the tutelage of Mel Avery.

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Mary Ellen Avery's research career – remembrance of things past

John Steven Torday*

Department of Pediatrics, University of California Los Angeles, Los Angeles, CA, USA

Edited by:
David Warburton, Children's Hospital Los Angeles, USA

Reviewed by:
David Warburton, Children's Hospital Los Angeles, USA
Megan Jane Wallace, Monash University, Australia
Martin Post, The Hospital for Sick Children, Canada

****Correspondence:***
John Steven Torday, Department of Pediatrics/Neonatology, University of California Los Angeles, 1124 West Carson Street, Torrance, CA, USA
e-mail: jtorday@labiomed.org

Mary Ellen Avery's research is recognized as a milestone in biomedical research. She had discovered the underlying cause of hyaline membrane disease, surfactant deficiency, fostering ever more vigorous efforts to reduce neonatal mortality in the burgeoning practice of Neonatology. Neonatology is the only clinical discipline that began as an experiment, making it a model for biomedical research. Avery knew that the concerted effort to treat preterm newborns could potentially do more harm than good, violating her oath to Hippocrates, if not held to the highest scientific standards. She remained true to that pledge throughout her career, as recounted in this Review.

Keywords: Mary Ellen Avery, lung surfactant, respiratory distress syndrome, evidence-based medicine, leadership

INTRODUCTION

I feel like the narrator recounting his tale at the wedding banquet in Coleridge's epic poem "The Rime of the Ancient Mariner." Of course anyone can go to PubMed and retrieve Mary Ellen Avery's publications, totaling 146 peer-reviewed papers, but the back story is what I am going to relate, largely based on my personal recall under her tutelage for 25 years.

Her interest in the breathing problems of newborn infants had been piqued by the awareness that the most common finding in the lungs of premature infants born alive who died shortly thereafter, was atelectasis and hyaline membranes. The pathology had been well-described by both George Anderson and Peter Gruenwald at Johns Hopkins. They both emphasized the lack of a clinical description of the course of the disease. In 1947, Gruenwald (1) described the unusual expansion patterns of the lungs of premature infants. He hypothesized that an unusually high surface tension could account for the high pressure necessary to introduce air into the lungs, but also that air was trapped in the lungs in a Swiss cheese-like pattern, as predicted by the Law of LaPlace.

Richard Pattle (2) was studying the foam of pulmonary edema in the Chemical Defense Establishment in Porton, England, since some gases used in wartime such as phosgene induce lung edema, so antidotes were being sought. The unusual stability of bubbles expressed from normal lungs led Pattle to conclude that the internal surface of the lung must be covered with a lining layer of very low surface tension. He suggested that absence of the lining substance of the alveoli might play a role in causing atelectasis. The appearance of hyaline membranes might be due to a defective lining layer causing transudation from the blood, or to excessive secretion of the lining substance itself.

Dr. Avery had completed her pediatric residency at Johns Hopkins in the 1950s, so she went off to Boston to study respiratory physiology at the Harvard School of Public Health with Jere Mead, in conjunction with a Fellowship to study newborn infants with Clement Smith at the Boston Lying-In Hospital.

Mead's laboratory had discovered that if the lung was filled with air it had greater elastic recoil than if it were filled with saline, leading to the realization that the surface forces of the lung, which are greater at an air–liquid interface than at a liquid–liquid interface, caused the elastic recoil of the lung. Mead's group used these observations to calculate lung surface area, which differed substantially from that estimated by the morphologists. That observation prompted Clements to measure the surface tension of material expressed from the lung. Clements, tried to reconcile the Mead laboratory data with Pattle's findings of stable bubbles expressed from lungs having zero surface tension. Whittenberger at the Harvard School of Public Health, a research advisor to Clements at Edgewood Arsenal, Maryland communicated Clements' findings to Mead and Avery back in Boston. Clements had reasoned that a dynamic method of measurement of surface tension would better reflect conditions in the lung, so he designed a modified Wilhelmy surface film balance to study changes in surface tension with area. His striking observation established the important feature of the alveolar lining layer, namely a change in surface tension with area, so that at large lung volumes surface tension is high, and at low lung volumes it approaches zero. He named the material presumed to be at the alveolar–air interface "pulmonary surfactant," and commented on its central role as an anti-atelectatic factor.

Avery visited Clements' lab at the Edgewood Arsenal in December, 1957 to see the surface film balance. On her return to Boston, Mead proposed a way to modify the method to allow them to study minced extracts from lungs of human infants. Samples of lungs were obtained courtesy of Kurt Benirshke, the chief of pathology at the Boston Lying-In Hospital at that time. The absence of foam in the lungs at autopsy was a prominent observation that might have led to the conclusion that these lungs were deficient

Row 1(front to back, L to R): Elaine Farrell, Barbara Kolan, Ann Stark, Morton, *ME Avery*, Liz Brown, Ivan Frantz, J Torday, Renee Fox, Marjorie Wilson, Kathy Carlson,
Row 2: Claudia Aleyne, Brad Thach, Vic Chernick, Barry Smith, Alan Styles, David Phelps,
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Row 5: Michael Fant, Ned Lawson, Sessions Cole, Chuck Simmons

FIGURE 1 | The Joint Program in Neonatology (JPN), 1984, in front of the Administration Building (Building C), Harvard Medical School. In 1984, on the 25th anniversary of the publication of the Avery and Mead paper, members of the Joint Program in Neonatology, which Dr. Avery had created in 1974, gathered for a group picture with her in front of the administration building at Harvard Medical School. Those in attendance were clinicians, clinician-scientists, and basic scientists alike as the embodiment of Dr. Avery's eternal effort "to do no harm."

in surfactant even in the absence of measurements on the surface film balance. The first measurements were made before Pattle had published his observations in 1958. His finding that the bubbles expressed from lungs of immature guinea pigs were unstable reassured Avery that she was on the right track in her studies of the lungs of infants who had died of hyaline membrane disease (HMD).

There were multiple theories for the pathogenesis of HMD when Avery began her study of lung surfactant. In the first edition of her book *The Lung and its Disorders in the Newborn Infant* (3), she objectively presented what was known at the time, and, although she presented observations on the possible role of surface forces, she admitted that the etiology of HMD was unknown. She recapped the arguments for the primacy of aspiration, asphyxia, heart failure, shock, disturbed autonomic regulation, fibrinolytic enzyme defect, prolonged acid–base derangements, and low serum proteins. Over the ensuing years these variables have been eliminated one by one, bringing ever-greater clarity to the ultimate role of surfactant deficiency. The first time Avery unequivocally stated that HMD was due to surfactant deficiency was in the fourth edition of her textbook in 1981.

