The examination of birth asphyxia from a historical perspective presents several intriguing problems. First, of course, there is no satisfactory definition. Clinicians, biochemists and pathologists all seem to use the phrase, but a universal definition is lacking. Dr. Eastman of Hopkins called asphyxia "an infelicity of etymology" since the Greek derivation of asphyxia meant "without pulse." A second problem seems to be that, within each specialty studying asphyxia, once a definition is established, the exceptions are enormous. For instance, to the pathologist, a defined "asphyxic" lesion may occur without any clinical or biochemical history of asphyxia. The term asphyxia when defined in physiology textbooks includes hypoxia plus hypercarbia. Alternatively, biochemical evidence of asphyxia is present in tremendous numbers of children who, in fact, are clinically completely normal.

A recent pair of published papers from the University of Pittsburgh describe the effects of neonatal asphyxia on children. The investigators demonstrated the relationship between prematurity and asphyxia, and showed the positive relationship between survival and gestational age. They reconfirmed the finding that the incidence and severity of birth asphyxia complications were not related to gestational age. This information was not especially new. What is intriguing about these papers, however, is the criterion used for diagnosis of asphyxia. In an age where technological advance is a daily occurrence, and where intricate cellular physiology is being studied in detail, these investigators used as their sole criterion for the diagnosis of asphyxia, "infants who required more than one minute of positive..."
pressure ventilation before sustained respiration occurred." The specific etiology leading to the absence of voluntary respiratory effort is not mentioned, nor is any reference made to blood biochemistry!

Research literature in birth asphyxia and its sequelae abounds with the names of truly superb investigators. The predominant goal of their research, however, has been the elucidation of mechanisms both macroscopic and cellular. Although this research is voluminous, the total impact on direct care, diagnostically and therapeutically, is very limited with respect to human application.

Lastly, it is also fair to state that perspective improves over time. It is, therefore, my intention to explore the past with greater abandon than the present. The acuity of one's perception is commonly befuddled concerning recent events. Bias and personal value systems can dim any of our judgments, a phenomenon obvious in the history of the retrolental fibroplasia (RLF) epidemic as described by William Silverman. [2] Such bias is also very apparent in the refusal of physicians to accept the physician vector concept of the transmission of streptococci on puerperal fever in the mid 1800's.[3]

Dr. William Little presented his paper defining a causal relationship between abnormal parturition and central nervous system damage in 1861. Dr. Little cautioned that the difference between apoplexy, asthenia and asphyxia was unknown but that in asphyxia, circulatory failure was clearly a factor and an important cause of the central nervous system (CNS) clinical pathology . In fact, his talk to the Obstetric Society of London was the culmination of a long series of studies published, in part, in *Lancet* beginning several years earlier. He mentioned other authors who characterized and commented on the immediate neonatal period but then he stated "they seem quite unaware; that abnormal parturition besides ending in death or recovery, not infrequently has another termination . . . in other diseases."

The expressions in vogue to describe birth asphyxia in Little's time included "asphyxia neonatorum" and "suspended animation," a descriptive term not terribly different from the 1980 Pittsburgh author's! He compared the appearance of these newborn children suffering from asphyxia to adult drowning victims. He certainly visited the autopsy area frequently to correlate the clinical findings and he traced the pathology of such infants who die to brain stem lesions. By contrast, a famous American physician is quoted in Dr. Little's article. J. Marion Sims, the founder of the Women's Hospital of the state of New York, the first American institution devoted to gynecologic diseases, attached "no importance to either tedious labour or to asphyxia at birth."

A survey of Little's 47 cases reveals a melange of pathology but is illustrative of his times. Children in those days were born, swaddled, and prayed for. Days could pass without their giving evidence of much life. In fact, during the spirited discussion which followed Little's paper, the intellectual giant, Samuel Johnson, who had "nervous disorders," was described as being "dead at birth." The Society members who heard Dr. Little were clearly enthusiastic about his thesis and the article ends by noting that Richard III was a premature breech which might have accounted for some of his well known physical and behavioral deficiencies.

Little's thesis included an allusion to the difference between *asphyxia pallida* and *asphyxia livida* with
the former the much more ominous event. Most interesting from the historical perspective is his observation that "it is obvious that the great majority of apparently stillborn infants whose lives are saved by the attendant accoucheur recover unharmed from that condition." Dr. Little, being a courtly speaker and author, excused the physicians who practiced midwifery from antedating his observations. He bemoaned the fact that a proper lying-in hospital was needed, and felt that his observations would be extended and supported by such a facility. Dr. Little was eminently qualified to discuss the advantage of specialized medical facilities. He founded the Royal Orthopedic Hospital. He also, it must be stated, was familiar with the politics and strife of administration. In a long and obviously aggravating series of articles, starting in 1851, in *Lancet*, he engaged in a public confrontation with one of the board members of the charity which solicited the original money for the Orthopedic Hospital. The board member opponent was claiming primacy as the founder and wanted recognition of the fact. The board member stated that he had proof, since his portrait was the first one hung in the board room. Needless to say, Little prevailed.

