



History and Perspective in the Perinatology: A Comprehensive Literature Review

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Abstract

At the turn of the 20th century and before this time, there was little that a physician could do for premature infants. Except keep them warm, feed them breast milk, isolate them from strangers and each other, weigh them daily, and hope for the best in this chapter we are going to show the general history of neonatology, to take an international outlook, and to review the Hungarian characteristics and our own personal experiences which embrace now more than 40 years.

Keywords: Ancient times of medicine; Early era of incubators; Some famous “high risk” newborn babies; New era of perinatal care; William A. Silverman; Neonatology in Hungary; Current issues and the future

Introduction

According to well-known phrase, "history is the school-master of life", and has a way of keeping us humble. The medical history is replete with examples of individuals who made discoveries or contributions to medicine and often received no recognition or reward for their work during their lifetime. Hippocrates (460 BC) was an ancient Greek physician [1,2] and was considered one of the most outstanding figures in the history of medicine. He is referred to as the "father of medicine" and he was convinced that "no fetus coming into the world before seventh month of pregnancy can be saved". This statement has been more or less true till the 1960s. We are also introducing here Soranus of Ephesus (98-138 AD) [3] as a tribute to that great physician of the Greco-Roman Era. He practiced in Rome, wrote on midwifery and newborn care. It is worth remembering the first "perinatologist" in the world.

Now take a great leap forward to find Gregor Mendel (1822-1884) the transmission of inherited traits had a profound effect on biology and medicine but no honors came to him during his life [4]. His work with pea plants was so brilliant and unprecedented at the time it appeared that it took thirty-four years for the rest of the scientific community to catch up to it. This simple test gave birth to the idea of heredity. The impact of genetic theory was no longer questioned in any one's mind. Ignaz Semmelweis (1818-1865) [5] suffered severe depression during his life which was accentuated by the lack of recognition for his contributions to medicine. Semmelweis was a Hungarian physician called the "savior of mothers" who discovered that the incidence of puerperal fever sepsis could be drastically cut by use of hand washing standards in obstetrical clinics. He began writing open and increasingly angry letters to prominent European obstetricians, at times denouncing them as irresponsible murderers. Semmelweis died in a mental institution, possibly after being severely beaten by guards.

Early Era of Incubators

Denucé was who first described an incubator (Figure 1) developed for care of the premature infants [6]. This instrument was a double-walled zinc tub in which the space between the walls was filled with warm water. Credé noticed that ophthalmia neonatorum caused by *Neisseria gonorrhoeae* was transmitted from mother to infant and introduced the simple technique of cleaning the eyes of newborn infants with 2% aqueous solution of silver nitrate [7]. Tarnier was a French obstetrician. His work involved the perinatal aspects of obstetrics, and particularly treatment of premature infants [8]. He realized that not only a constant temperature but isolation, hygiene, appropriate feeding, and a warm, humid environment were also necessary for premature infant's survival. Tarnier's prototypes of infant incubators were basically wooden boxes with glass lids and compartments that contained hot-water bottles, named "couveuse". In France, Pierre Budin, an obstetrician, introduced the radical concept of the well-babies clinic (1892) [9]. He introduced the systemic nutritional status

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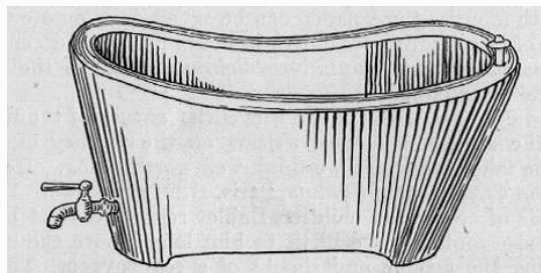


Figure 1: Denucé's incubator (1857).



Figure 2: First transport incubator for newborns (1922).

check-up of infants by weighing and measuring as well as educating mothers on the maintenance of breast feeding and substituting the use of sterilized milk if natural nutrition failed. Archibald E. Garrod (1857-1936) postulates that genetic defects cause many inherited diseases [10]. Garrod, a prominent physician working in London, understood both the new science of biochemistry and the emerging discipline of genetics. Fifty years would pass before biochemists understood all of the steps in the pathway he described, and accepted the term "inborn errors of metabolism" created by him [11]. In the early 1920s, Julius Hess in Chicago designed an incubator in which he used electricity to generate hot water that circulated between the inner and outer walls of a metallic box. He compiled 21 cases of long-term survivals less than 1000 g birth weight. He also developed the Ambulance Box – a miniature version of his incubator (Figure 2) and organized an infant transportation program in Chicago. It is an interesting fact that the incubators remain one of the most enduring symbols of the successes and the failures of the modern neonatal intensive care as well [12].