RESPIRATORY DISTRESS SYNDROME AS SURFACTANT DEFICIENCY – EVIDENCE-BASED MEDICINE

The first four peer-reviewed papers Avery published were case reports, beginning in 1955 (4). But then there was that watershed year of 1959 when she and Jere Mead published their groundbreaking paper on HMD as surfactant deficiency (5). She would tell her students how difficult it was to publish this manuscript because it went against convention – Hochheim had declared that HMD was an obstructive disease due to the eosinophilic membranes found in the airways of the newborns who had died of this disease. But Avery was aware of the studies done by Von Neergaard and Pattle, showing that there was surface tension reducing activity in the alveoli of the mammalian lung. She reasoned that if these infants were surfactant deficient that that would have accounted for the atelectasis and exudation of fluid across the alveolar wall, producing the hyaline membranes. If she was right, there was an opportunity to correct the disease, in contrast to the assumed intrauterine obstructive mechanism associated with HMD. From that point forward Dr. Avery published another 141 papers, but of those there were 26 that would plot her arc as the clinician-scientist who conquered HMD. I would like to recount those studies within

the context of Dr. Avery's effort to validate HMD as Respiratory Distress Syndrome, or surfactant deficiency disease. In early studies excised lungs of human newborns were used (6) in tandem with animal models to establish the relationship between surfactant and lung function (7), and the expression of lamellar bodies in alveolar type II cells as a function of development (8). And since the functional surfactant was predicated on its secretion by the alveolar type II cell, an elegant histologic study was published demonstrating this property of the alveolar epithelium (9). In a series of follow-up studies, Avery and her colleagues demonstrated relationships between conventional knowledge of pulmonary alveolar homeostasis and lung surfactant at the cellular, functional, and pathophysiologic levels (10–15) to further convince the scientific community of the mechanistic relevance of the surfactant system to alveolar homeostasis. Subsequent studies were designed to try and identify factors that might accelerate the appearance and activity of surfactant in order to prevent RDS (15), including observations that hormonal acceleration of lung maturation was physiologic in nature (16). Such studies were done in conjunction with the further elucidation of those factors that merely caused respiratory distress, such as edema (17) and retained fetal lung fluid (18), versus those that specifically caused RDS as surfactant deficiency disease, strictly defined as dependence on oxygen support in association with grunting, flaring, and retracting of the thorax, and a ground-glass appearance of the lung on x-ray examination.

The breakthrough in the treatment of surfactant deficiency *in utero* came when Liggins discovered that antenatal glucocorticoids could accelerate lung maturation. Avery's laboratory performed a systematic series of studies to demonstrate the physiologic effect of glucocorticoids on lung surfactant production in both rabbits (19–23) and lambs (24), including untoward effects like the inhibition of lung growth (25) for "full disclosure" – Avery wanted her colleagues to be totally informed about this emerging therapy. Subsequent studies filled in gaps in the relationships between physiologic and pathophysiologic agents and surfactant dynamics (26, 27) so as to further elaborate on the basic and clinical aspects of surfactant biology for the scientific community. Among these was the study by Wyszogrodski (28) showing that beta adrenergic agents caused surfactant secretion, an important observation for both basic and clinical understanding of surfactant's properties. The last scientific peer-reviewed paper that was co-authored by Dr. Avery was the demonstration of the sexual dimorphism in the rate of lung maturation during human fetal development (29), capping a series of animal studies conducted in my laboratory with Heber C. Nielsen. Those studies were designed to determine why males were not as responsive to antenatal glucocorticoids as females, an observation first reported by Kotas and Avery (30).

In 1984, on the 25th anniversary of the publication of the Avery and Mead paper, members of the Joint Program in Neonatology, which Dr. Avery had created in 1974, gathered for a group picture with her in front of the Administration Building at Harvard Medical School (see **Figure 1**). Those in attendance were clinicians, clinician-scientists, and basic scientists alike as the embodiment of Dr. Avery's eternal effort "to do no harm."

In addition to her research efforts, Dr. Avery was a champion for women in the field of medicine. Along with Lynn Reid and Mary Ellen Wohl, she strongly advocated for a level playing field as the first woman ever to have become the Chair of a clinical department at Harvard Medical School. When she was applying to medical school she was rejected by Harvard Medical School because of their policy of excluding women – always the student of history, fighting the hard fight for what was right despite the prevailing attitudes, whether in science or social justice.

Dr. Avery's last cited paper, entitled "What is good for children is good for mankind: the role of imagination in discovery" was her formal Address to the American Association for the Advancement of Science as the President of the society in the year 2004 (31). In her speech, she emphasized the power of the imagination to overcome mankind's problems. She certainly demonstrated her own ability to achieve that goal, and even surpassed it through her leadership and mentoring.

I can only hope that her spirit will marshal on.

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Mel – personal reminiscence[†]

H. William Taeusch*

Department of Pediatrics, San Francisco General Hospital, University of California San Francisco, San Francisco, CA, USA
**Correspondence: btaeusch@sfghpeds.ucsf.edu*

Edited by:
Henry J. Rozycki, Children's Hospital of Richmond at Virginia Commonwealth University, USA

Reviewed by:
Martin Keszler, Alpert Medical School of Brown University, USA
William Oh, Alpert Medical School of Brown University, USA
Rita Marie Ryan, Medical University of South Carolina, USA
Ilene R. S. Sosenko, University of Miami Miller School of Medicine, USA

Keywords: Avery, lung, pulmonary, surfactants, neonatology, medical research, lungs

On July 1, 1970, I started my fellowship in neonatology under the tutelage of Mary Ellen Avery. I entered her lab in the MacIntyre Building at McGill University in Montreal. There were no other fellows or techs working in her lab at the time. The lab was spacious but sparsely furnished. In one corner was a pneumatic surface balance, hand-built, from the design of John Clements. A lab book lay on the bench with entries dated June, 1970, by Bob Kotas, my predecessor, who had neatly recorded data on lungs from fetal rabbits. I was alone and knew no one in the building. Mel's office was several miles away at Montreal Children's Hospital where she was, surprisingly, the new Chief of Pediatrics (An American! A Woman!).

She was readily accessible in her hospital office but came to the lab only on Wednesday afternoons. There we sat nose to nose for 3 h while she reviewed my week's work. Not yet trained in the academic art of self-promotion, I once told her in three brief sentences of my past week's efforts. She waited for more and then looked startled when I remained quiet. With her usual candor she said that after she returned to her office at 5 p.m., by the end of her workday, she would have completed more, much more, than I had managed to do in a week. In heated response I blatted out all of my week's successes and failures in extenso. She smiled and said, "Well that's better. You not only have to do well, you have to show that you are doing well." (**Figure 1**).

One of my many learned lessons at her knee. Not only has she been my mentor for life, she was generous enough to push me to learn from others with talents in some areas that exceeded her own (Jere Mead, David Bates, Joseph Milic-Emili, Peter Macklem, and John Clements, the first Mel Avery awardee of the Pediatric Academic Societies, Vancouver, 2014). Mel believed that cross-disciplinary collaborative research was key for major developments in the field, long before medical centers dressed up this concept as a novel way to get funding. She was impatient of "me-too" research. She recognized and rewarded those that could produce results fitting her Venn diagram (new, true, and useful). Her curiosity extended from the Eskimos in Baffin Bay to hibernating turtles in Newfoundland to prematurely born sheep in New Zealand. She pored through my novel (about a mother deciding whether to allow surgery on her Down Syndrome newborn with multiple life-threatening anomalies) as if it were an NIH grant application (Even those have more chance of approval these days). She did all this with an irrepressible optimism, a robust sense of humor, and an appreciation of her own foibles. Robert Usher once introduced Mel as unique in her ability to sense which path to choose when she came to a research crossroad.

Her principles colored her feminism. Men and women were unequal – women in medicine had heavier burdens to shoulder – often, kids and husbands. Nonetheless Mel expected the time expended/results achieved ratio to be equal for those she chose to work with her, regardless of gender. Her sole criterion for accepting someone was enthusiasm for the task. When a female trainee was paged to leave a research conference for a sick child, Mel loudly asked, "Where's her husband?" The under representation of women in medicine, however, affronted Mel's sense of fairness, and she made sure opportunities were made known to qualified women.