In reviewing the history of birth asphyxia, one name in perinatal medicine which should be central is that of N. J. Eastman. Eastman's contributions to birth asphyxia are of inestimable value. Dr. Eastman's work began in the early 1930's and was based on sound physiologic principles derived from the great physiologists who were working in the area of respiration at that time. Dr. Eastman defined asphyxia as "an inability of the child to breathe and apnea associated with oxygen deficiency during labor." It was this very issue, the initiation of respiration at birth, that stimulated Dr. Eastman's original contributions. Dr. Eastman was vitally interested in the concept of whether hypercarbia or hypoxia was responsible for the initiation of respiration.[5] He was aware of the work of Barcroft and others in England, including Hugget's work with goats. He felt that only by understanding the normal initiation of human respiration and the biochemistry involved at the time of initiation of respiration, could we know the abnormalities associated with abnormal respiration, i.e. asphyxia. His studies proceeded in a series of five articles published between 1931 and 1936. He first studied the oxygen concentration and oxygen delivery of maternal and fetal blood through the umbilical vein and the return of blood to the mother via the umbilical artery, in 16 patients. The details involved in collecting the blood, and the mechanisms, are remarkable. He guessed, as a result of his experiments, that there was likely intrauterine cyanosis (!) but that the minimal oxygen unloading was sufficient for a dormant, thermostable organism.

His next paper used these 16 patient models as controls for the identification of deviations from normal. He measured lactate in cord blood of 24 patients, 7 of whom had birth asphyxia.' Three of these infants died and he reported that at autopsy they had no evidence of trauma or hemorrhage. He showed the maternal-fetal lactate relationships and indicated that this was likely a measure of mild oxygen deficiency. He stated that the absence of hyperlactatemia demonstrated fetal oxygen adequacy. He quoted a paper by Heinbicken, a German investigator, who in 1929 demonstrated that cellular acidic products generated from anoxemia could cause cellular damage! The summary of these two inquiries and their clinical application is encompassed by Eastman's third paper on the subject.[7] He quoted the Kane and Kreiselman study of 1930 showing increased carbon dioxide in the blood of asphyxiated adult patients. Dr. Eastman then measured the carbon dioxide and pH in normal and abnormal fetal and maternal blood. Lastly, he demonstrated that neonatal acidosis accompanies asphyxia.
Schmidt in 1928 had published a theory of "reversal" of which Eastman knew. Schmidt stated that after prolonged oxygen deprivation and acidemia including hypercarbia, cerebral cells, including the respiratory center, no longer could utilize oxygen and, rather than stimulating increased respiratory activity, respiratory depression ensued. Mathison in 1910 had demonstrated the effect of asphyxia on reducing cardiac output. Dr. Eastman postulated from this pathophysiologic observation that the well known ominous process of asphyxia pallida equalled circulatory failure. Eastman then concluded that high carbon dioxide or low oxygen were not the primary initiators of respiration. He also made very clear that the goals for resuscitation are evident! He wrote, "There seems to be only one urgent indication in the treatment of asphyxia neonatorum, and that is to introduce oxygen into the circulating blood of the infant." He continued "that the usual forms of stimulation (including slapping, bathing and carbon dioxide inhalation) produce depression . . . and may even result in irreparable damage to the brain cells."

A subsequent paper apparently was the first to identify the human alterations of fetal hemoglobin on oxygen affinity as compared to the adult hemoglobin and its oxygen affinity.

Dr. Eastman's investigations then led him into an inquiry into the role of anesthesia in neonatal depression and production of asphyxia. In the 1930's, there was considerable suspicion which indicated that part of the narcosis associated with the administration of anesthetic agents was the hypoxia associated with their use, and that the hypoxia was as responsible for the central nervous system depression as was the agent itself. Dr. Eastman proceeded to look at the oxygen concentrations in both mothers and babies and came to the conclusion that under most circumstances depression seen following anesthesia in the neonate is, in fact, not related to oxygen deficiency but is related to the drug used. He urged caution, however, and agreed that the inappropriate concentrations of drugs resulted in apnea due to asphyxia, not apnea due to anesthesia. It was this distinction that was probably the first great scientific differentiation made in modern day perinatal medicine concerning respiratory neonatal depression.