Starting in the late 19th and early 20th centuries, a precipitous decline in infant mortality was observed both in Europe and America. The cleaning the market milk supply was the single most important contributor to this decline and this development played a far more important role than family income, other sanitary measures, or medical interventions. At the same time premature infants served as carnival attractions exhibited them at fairs and amusement parks for 25 cent "fee" at the turn of the 20th century. In fact, many preemies were cared at home, sometimes in primitive circumstances [13].

Some Famous "High Risk" Newborn Babies

- Kepler, J: Astronomer (1571-1630) I.Q. 160
- Newton, I: Physicist (1642-1727) I.Q. 170
- Voltaire (also known as Francois-Marie Arouet): Philosopher (1694-1778) I.Q. 180

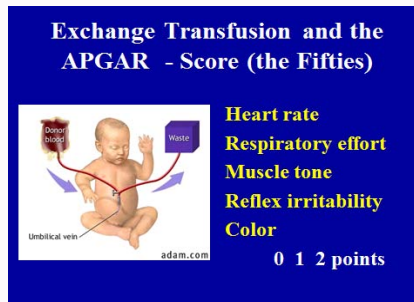


Figure 3: ET and the APGAR-score.

- Goethe, JW: Poet (1749-1822) I.Q. 200
- Furthermore: Churchill, Thomas Hardy, Picasso, Roosevelt, Anna Pavlova..., etc. [12].

Despite the promises of advances in neonatology, many people still believe that babies small and sick at birth will remain weak and dull in adult life. In reality, with the exception of a small number of infants with severe neurological illness, the outlook for premature babies is just as good as that for babies born at term.

New Era of Neonatal Care

As technology became more complex, and care of infants became the exclusive domain of specialized units within hospitals, the sociology and ethics of neonatal care became more complex. Such use included data from Wilson et al. [13] that administration of oxygen stabilized irregular respiratory patterns commonly seen in preterm infants. From such an observation in 1942, widespread administration of high concentrations of inspired oxygen became routine. Diamond was the founding father of pediatric hematology [14], and inventor of the exchange transfusion (ET) via umbilical vein for erythroblastosis fetal. Virginia Apgar [15] was an American physician who specialized in anesthesia and pediatrics. She is best known, however, as the developer of the Apgar test, a method of assessing the health of newborn babies that has drastically reduced infant mortality over the world. It is well-known that extremely high levels of serum bilirubin (SEBI) can lead to brain damage. Removal of blood from the affected infant and replacing with fresh blood from the blood bank that is ET (Figure 3) is used as the treatment for severe jaundice in newborn infants. This intervention, which was performed unnecessarily in many cases in Hungary in 1960s and 70s, has been shown to reduce brain damage; however it is associated with serious adverse events including death. In 1953, Apgar introduced her score-system which is administered one minute and five minutes after birth, and sometimes also at 10 minutes.

Karl Landsteiner was an Austrian biologist and physician [16]. He is noted for his development of the modern system of classification of blood groups and received the Nobel prize in 1930 with Alexander Wiener who identified the Rh factor in 1937 [17]. Astrup was the father of the pH-electrode and we are thankful for the opportunity of having been able to have met him in a conference held in Copenhagen in 1979 [18].

One of the famed and leading neonatologists of the second half of 20th century was Bill Silverman (Figure 4) [19]. He was our mentor and also a good fatherly friend. Others called him "the pope of neonatology". Bill devoted much of his research to retrolental fibroplasia and became an indefatigable advocate of "evidence

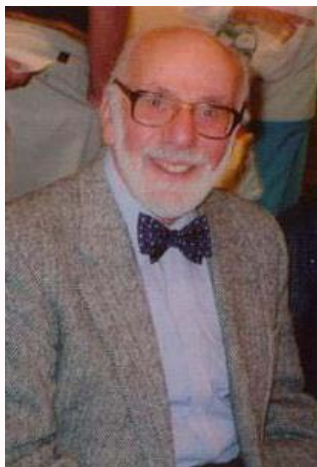


Figure 4: Professor William A. Silverman (1917-2004).

based medicine" (EBM) almost half a century before the term was coined, and decades before the principles were widely appreciated in medicine. In the latter stage of his career, he became a controversial critic of neonatology practices that saved the lives of extremely premature infants but left them with a lifetime of severe physical and mental disabilities. In 2003, the American Foundation for the Blind awarded him a Migel medal, its highest honor.