Mel was loyal to a fault, but unaccepting of excuses used to explain an absence of productivity, however measured. My favorite excuse was too much clinical time, until she pointed out that in another division, there were some with more clinical responsibilities, and with a greater research output.

She could blow through thickets of verbiage to find and state the truth. One famous example was a seminar where one of us (a hapless unnamed research trainee with the initials JT) was expounding his research results while Mel held the switch that advanced his slides (remember slides?) on the projector. Impatiently she advanced his slides faster and faster in search of the main point. He stood in front of the rest of us talking faster and faster as his slides flew by on the screen. A larger example was her consultancy to the UN where it was politically correct in some quarters to defend female circumcision on religious principle. Mel called it by its right name – child abuse akin to torture.

Mel's interests when I first met her were the two subjects I disliked most in

[†] For those interested, Bojan Jennings completed a biography entitled, *Mel: A Biography of Mary Ellen Avery*, not long before Mel died. Unfortunately, it is no longer available from CreateSpace. Currently, Dr. Jennings is considering republishing it as an eBook. She can be reached at bojan.jennings@gmail.com.

FIGURE 1 | Montreal lab, about 1970. Arrayed around Mel from left to right are Nai San Wang, Izzy Wyszogrodski, Kwabena Kyei-Aboagye, and the author (with the bashful bunny). When the sequence of authorship for a paper arose for discussion, Mel, even though she merited being listed first, said, "Put my name last and I'll still get all the credit, because nobody can remember the names of you jokers."

medical school: pulmonary physiology and steroid biochemistry. So for a time, alone in her lab I injected rabbit fetuses with glucocorticoids or saline, then recorded pulmonary volume curves on lungs from the prematurely born rabbits. After about 5 months of this, I complained to Mel that I had not yet published a research paper (I was young). Mel hid her amusement, almost completely, and said that she appreciated my enthusiasm. The next week she showed up with a young pathologist, Nai San Wang. She sat him down at a microscope and asked him if he could distinguish fetal lung maturity by looking at the H&E slides from newborn rabbits born by cesarean section at different late days in late gestation. That was easy for any pathologist. But Mel forced him to break down the attributes that determined maturity and we spent the afternoon scoring lung maturity of steroid injected and saline-injected fetal rabbits. The next week we did the same thing for the skin specimens from the same rabbit fetuses. And voila! I helped author a paper that indicated a discordance in maturational rates of fetal skin and lungs (1). Just for good measure she added me as a coauthor on a Scientific American article (2).

Mel's wisdom included the ability to integrate disparate findings for the benefit of babies. She also had the ability to sweep up skeptics and attract new trainees with her keenness. She tutored and encouraged her loyal recruits to take on tasks that they themselves had no idea they could accomplish. The wisest (maybe luckiest) decision of my life (and the moral of this tale) was to choose the most inspiring teacher to work with, rather than a merely interesting subject.

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My tribute to Mary Ellen Avery

Ann R. Stark*

Division of Neonatology, Department of Pediatrics, Monroe Carell Jr. Children's Hospital at Vanderbilt, Nashville, TN, USA
**Correspondence: ann.r.stark@vanderbilt.edu*

Edited by:
John Steven Torday, University of California Los Angeles, USA

Reviewed by:
Lynne Smith, Harbor-UCLA Medical Center, USA

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I was so pleased to learn that the inaugural issue of the neonatology specialty section of Frontiers in Neonatology would highlight Mary Ellen "Mel" Avery's contributions to decades of neonatal research. Mel was my mentor and friend for more than 30 years, and it is a great honor for me to write about some of her substantial accomplishments. Among her many contributions, three are especially notable because they have saved the lives and improved the health of countless newborns: identification of surfactant deficiency as the cause of respiratory distress syndrome (RDS), treatment of RDS with artificial surfactant, and prevention of RDS with antenatal steroids.

In a paper she wrote about how it really happened, Mel dated her interest in respiratory physiology to the start of her pediatric internship at Johns Hopkins in 1952 (1). Only 1 month after she began her training, a routine tuberculin skin test that was positive and a small upper lobe infiltrate on a chest radiograph consistent with tuberculosis prompted a course of antibiotics and a prescription for 6 months of bed rest. During this period, questions about her own treatment spurred her quest for more knowledge of respiratory physiology.

Returning to her pediatric residency at Johns Hopkins, Mel cared for many premature infants with a lung condition then called hyaline membrane disease (HMD), and now known as RDS. Nearly half of the affected infants died, usually in the first 3 or 4 days, with pathology characterized by atelectasis and hyaline membranes (2). Infants who survived the first few days typically made a complete recovery.

Mel wanted to learn more about the lungs of newborn infants, especially those with HMD. In 1957, following her residency, she moved to Boston to study respiratory physiology with Jere Mead in the Department of Physiology at the Harvard School of Public Health and to learn more about newborn infants from the pediatrician and physiologist Clement Smith who worked across the street at the Boston Lying-In Hospital. Military funding targeted at chemical warfare, especially the effects of nerve gas on the lung, supported many laboratories, including those of Jere Mead, who was studying pulmonary edema, and John Clements, who was interested in surface properties of lung extracts. Clements had modified a surface balance in order to measure changes in surface tension with changes in area, as occurs during breathing. He found that surface tension of the lung extracts was high when the area was large, corresponding to higher lung volumes, and very low when the area was small, similar to low lung volumes (3). This was due to a saline extractable surface-active material at the alveolar air interface that he named pulmonary surfactant.

Mel visited Clements in Maryland soon after his publication to learn his techniques. When she returned to Boston, she and Mead modified Clements' method to enable them to study minced extracts of lungs from human infants that they obtained from Kurt Benirshke, chief of pathology at the Boston Lying-In Hospital. Their observations led to their landmark publication (4). Using the modified surface balance, Avery and Mead measured the lowest surface tension obtained with compression of lung extracts from infants who died of HMD and infants who died of other causes. They found low values in lung extracts from the larger infants without HMD, similar to older children or adults, and high values in infants who died with HMD and in the smallest infants. They concluded that HMD is caused by the absence or delayed appearance of a substance that, when present, would result in a low surface tension at low lung volume and thus prevent alveolar collapse.

A second key contribution was Mel's role in the translation of her discovery of surfactant deficiency in HMD to its clinical application, treatment of affected newborns with artificial surfactant. In the 1970s, Dr. Tetsuro Fujiwara studied surfactant biology with Forrest Adams in Los Angeles before he returned to Japan to continue his study of experimental surfactant replacement. Hearing about his work, Mel visited Fujiwara in Japan in 1979. At the time, he was working with a pharmaceutical company to develop an artificial surfactant from bovine lungs. He subsequently performed the first study of surfactant replacement in human infants, reported the next year (5). Mel returned to Boston to help plan a randomized trial of surfactant replacement in the US, using the product characterized by Fujiwara (6).

That study and others at the time led to a new era in neonatology. Between 1989 and 1990, infant mortality in the US declined more rapidly than any other year since 1977, when the rate was much higher. Most of the decline was in neonatal mortality which accounts for about two-thirds of infant deaths, and most in the categories involving respiration. This was clearly due to the wide availability of surfactant beginning in July 1989 and followed by rapid FDA approval in 1990.