No review of birth asphyxia can ignore the Apgar score. Dr. Apgar, in her original paper published in 1953, was obviously disturbed by the lack of specificity in resuscitation. She decried the lack of systematic evaluation of newborns which limited the evaluation of resuscitation methodology. She chose her criteria in part to obviate the need for intervention during the resuscitation efforts and felt that her criteria could be delineated without compromising care. She then correlated her score with a variety of birthing variables including perinatal mortality and type of anesthesia, and showed the inverse relationship of the score to the need for active resuscitative needs. She clearly did not intend to have her score used to do more than focus attention on the baby and its immediate needs, as well as to objectify and systematize the process for observer communications.

Dr. Apgar's work was extended by several of her associates, notably Dr. L. S. James. James and his coworkers converted the pathophysiology of the Apgar criteria into human acid-base biochemical correlates. On this latter subject, Dr. James and his group performed a notable service. Since one of the weaknesses of historical observation in asphyxia is the lack of coordination among clinical,
biochemical and pathological phenomena, this less dramatic work is of critical importance.

It is difficult to ignore the relationship of lower animal research to human pathology. Most of the great bench researchers in the area of birth asphyxia applied qualifiers to their research and cautioned against over-interpretation. Dr. Louis Gluck, in prefacing his superb symposium on intrauterine asphyxia, alluded to the problem with reference to the heart rate quantification controversy of the early 1960's. "Bench laboratory" researchers had trouble confirming Dr. Edward Hon's work in humans. Gluck wrote, "This was the classic example of a faulty basic premise carried out to an untenable conclusion."[16]

Although many investigators have contributed to the mystery of mechanisms in asphyxia, Dr. William Windle deserves special mention.[15] Primarily because of his methodology and his gradual decision to use the subhuman primate as a model, much of the pathophysiology of the sequelae of asphyxia is clearer. Dr. Windle has published two excellent summaries of his research as well as dozens of papers. [16,17] He also was responsible for developing an extraordinary multidisciplinary effort in Puerto Rico, in conjunction with Pierce Bailey. The intense environment, coupled with the concentration of several fine minds, was phenomenal not only in terms of content but in range of exploration. During its 15 year history, the lab was visited by many of the most productive fetal physiologists in the world and served as a training area in both perinatal and neonatal care for many young investigators. Dr. Ron Meyers eventually followed Windle and became the primary investigator in the Puerto Rico project from 1964-1970 when the lab closed. His work is most notable because it reflects the summation of the most important correlates between clinical state, biochemical measures and pathological findings. Dr. Meyers described the cycle of hypoxia leading to lactate dependent cellular damage which is likely causal in brain damage. As the cells swell with secondary loss of membrane transfer integrity, ischemia occurs, further decreasing oxygen delivery. Since, simultaneously, cardiac muscle is being affected, resulting in reduced cardiac output, further hypoperfusion occurs.[18] (Remember that such cardiac data predicting reduced cardiac output first appeared around 1910!) It seems fair to say that these laboratory findings built upon empiric human data such as that of Little, careful clinical observation as exemplified by Eastman, and systemization as developed by Apgar, resulted in altered approaches to both resuscitation and prevention.

It is from a more current historical perspective that Dr. Edward Hon is mentioned.[19] Dr. Hammacher[21] and Dr. Calderyo-Barcia[20] also deserve historical consideration relative to diagnosis of intrapartum distress. Since the goal of observed pathophysiology should be prevention, based on the understanding of the involved mechanisms, the work of these investigators must be considered central. Unfortunately many exaggerated claims for the value of fetal monitoring using inappropriate or absent controls have been made. The magnificent obstetrical inconoclast, Dr. Robert Goodlin, in his remarkable article on fetal monitoring quotes Shakespeare: "All that glitters is not gold," with reference to fetal monitoring.[22] His cynicism is justifiable in that many confounding variables, such as marked improvement in neonatal care and increased risk assessment, became operative essentially simultaneously with the development of continuous fetal monitoring. But omit the argument whether the exact information derived distinguishes "benign" from "malignant" patterns, the absence of patterns is clearly reassuring and a valid indicator of fetal well being. Alternatively, abnormal heart rate is very positively correlated with
both poor outcome and fetal acidemia. The current problem, from a historical perspective, then becomes our inability to precisely distinguish the false positive affected from the true positive asphyxiated or compromised fetus. As a screening device to aid nurses and physicians, however, these techniques simply have no peer. With the addition of fetal scalp sampling developed by Saling, to further delineate fetal health in deviations of heart rate from normal, we indeed have tools to help identify the fetus with asphyxia.[23]

The benefit to the author of such a historical review as herein presented is incalculable. This exercise makes one feel, however, that we may be, from a relative historical perspective, in a very primitive period, as regards birth asphyxia prevention. As the world turns, we are only some 120 years from Little's presentation. With microprocessors, magnetic chips, ultrasound, and minicomputers burgeoning in our society, future historical perspective chronicles will hopefully marvel at how well we did, with so little technical capacity!

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