NICUs of the 70s I.

- Erythroblastosis
- GBS-sepsis
- IDM-birth defects, hypoglycemia
- RDS+PPHN in large preemies
- Meconium aspiration
- Malformations
- Prenatal corticosteroids

Neonatal Intensive Care continued to be a rapidly changing area of work at that time [20]. We focus now only on the problem of Group B Streptococcal disease (GBS). Since emerging as the leading infectious cause of neonatal morbidity and mortality both in North America and Europe during the 1970s, rates of GBS sepsis have dramatically declined, primarily because of the discovery that administering antibiotics to at-risk women during labor could prevent invasive disease in the first week of life. Maternal intrapartum GBS colonization is a major risk factor for early-onset disease in infants, and vertical transmission of GBS from mother to fetus primarily occurs after the onset of labor or membrane rupture.

NICUs of the 70s II.

- Rhogam
- Screening and penicillin
- Fetal monitoring
- CPAP
- Antenatal ultrasound

Numerous studies have documented that the use of Rho (D) Immune Globulin (Rhogam) can prevent the immunological

condition known as Rhesus hemolytic disease of newborn. Therefore, in a Rhesus negative mother it can prevent sensitization of the maternal immune system to Rh D antigens, which can cause rhesus disease in the current or subsequent pregnancies. We would like to stress the role of antenatal steroids used with the intention to help the lungs of a premature fetus develop before the fetus comes out. Over and above close fetal monitoring and application of antenatal ultrasound technique, the Continuous Positive Airway Pressure (CPAP) ventilation developed by Gregory in 1971 [21] was a significant progress in the help of respiratory efforts of premature infants.

Issues in the 80s

- Transcutaneous monitoring
- Technologic Improvements: better ventilators & monitors,
- CT, doppler echo, MRI, ultrasound, ECMO
- Surfactant trials
- Benzyl alcohol, E-Ferol, etc. tragedies [22]

As far as the issues of the 1980s are concerned we would like to highlight some unfavorable events from the series of undoubtedly successful methods. Many tragic episodes — such as benzyl alcohol, hexachlorophene or E-Ferol, etc. — in the history of neonatology testified to the dangers of aggressive treatment for treatment's sake, or the rash adoption of new techniques or drugs without carefully controlled trials.

Progress in the 90s

- Folate to prevent NTDs
- Antenatal Steroids
- Improved survival of micropreemies (fetal infants)
- Nitric Oxide therapy
- Fetal therapy
- "Back to Sleep" reduced SIDS (Sudden Infant Death Syndrome)

During the 1990s, significant improvement in the survival of extremely low birth weight infants [23] has been reported. Now we are dealing a little bit with this very delicate question, while we admit that in this decade there was further spectacular progress indeed in the field of perinatal care. At the same time there is a long time debate regarding the limits of viability and the ethics of resuscitating these infants because of increasing evidence that these fetal infants face significant neurologic and developmental handicaps as they grow older [24]. The debate regarding who is too small and too immature to live will probably never end.

The effectiveness of the neonatal intensive care technology at the extreme limits of birth weight or gestational age is essentially unknown in the developed countries. There is, however, very little information about long-term outcomes, as the medical and developmental status of few of these infants has been followed carefully.

Neonatology in Hungary

- In the 1960-1970s it was like 20-25 years before in west countries



Figure 5: Premature care in "air-conditioned" wards.

Neonatal Intensive Care Technologies and Procedures in Debrecen NICU

- ❑ Located close to the delivery room
- ❑ Delivery room resuscitation
- ❑ Modern (Draeger) incubators, control of noise and light
- ❑ Appropriate diagnostic imaging (CT, MRI, US etc.)
- ❑ Physiologic monitoring (CR, CVP, Trecut, PO₂, PCO₂)
- ❑ Laboratory testing (micro sampling methods)
- ❑ Respiratory support (surfactant, CPAP, HFO, NO etc.)
- ❑ Neonatal (developmental) pharmacotherapeutics

Box 1: Neonatal intensive care in Debrecen NICU.

- It was a division of Pediatrics: there were many infections, jaundices, congenital malformations, etc.
- High mortality rate, especially in the perinatal period
- In the 1980s: launching Neonatal Intensive Care Units (NICU)s

As far as the neonatology is concerned in Hungary, we lagged several decades behind west countries. We had to fight with various types of infections, hyperbilirubinemias, malformations etc. At that time there was a high mortality rate especially in very low birth weight infants. The first NICU was launched in the middle of the 1980s in the Department of Pediatrics, University Medical School of Debrecen. Until that time we had to work in very uncomfortable circumstances called "air-conditioned division" consisted of some wards with small beds for neonates. We — doctors and nurses, and sometimes newborn infants — were suffering from the great heat and the high humidity. We felt as if we had been in a Turkish (steam) bath (Figure 5).