A third key contribution was Mel's work on prevention of HMD. At a conference in New Zealand in 1968, she reported that lungs of fetal lambs less than approximately 126 days gestation (146 days is full term) did not retain air. At the same

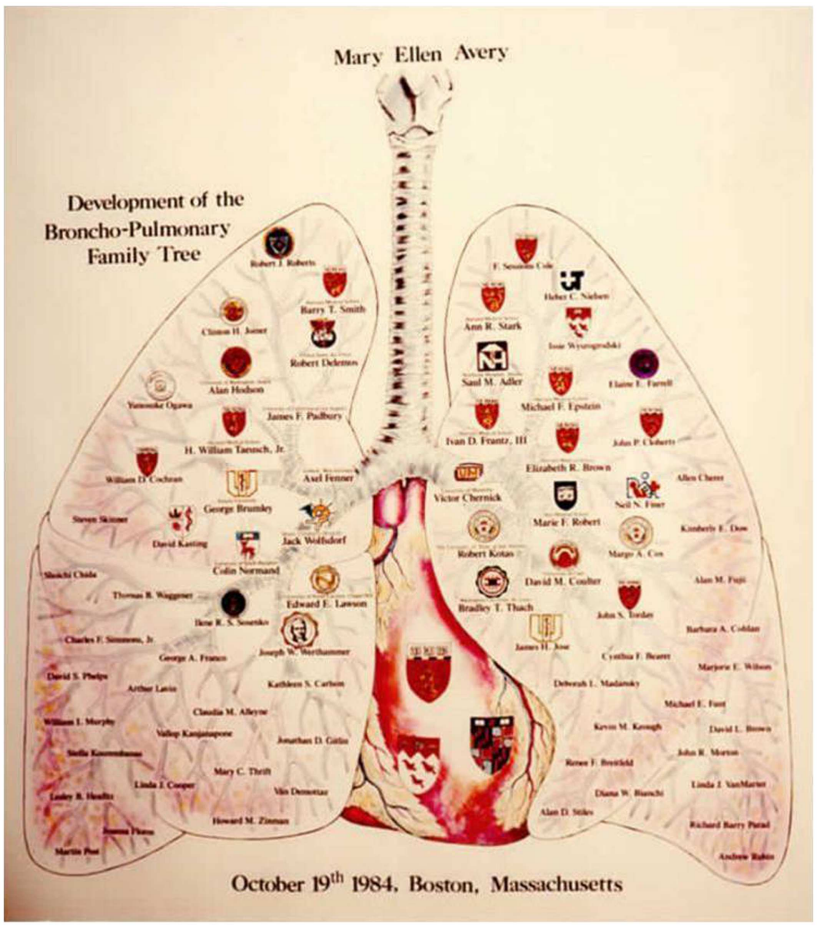

FIGURE 1 | Bronchopulmonary tree illustrating Dr. Avery's trainees through 1984.

meeting, she heard the obstetrician Graham "Mont" Liggins report treating pregnant ewes with corticosteroids to stimulate early labor. The resultant lambs were born at a slightly earlier gestational age than Mel's (117–123 days) and had well-aerated lungs, suggesting accelerated appearance of surfactant, possibly induced by the corticosteroids. With others, she confirmed Liggins' finding of accelerated lung maturation with antenatal steroid administration in lambs and rabbits (7–9). Liggins and Howie performed the first randomized trial of antenatal steroids in humans in New Zealand (10), and with Bill Taeusch, Mel participated in an early US human trial (11).

Mel received many awards for her extraordinary contributions that led to understanding the mechanism of RDS as surfactant deficiency, treatment with surfactant replacement, and prevention by antenatal corticosteroid treatment of women with anticipated preterm birth, as well as other accomplishments. These included the Edward Livingston Trudeau Medal from the American Lung Association, the E. Mead Johnson Award from the Society for Pediatric Research, the John Howland Award from the American Pediatric Society, and the Virginia Apgar Award from the American Academy of Pediatrics. In addition, she was the first pediatrician to receive the National Medal of Science.

In summary, Mary Ellen Avery was an outstanding leader in pediatrics for both her scientific contributions and her sustained efforts to improve health of newborns and children in the US and around the world. In addition, her support and continued encouragement of the next generation provides another enduring legacy. Mel directly mentored at least 75 individuals and influenced many more scientists and clinicians who have made and continue to make important contributions and train others (**Figure 1**). Those of us who had the good fortune to work with Mel treasure her critical insights, imaginative approach, and personal support.

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My personal tribute to Dr. Mary Ellen Avery

Ilene R. S. Sosenko*

Division of Neonatology, Department of Pediatrics, University of Miami Miller School of Medicine, Miami, FL, USA
**Correspondence: isosenko@miami.edu*

Edited and reviewed by:
John Steven Torday, University of California Los Angeles, USA

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Because my husband was planning to pursue a fellowship in adolescent medicine at Boston Children's Hospital, I was set to interview there in July of 1974 for a third year of pediatric training. I was just starting my second year of pediatrics in Los Angeles and had been focusing more on the mechanics of completing pediatric training than on choosing a fellowship. Dr. Mary Ellen Avery had just become Children's Physician-in-Chief. In fact, she was still finding her way about the place, both physically and professionally. It was my second interview, the first resulting in less than positive news about the possibility of my obtaining a senior pediatric residency for the coming year. She did not let me be discouraged, made it known that she would welcome me there, and suggested I could pursue the start of a fellowship before completing my full pediatric training. What type of fellowship? I certainly hadn't spent much time contemplating this. How about neonatology, she suggested, and immediately arranged for me to see Dr. Bill Taeusch, newly appointed Neonatology Division Director. So serendipity, and more importantly, Dr. Mel Avery are responsible for my career in neonatology: I joined the first official JPN fellows' group that started training in July of 1975.

Dr. Avery was a pioneering researcher in the field of neonatology and a great research motivator as well. She had overseen a recent publication associating an increased risk of hyaline membrane disease in infants of diabetic mothers (1). She "shepherded" me into examining this further, thus leading me both to the delivery room to collect infants' cord blood for C-peptide measurements (2) and into the animal lab with alloxan-diabetic pregnant rabbits and the lung development of their offspring (3–7). I remember her delight when I presented my findings at research meetings and had my first peer-reviewed publications in the *New England Journal of Medicine* (2) and *Journal of Applied Physiology* (3). In fact, when I moved on to University of Miami, I continued the line of research looking at lung development in the animal model of the IDM, this time examining pulmonary antioxidant enzyme development in offspring of streptozotocin-treated rats (8).

She opened her heart to me not just professionally but socially and personally as well. I remember a cozy Thanksgiving evening when just she, my husband, and I sat by the fire in her Wellesley condo and dined on delicious leftovers from the day. She hosted the two of us to a very special Boston evening: a "double date" with Dr. Fred Rosen for dinner at the Harvard Club and then to hear the Boston Symphony. When I was about to have my first child, she was glowing when I came to her with the news. She wanted to make sure I would be nursing him which of course I was. When he was born, she presented us with a beautifully framed print of a mother rabbit and her pups (how appropriate!) which we hung above his changing table. And once I had successfully established nursing and returned to work, she invited me to write an article with her on the benefits of breast feeding for the Harvard Medical School Health Letter (9).

My respect and admiration for Dr. Mary Ellen Avery are without bounds. There is no doubt that Mel brought me into neonatology, fostered my career, and opened her intellect and heart to me many years ago. For this I am eternally grateful.

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"PADding" my career with Dr. Mary Ellen Avery

Heber C. Nielsen*

Department of Pediatrics, Tufts Medical Center, Boston, MA, USA
**Correspondence: hnielsen@tuftsmedicalcenter.org*

Edited by:
John Steven Torday, University of California Los Angeles, USA

Reviewed by:
Lynne Smith, Harbor-UCLA Medical Center, USA

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On Wednesdays at 2:00 p.m., faculty, fellows, and research associates in the Joint Program in Neonatology (JPN) at Harvard would meet in the conference room of the Seeley Mudd building for Research Conference. Dr. Avery would come bustling in, settle in a chair, and ask the group "So, what exciting discoveries have you made this week?" Those Wednesday conferences with Dr. Avery became one of the major mentoring environments of my neonatal fellowship training. I now group the many opportunities to gain mentoring from Dr. Avery into three main categories, which I like to think of as Prepare, Ask, and Discover (PAD).

Very early in my first year of training, I conceived a research question involving perinatal/neonatal hypoxia and pulmonary hypertension. I thoroughly studied the literature to educate myself on what was known about oxygenation and pulmonary blood pressure, and created a research hypothesis and approach. Soon it was my turn to present a proposed fellowship research project to the Research Conference. I discussed the background to my idea, the science it was based on, my hypothesis, and my proposed approach. At the end there were, of course, many questions. After all, I was just a first year fellow and needed to learn my place. The discussion was capped off with Dr. Avery's comment "there is a huge literature in adults on hypoxia and pulmonary hypertension; I think you need to go back to the library and study that to better develop your rationale, hypothesis, and study approach." I knew about that literature; I had studied it carefully and it had definitely influenced the project I had so carefully designed and presented. I was strongly tempted to say "yes, I know, I read all of that," fortunately, I did not. As I thought about that humbling comment from Dr. Avery over time I realized there was a significant learning insight for my career. If I cannot show that I am intimately familiar with all the relevant literature as I present a research idea or study, then I cannot expect to get others interested and excited about the project. This truth has had a major impact on the development of my skills in presentations and writing of papers and grants. "Prepare" is a necessary component for success in our academic life.

We frequently had outside speakers at these Wednesday conferences, including speakers on topics far afield of the research interests and even expertise of the group. Dr. Avery was always attentive. What impressed me was that she was always there with questions. It didn't matter if the questions were clever or if they were simply way off the mark. She didn't hesitate to state or even show that she simply was not informed on the topic. A few times she asked a question that caused private smiles, because it seemed that she had overlooked some of her basic biology in posing the question. But she was never embarrassed. As time went on I noted that by asking questions, no matter how basic or uninformed on the subject, her personal knowledge of that subject grew such that in the future she was able to converse knowledgeably on the topic. This was the second major learning insight for me. "Ask" questions; no one should be embarrassed by a lack of even basic knowledge on a subject. Don't worry about the possibility of coming across as uneducated. "Ask" is the major way we have to learn about things. This component of Dr. Avery's mentoring is one I have had to continue to work on throughout my career.

Let me come back to Dr. Avery's signature question "What exciting discoveries have you made this week?" For a while this seemed odd. How could she expect that new discoveries would be made each week? Obviously, research is time-intensive; new discoveries don't just pop up each day! But with time I saw that she was teaching us two important attitudes. First, our research is exciting and we should always approach it that way. Second, every finding, no matter how small, is new and unique, and deserves to be celebrated. We don't have to wait until a research project is finished to derive the joy of scientific learning and discovery. Thus, "Discover" is an element of every day in the lab. Without it we just aren't approaching our work with the right attitude.

Prepare, Ask, and Discover was central for Dr. Avery. It governed our relationships with her, it stimulated her interest in following us in our careers after we left the incubator, and it led to some of the most imaginative thinking I have witnessed. For example, in a Wednesday conference Dr. Avery proposed the concept that male and female cells from non-reproductive organs have fundamental differences in their biology. This concept has only recently become a major consideration in human translational biology research. In 1980, Dr. Avery told us to begin to look out for unusual cases of neonatal respiratory distress syndrome, because we would begin to find mutations in surfactant protein genes that underlie some cases. This preceded the identification of such mutations by some 20 years. In retrospect, it was obvious, but in 1980, it was a new and far sighted prediction.

One final tribute. As a mentor I am only as good as the people who mentored me. Dr. Avery has had a profound impact on my career and I hope on those who have developed under my guidance. The impact

and legacy of a great physician–scientist like Dr. Avery will go on and on through the generations of medical science.

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My tribute to Mary Ellen Avery

John Steven Torday*

Department of Pediatrics, University of California Los Angeles, Los Angeles, CA, USA
**Correspondence: jtorday@labiomed.org*

Edited by:
Heber C. Nielsen, Tufts University School of Medicine, USA

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Charles Michael Cotten, Duke University, USA

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"Life is that which can mix oil and water"
– Robert Frost

Mary Ellen Avery was a force of Nature.

I first met her while I was a graduate student at McGill University in the early 70's. She and her colleagues had been studying the effects of glucocorticoids on fetal lung maturation and surfactant production, and had stumbled onto a curious "neighbor effect" – when they treated one of the fetal rabbits in the womb by direct injection, they found an effect on the maturation of the lungs in the collateral pups. I was studying fetal endocrinology at the time in Claude Giroud's Laboratory at Montreal Children's Hospital, and had access to radiolabeled cortisol, so I could determine if the hormone was passing from one fetus to the other. Having demonstrated this effect, Dr. Avery named me as a co-author on their paper describing this phenomenon, which was quite generous of her – but that was in her nature, as I was to discover in a 20-year journey with her as my mentor.

In the spring of 1974, while on an elevator at Montreal Children's Hospital, Dr. Avery invited me to join her research group at Harvard Medical School. She said that it was important to maintain the highest scientific standards in developing the burgeoning discipline of Neonatology because she was concerned about doing harm in the name of doing good. I had already committed to a post-doctoral position with Jack Gorski and N.L. First in the NIH Reproductive Endocrine Program at the University of Wisconsin-Madison, so I had to decline the invitation, with the understanding that I would come to Boston after my Fellowship. I joined the Joint Program in Neonatology in July, 1976 as a Research Associate. During my early years at the Boston Lying-In Hospital (BLI), where in the 1950s Dr. Avery had previously discovered that Hyaline Membrane Disease was due to surfactant deficiency in preterm newborns, I conducted studies on the physiologic role of hormones in fetal lung development in support of the clinical use of antenatal steroids to accelerate the production of surfactant. Antenatal steroid treatment dramatically improved the survival of preterm infants. It is considered one of the major breakthroughs of twentieth century medicine, saving the lives of hundreds of thousands of newborns. During the course of the first clinical trials of antenatal steroids for the prevention of Respiratory Distress Syndrome, it was found that males were much less responsive to such treatment than females, reprising my interest in the sexual dimorphism of fetal development, the subject of my Masters' thesis in graduate school at McGill. As always, Dr. Avery was open to whatever we wanted to study, so one of her Neonatal Fellows, Heber Nielsen, and I began a 20-year investigation of this mechanism in trying to maximize the benefit of antenatal steroid therapy.