At the turn of the 21st century as technology became more complex, spectacular changes and improvements took place in the neonatal intensive care both in Hungary and in Debrecen. The neonatal intensive care unit can be a confusing place, like a "manufacturing company" today. One can see there lots of equipments, electronics, dials, wires, tubes, strange noises, alarms etc. We can say that the Debrecen NICU is a modern "factory" now (Box 1), equipped with all tools which are necessary to modern care of newborn infants. We have to stress that the incubator is a "central figure" during premature care nowadays, as well.

Neonatal Intensive Care in Debrecen NICU

The incubator keeps the baby warm with moistened air in a clean environment, and helps to protect the baby from noise, drafts, infection, and excess handling. The very tiny and sick infants are

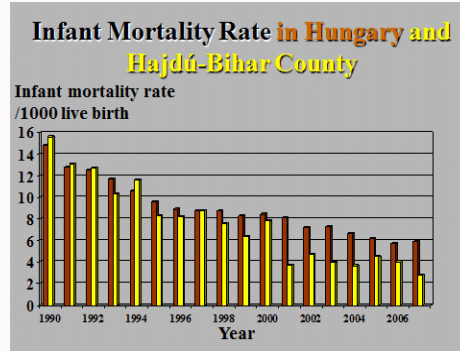


Figure 6: Infant mortality rate in Hungary and Hajdú-Bihar County.



Figure 7: Debrecen NICU.

requiring sophisticated systems for monitoring their cardiorespiratory functions and supporting their respiratory efforts. Recent models of infant ventilators are heavily computerized and support diverse modes of operation, including "assist control".

Now we are going to show the present situation concerning the perinatal care in Hungary and closely in Hajdú-Bihar County. In the period from 1990 to 2006 infant mortality rate (per 1,000 live births) decreased both in Hungary and in Hajdú-Bihar County. These declines were substantial and steady, and a few increases of infant mortality rates that occurred in selected years were of minor value, possible due to vagaries of chance. Recent years — as it can be seen in the Figure 6, the lowest infant mortality rates were observed in Hajdú-Bihar County (from 2007: less than 3/1,000 live births). These values are indeed below the European Union average [25]. The explanation of this phenomenon based on some changes of pregnant women behaviour (like decrease in smoking prevalence), and mainly the wider availability of modern medical technology.

Let's have a look on picture of the modern NICU in Debrecen in which the "Turkish bath", we mentioned, doesn't exist anymore. This was the scene when a new patient arrived (Figure 7).

Coming back to the original topics of this historical review, we would like to stress the importance of evidence based medicine (EBM) concerning the current issues of neonatology [26]. Practicing EBM requires clinical expertise, but also expertise in retrieving, interpreting, and applying the results of scientific studies and communicating the risks and benefits of different courses of action to patients. Using techniques from science, statistics and prospective randomized controlled trials EBM aims for the ideal that healthcare professionals should make "conscientious, explicit, and judicious use of current best evidence" in their everyday practice. As a memorial of

Current Issues and the Future

- ❑ Prevention of major morbidities (ROP, BPD, brain function)
- ❑ Practicing EBM
- ❑ Providing adequate sedation & pain relief
- ❑ Minimizing invasive procedures (ET, ECMO, eye surgery etc.)
- ❑ Antioxidants (DPA?) to reduce lung injury
- ❑ Sildenafil (Viagra®) to treat severe BPD
- ❑ Fetal surgery for NTDs

Box 2: Current and future issues.



Figure 8: Fetal surgery.

Bill Silverman we quote his remarks “there is no other way to know when our observations about complex events in nature are complete (Box 2). Our knowledge is finite, but our ignorance is infinite. In medicine, we can never be certain about the consequences of our interventions, we can only narrow the area of uncertainty [1].

Finally, a fantastic photo (Figure 8), made in the course of an intrauterine operation due to neural tube defect (NTD) of a 23rd gestational age fetus in Nashwill, US. During the procedure, the doctor removes the uterus via C-section and makes a small incision to operate on the baby. The photographer arrested moment when the fetus seizes operating surgeon's finger. The photograph captures this amazing event with perfect clarity. The editors titled the picture, "Hand of Hope [27]".

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