During that era, the Director of the Joint Program in Neonatology, H. William Taeusch, asked me to start a clinical laboratory for the measurement of lung surfactant at the BLI. Since this was a direct extension of my basic scientific work, I accepted the challenge. The laboratory began processing amniotic fluid samples in the spring of 1977 in parallel with the advent of the clinical implementation of antenatal steroids. At that time, the standard method for measuring surfactant was the L/S ratio, which was known to lack sensitivity and specificity, but prior to the implementation of steroid therapy the management of preterm birth was essentially passive, so that method was adequate. But with the onset of the use of antenatal steroids, there was a sea change in Neonatology, the fetus becoming a patient treated in the womb. To improve on the antenatal testing for lung maturation, I developed the Saturated Phosphatidylcholine Assay, which was far superior to the L/S Ratio, being more than 90% accurate in predicting the risk of Respiratory Distress Syndrome. So here was an example of how the burgeoning discipline of Neonatology was able to use experimental methods to optimize the well-being of preterm newborns.

During that era, we used to have 4th of July picnics for the Joint Program in Neonatology. We'd inevitably have to play softball because it was Dr. Avery's passion. She loved to pitch. I was sitting on the sidelines with my then 2-year old daughter, who turned to me at one point and said loud enough so all could hear, "Dr. Avery doesn't do that very well." It was then and there that I knew I would not live out my days at Harvard.

Meanwhile, our basic research effort to understand why males were refractory to antenatal glucocorticoid treatment was advancing. We were able to determine that this was due to a physiologic mechanism by which androgens delayed the maturation of the fetal lung, allowing for persistence of the growth phase of lung development. This was due to androgen perpetuating the production of Transforming Growth Factor Beta in the connective tissue cells surrounding the alveoli, promoting more, but immature alveoli.

I left Boston in 1991, joining the Neonatal Division at the University of Maryland. It was there that I discovered the Neutral

Lipid Trafficking phenomenon – the active movement of lipid substrate between connective tissue and epithelial cells mediated by specific signaling mechanisms stimulated by both hormones and mechanical stretch. Dr. Avery had kept in touch with me, and knew of my interest in the role of "stretch" in lung development, sending me scientific papers to keep me on-track. The annual meeting of the Society for Pediatric Research was held in Baltimore in 1992, so while attending the meeting Dr. Avery paid me a visit in my new laboratory. She handed me a book, entitled *Soap Bubbles: Their Colors and Forces Which Mold Them*, by C.V. Boys, saying that everything she knew about lung surfactant was in that book! Telling me in her own way to keep it simple (KISS). In fact her perennial question to her students regarding whether something was worth studying was "can you live without it?"

Further study of the cellular–molecular signaling mechanisms for alveolar surfactant homeostasis have led to a fundamental understanding of how physiology has evolved. Now there is a way of understanding the how and why of physiology from its origins in unicellular organisms, providing a "logic" that simplifies what had become artificially complicated. I am indebted to Mary Ellen Avery for giving me the opportunity to pursue new knowledge.

She is missed.

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How Mary Ellen Avery influenced my career as an investigator

Cynthia Frances Bearer*

Pediatrics, University of Maryland School of Medicine, Baltimore, MD, USA
**Correspondence: cbearer@peds.umaryland.edu*

Edited and reviewed by:
John Steven Torday, University of California Los Angeles, USA

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I arrived in Boston during the summer of 1984, having been coaxed there by F. Sessions Cole, III. The carrot was the shortening of residency to 2 years, and thus a return to the lab all the quicker. Dr. Avery was the chair of the department at that time, and so supported my bid to enter the Special Alternative Pathway. While that may sound easy, I had unintentionally made it more difficult by doing my internship as my fourth year of medical school. To the American Board of Pediatrics, on paper, I had done only a year of residency, and would not be board eligible if I left my residency program. After much negotiation, the Johns Hopkins University School of Medicine recalled my diploma, and reissued it with a graduating date of 1982 rather than 1983. And thus I started my fellowship after 2 years of official residency! And did get back to the lab a year sooner than otherwise.

The next issue to be solved was one of housing. In order to access the Harvard University housing office, I needed a note from the chair. I believe this is the only personal note I have signed by Dr. Avery, but it guaranteed me a place to live while getting to work on my clinical and research training.

More importantly, her own research work was inspirational for me in my research career. Namely, the ability to see the importance in common observations that others did not recognize. Her observation that babies who died of respiratory distress syndrome (RDS) had no bubbles in their airways, whereas babies who died of other causes had these bubbles (1). This seemingly simple observation lead to the gastric aspirate shake test (2), the identification of lack of surfactant in RDS (3), development of surfactant therapies (4), development of pharmacotherapies (prenatal steroids) for the preventions of RDS (5), etc. For my own work, I have tried to make simple observations. My first simple observation was that the then recently described non-oxidative metabolites of ethanol, fatty acid ethyl esters (FAEE), accumulate in adipose tissue, so they might accumulate in meconium. Meconium is the accumulated gastrointestinal contents during gestation which is passed soon after birth and is presumed to be metabolically inert. Thus, meconium could be a dosimeter for prenatal ethanol exposure. I developed a simple method of extracting FAEE from meconium (6), and then was able to validate that they were associated with maternal self-reported drinking during pregnancy in several different populations (7–9), and that they indicated children at risk for poor neurodevelopmental outcomes (10). I was even able to demonstrate that they accumulate in sheep meconium (11)! For these experiments, I received NIH funding, several publications, and a patent!

The next simple observation was actually made by someone else – that patients with fetal alcohol syndrome and patients with a mutation in the gene for L1 cell adhesion molecule (L1) had very similar neuropathologies (12). This observation led to the hypothesis that L1 is a target for ethanol developmental neurotoxicity. I was able to build on this observation that the neurite outgrowth promoted by L1 was exquisitely sensitive to ethanol, whereas that promoted by laminin or N-cadherin was not (13). This lead to my own simple observation that, since L1 promotes neurite outgrowth via trafficking through a lipid raft compartment, and laminin and N-cadherin do not, then ethanol may target the L1–lipid raft interaction (14). These observations lead to the next series of simple questions, such as, if ethanol has an effect on lipid raft trafficking, do other solvents? (Answer – yes). If the lipid raft is the target for ethanol, are there unique and novel interventions for the impact of ethanol on the developing central nervous system? (Answer – yes). So, after several grants and many publications, we are poised to begin the next series of simple observations that will hopefully improve neurodevelopmental outcomes following neurotoxicant exposure, including ethanol, toluene, bilirubin, volatile anesthetics, and chlorhexidine.

One more simple observation occurred to me early in my career. The observation was that we use adult blood to transfuse into our very low birth weight (VLBW) babies. Adults are known to be exposed to lead, mercury, and other heavy metals, some at occupational levels of exposure that would be inappropriate and dangerous for children. Adults who work with lead are monitored for their blood lead level which can be as high as 45 mg/dL before being removed from the position that is causing the exposure. Yet, donated blood is not screened for potentially high levels of heavy metals. We have shown that the blood lead concentration increases following transfusions in VLBW, and that about 25% of donor blood has concerning levels of lead (15, 16). We are now engaged in research to determine if the cumulative dose of lead or mercury is a risk factor for poorer neurodevelopmental outcome of our most vulnerable patients.

Thank you Dr. Avery for your gift of simple observations!

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Mel Avery: mentor, role model, friend, mother of us all

Mary E. Sunday*

Pathology, Pediatrics, Medicine, and Cell Biology, Duke University Medical Center, Durham, NC, USA
**Correspondence: mary.sunday@duke.edu*

Edited and reviewed by:
John Steven Torday, University of California Los Angeles, USA

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Dr. Mary Ellen Avery, affectionately known as "Mel," was a woman of courage, with a sense of humor and deep humanity. She was an intellectual powerhouse, highly creative, and productive, similar to many leaders. Yet she became the most beloved mentor for many. Here, I share some personal memories hoping to inspire others juggling life and career responsibilities.

I first met Mel in 1977 when she taught our Harvard Medical School (HMS) class about respiratory distress syndrome (RDS). She held a critical audience entirely captive, listening with rapt attention. In 1979, while I was doing a medical school rotation in obstetrics at St. Thomas's Hospital in London, Mel visited as Grand Rounds speaker. A gracious guest, she cited recent work by St. Thomas's faculty. Always do your homework! she later said. She was also hospitable. Mel hosted Mother Teresa when the sister received an honorary degree at Harvard in 1982. Later, at Children's Hospital (CHMC), she hosted Mildred Stahlman, who was the first to ventilate a baby. Originally competitors, Mel and Millie had become good friends.

In 1980, Mel spoke to the women MD-PhD students at HMS, recalling her father's loving support. She shared some personal challenges, especially convalescing from TB during internship. "I had a lot of time to think about the lung – and I did!" she laughed, closing with: "don't simply do well in your field. Create a new field. For example, we could really use a field of Information Technology!" Mel often had innovative ideas (1).

Starting my laboratory at Brigham and Women's Hospital (BWH), seeking to learn methods of studying lung development, I collaborated with John Torday, whom Mel had brought from McGill to Harvard. When I asked for Mel's feedback on our first manuscript (2), suggesting a meeting in her office, she replied, "Absolutely not! We're going out to lunch!" Thus began a great friendship.

When I first presented at an American Thoracic Society meeting, Mel sat beside me, commenting, "Interesting data, but you have to change your slides from black-on-white, which doesn't project well. Use yellow-on-blue." Very constructive – very Mel! Writing a grant with Jackie Coalson about bronchopulmonary dysplasia (BPD), I called Mel. At lunch, she patted my arm, "Mary, BPD isn't a problem anymore." By the 1990s, with surfactant therapy for RDS, BPD had become milder than originally described (3). Regardless, Mel knew BPD remained a challenge, and even collaborated with Jackie herself (4).

Mel encouraged countless young professionals, especially women, but also men. Her magic stemmed from unconditional faith in others. Lewis First, then Assistant Professor and previously Mel's intern, was asked by Mel to co-edit a new Pediatrics textbook with her (5). Lewis is now a Pediatrics Chairman (6). Mel thought highly of Mary Williams from Boston University, who had done a sabbatical in CHMC Neonatology, and often sought Mary's valuable critique. When Stella Kourembanas became a Neonatology SCCOR Program Director at CHMC, Mel was delighted and attended monthly meetings, closely following our progress with interest. During those years, it seemed that Mel was passing the baton to Stella, one of her closest protegés. Now, Stella is Director of Newborn Medicine at CHMC.

Mel's enthusiasm was infectious. Once she asked me to tour the new Beth Israel NICU with her. The facilities and care were impressive, yet the highlight was one infant who would only drink mother's milk, but not from a bottle – so they tried feeding her milk from a cup. Breakthrough! Mel was excited because many developing countries have insufficient bottles. This simple success could save lives. Another day, Mel whisked me to lunch with another pediatrician who was returning to clinical work after years of disability. By dessert, we were energized, embracing the future with Mel.

When someone asked Mel how she felt about not having any children, Mel smiled, "What do you mean? I've had thousands of them!" There were no problems, only challenges; no regrets, only opportunities. Working with UNICEF deepened her awareness of global health needs, often simple yet unattainable. In India, she saw three babies in one NICU incubator and asked if they were triplets. No, they said, it was their only incubator. There weren't sufficient resources to save all babies. She spread the word.

Mel rejoiced when her trainees had children. When I was 8 months pregnant with my third child, I invited Mel for dinner at our home. She brought Maine blueberry jam, happy to meet my family. My 2-year-old son delighted her by ooh-ing and ahh-ing over the dessert, hoping to skip dinner. She later sent a warm thank you note, including 20 unusual baby names she'd collected from the NICU.

In 1994, Mel was elected into the National Academy of Sciences for her discovery that newborns require surfactant to breathe (7, 8). Her comment? "Imagine that! I never even published in that journal!" Later she ran for AAAS President (9) opposite an engineer whose essay detailed his leadership experience. Mel's essay simply addressed many challenges facing science: needs for improved rice production, vaccinations, clean water, recognizing children as our most precious resource. Mel won the election.

Mel was nobody's fool. She would tell her new ideas to over 14 people so everyone knew the ideas were hers; then she would publish quickly. She was neither offensive nor defensive. In Japan (10), Mel

FIGURE 1 | The Rose sent by Mel: the Redouté Rose was named after Joseph-Pierre Redouté, a Belgian artist who painted roses for Marie Antoinette, then for Josephine Bonaparte, "the rarest and most beautiful plants obtainable." He was immortalized through his timeless inspiration of others. **Just like Mel**.

said: "I close with a quotation attributed to a famous German pathologist in the last century (Virchow): all new knowledge goes through three phases: (1) it is ignored; (2) it evokes hostility; (3) haven't we known this all along?"

Mel lived a full life. She often traveled with a companion. Her niece, Sue, wrote: "everyone in our family had trips with Mel including my folks. Moreover, she often took friends/colleagues with her on trips to various parts of the world." CHMC Neonatology held a surprise 70th birthday party for her, with ~30 people telling Mel stories. When she received the Howland Award, Pediatric's greatest award, her previous intern, Margaret Hostetter presented it (6). Her post-award celebration included Lewis First's musical rendition of "Mel," which she enjoyed singing at home. She was delighted to stop and smell the roses.

After moving to Duke in 2004, I visited Mel every year around Thanksgiving. Once, I drove her to pick up a complete turkey dinner for her family. Mel had never learned to cook, but that never stopped her from having a party. Another time at her home, Mel showed me her nametag collection from the meetings she had attended. In 2007, Mel was animated about the BBC coming to interview her.

Then, Mel became increasingly forgetful and stopped coming to CHMC. She had live-in nursing care, thanks to her family: Sue, Bill, Jennifer, and Carl Smith. At home, Mel held tightly to her biography, written by Bojan Jennings, her chemistry professor from Wheaton College (11). She was clinging to memories, precious jewels slipping away.

The last time I saw Mel was 5 days before she died, at a nursing home near her childhood home. Sue and Bill had filled her room with her awards, nametags, and family photographs: a lifetime of love and accomplishment. At that moment, all I did was sit beside her, holding her hand. She was awake and comfortable, gazing into the distance and speaking in an unknown language to someone only she could see.

On December 4, 2011, with Sue and Bill beside her, Mel became a free spirit. Her funeral was at the church she'd attended as a child. Like Mel, it was unpretentious and heartfelt, with family and a few friends Linda van Marter and I went together. Fred Lovejoy extolled her influence at CHMC. Sue spoke a universe of love. Bill introduced Mel as The Personal Physician for the Smith Family: "take 2 aspirins and call me in the morning." How marvelous that Mel's family has the same sense of humor!

Returning home from Mel's funeral, I gazed out at our brown December garden and a rose bush that had been dead for over a year, surprised to discover – a piece of paper? No, it was a perfect full-blown pink rose (**Figure 1**). "Mel did it!" I thought. She could move mountains – of course it was Mel! That single rose lasted over 3 weeks in winter weather. Mel, you were right: we only have to do one thing well. Love is the key: love of scientific discovery and humanity. Giving everything to help children, Mel transcended departmental expectations by founding neonatology. She transcended academics by making the world her institution through UNICEF. Ultimately, she transcended time by living on in the hearts of all. Mel's greatest legacy was her inspiration of so many to believe in themselves and what they can do to make the world a better place, symbolized by a perfect rose.

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In remembrance of Dr. Mary Ellen Avery

Joanna Floros*

The Pennsylvania State University College of Medicine, Hershey, PA, USA
**Correspondence: jfloros@psu.edu*

Edited and reviewed by:
John Steven Torday, University of California Los Angeles, USA

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Dear Mel,

People the world over know about your academic and medical accomplishments. I would like to share with your colleagues, the Mel that in the 1980s I got to know and spend time with outside the laboratory (although science and how science can benefit "your" babies was just a breath away in anything we did).

The time I really got to talk with Mel outside the Harvard confines was when I first roomed with you in DC, USA. It was a last minute decision to attend the meeting and you so graciously offered to let me room with you. That was a great experience for a young academician to have the exclusive attention of a "giant" like you. The most memorable incident was when you locked me out one evening. What a surprise when the door did not open. Do I risk waking up the "giant" or do I make alternate plans – of course if I didn't show up all night what would you have thought? You were very kind and apologetic for not thinking when you pulled the lock on. The subsequent evenings I made sure to be the first in the room. Also not to be forgotten on that trip was when you suggested we all stop and play pinball, much to the amusement of some teenagers on a nearby machine.

The trips to "Echo" Lake – what unforgettable memories these were for the entire family. The fish experiment you had planned so carefully. The hypothesis you wanted to test was that application of surfactant (TA surfactant) between the gills of freshly caught and still jumping fish will allow them to breath and survive longer out of the water than their untreated counterparts. Andreas and Nikos (the youngest science helpers you probably ever had) kept track of the timing until the fish stopped kicking. You had them also participate in the actual experiment, holding the fish and opening the gills to apply surfactant while we kept timing. As a good scientist you collected the data. You wrote the manuscript, naming my two young sons, then 8 and 4 years old, as coauthors. The experiment was fun, the hypothesis did not prove correct (if I recall correctly). Unfortunately, this valuable manuscript got lost somewhere between a move to Pennsylvania and a house flood a few years ago.

Not to mention the lobster dinners and the boat rides on Echo Lake with the best captain I ever had who knew all the nesting trees for the ospreys and the best fishing spots. Echo Lake getaways with Mel and family were amazing. It was the first for me to hear the calling of the loons and to see the Aurora Borealis.

Traveling with you whether in Nigeria, Greece, or USA was always a lot of laughs. I miss that! In the midst of laughing and joy you coached me to go where I belonged – to a basic science department. In the ever candid Mel way, you said, "If you stay, we will take advantage of you." I did move to a basic science department, but now I am back in the Department of Pediatrics. There was something about that early "imprinting" being in Peds. But guess what? It "ain't" the same without Mel.

Thanks for all you did. You are never far from our thoughts!

Yana

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A remembrance of Mary Ellen Avery, M.D.

Julie R. Ingelfinger [1,2] *

[1] *Pediatric Nephrology, MassGeneral Hospital for Children, Massachusetts General Hospital, Boston, MA, USA*
[2] *Department of Pediatrics, Harvard Medical School, Boston, MA, USA*
**Correspondence: jingelfinger@partners.org*

Edited and reviewed by:
John Steven Torday, University of California Los Angeles, USA

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I was a recently hired member of the newly established Division of Pediatric Nephrology and an Instructor in Pediatrics at Harvard Medical School when Mel Avery became the Chief of the Department of Medicine and Physician-in-Chief at Children's in 1974. There was excitement, as Dr. Avery's appointment was a "first" unfolding right in front of those of us who, as young women physicians, hoped to have careers in academic pediatrics, and anticipatory talk filled the corridors of Children's. On her arrival, Mel Avery was an automatic role model for the women among the faculty. She had made a major scientific discovery that a lack of surfactant caused respiratory distress syndrome in neonates, and she was still young (in her mid-forties), with abundance of energy. I was delighted and proud to have a woman, and one so accomplished, become the Physician-in-Chief at Children's. Her hiring and her achievements allowed us to see that a woman could have a prominent role in academic medicine. The sense I had as a young faculty member was that Dr. Avery expected hard work and dedication, which was a self-selected trait among those women in the Department of Pediatrics at Children's. So, the fit for us was a good one.

It was a boost in the arm to see that Dr. Avery supported women in medicine, and she was instrumental in asking Dr. Mary Ellen Wohl, who had come to Children's in 1969, to become the chief of the Division of Pediatric Respiratory Diseases, and in the ensuing years Dr. Wohl became a pioneer in her own right. And in 1975, Dr. Lynne Reid, a pulmonary pathologist became the Chief of Pathology at Children's.

I feel it is important while thinking about Mel Avery to remember that at the time she went to medical school at Johns Hopkins, few women were entering the field medicine – not all schools accepted women, and those that did still, accepted few per class. There were 4 in her class (of 90). An extraordinary student, she had been encouraged by a next-door neighbor who was a physician, the pediatrician Dr. Emily Bacon. Mel's trajectory was admirable, in that she made her seminal discovery at a relatively young age. The number of women in most classes had more than doubled by the time I went to medical school, but it was still pitifully low. And Dr. Avery predicted that before long at least a third of most medical school classes would be women – a prediction that anticipated an increase but falls short of current statistics.

I do not think Mel fully understood how important a mentor she was for those of us who were house officers and junior faculty, even those of us with whom she did not work closely as individuals. What she shared in formal interviews, for example, with Georgia Litwack, with whom she subsequently wrote a book, would have had an extremely empowering effect had she been able to share it more directly with those of us who were coming along in the department at that time. However, a number of people became closer to her over time, with excellent effect.

Dr. Avery realized that the expectations of patients and the public were changing, and she made efforts that Children's would pay attention to this trend, which proved prescient. I think she helped Children's get ready for these changes.

In some published interviews, Mel acknowledged those things in which she was and was not comfortable. She was most at home with younger, not older children, and she always wanted to do her best. She noted that cutting corners made her tense. Mel appeared to be somewhat uncomfortable in many situations, and she was not a natural politician – probably not surprising given the era and her wish to complete all charges and tasks to perfection.

I thought she was also, in a certain way, shy. What I perceived as Mel Avery's shyness and reticence to speak of her accomplishments was, in my view, a mixed blessing. It was refreshing to have a chief who did not seem to have a big ego, as many do. She clearly had vision, but it was hard to ferret it out on a daily basis. But vision, she had, and it was something I particularly appreciated.

One of her lasting accomplishments while at Children's was the establishment of the Joint Program in Neonatology at Children's and the other nearby Harvard Hospitals. It strengthened the residency program and was an improvement for all the programs concerned. Under Mel's hand, neonatology became a major strength in Boston Pediatrics.

After her years as Physician-in-Chief at Children's, Mel turned her attention to global health, and was particularly concerned about human rights and socioeconomic disparities. She worked hard with UNICEF as a health ambassador, advocating world wide to encourage polio vaccination and oral rehydration therapy.

While thinking about Mel Avery, I feel that her contributions were both focused and broad. I feel fortunate to have had her as my chief.

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