Review

Developmental language disorder: evidence of error?

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Abstract

The obstetric clamp was introduced in 1912 with explicit instruction to apply it only after all pulsations in the umbilical cord had ceased. Now, nearly 100 years later, evidence from randomized controlled trials is being obtained to demonstrate that delay in clamping the cord appears to cause no harm. Why are evidence and understanding gained long ago so neglected? Clamping the umbilical cord while it is still pulsating disrupts continuing postnatal circulation from infant to and from the placenta. This may cause a lapse in respiration, with impairment (or clear-cut damage) of nuclei in the brainstem auditory pathway. Injury of auditory nuclei in the midbrain causes loss of speech comprehension. Perinatal injury of this midbrain area should be investigated as a possible cause of developmental language disorders.

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Keywords: language development, auditory system, autism, brainstem injury, kernicterus, blood-brain barrier, umbilical cord clamping

Questions

Many, if not most, parents have concerns about the safety of vaccines [1–5]. On the other hand, how many prospective parents embrace the idea of banking their baby's umbilical cord blood? Prospective parents should ask how soon after birth the cord needs to be clamped to obtain sufficient blood for storage [6–9]. Or, should the cord be clamped at all?

Over the past 20 years, clamping the umbilical cord immediately after birth has become part of textbook instruction in obstetrics [10–5]. This may lead to oxygen insufficiency if the baby does not begin to breathe right away. Immediate clamping of the cord goes against a long tradition in obstetrics to wait for breathing to be established, and preferably to wait for pulsations of the cord to cease [16–78]. Pulsations are from the baby's heart continuing to pump blood back to the placenta for oxygen until the lungs have fully taken over the function of respiration [16, 38, 60, 64, 78].

"Respiratory depression" occurs in 5 to 6 per 1000 newborn infants [79, 80]. This statistic is similar to that for the recent increased prevalence of autism [81–4].

Autism is not evident in the neonatal period. The number of infants, 5 to 6 per 1000, with initial respiratory depression is regarded to be small [80]. The same statistic for numbers of children developing autism is shocking, the 1 in 150 statistic. Can this be dismissed as mere coincidence, or does it merit investigation?

Oxygen insufficiency plus secondary factors

Symmetric bilateral damage of brainstem nuclei was found in monkeys subjected to asphyxia at birth, with most serious involvement of nuclei in the auditory pathway [54, 67, 68]. The same symmetric pattern of brainstem damage has been reported in children who died in infancy [85–95]. Maturation of the brain did not follow a normal course in monkeys subjected to asphyxia at birth [67]. The maturational abnormalities resemble defects found in the brains of people with autism from childhood [96–8].

Ranck and Windle (1959) commented on the similarity of the brain damage caused by asphyxia at birth to that of kernicterus, but they pointed out that in kernicterus the damaged brain nuclei are yellow from bilirubin staining [54]. Zimmerman and Yannet (1933) summarized several case reports of kernicterus [99]. They proposed that yellow coloration occurred only in brain nuclei affected by anoxia, and that "any intravital dye will localize in zones of injury and will leave unstained tissues which are not damaged" [99, p757]. This was confirmed later by Lucey *et al.* (1964) and Lou *et al.* (1977, 1979) in experiments with monkeys and sheep [100–2].

Mercury, lead, and other toxic substances also cause symmetric bilateral damage of brainstem nuclei [103–15]. Administration in the neonatal nursery of a thimerosal preserved vaccine (like that against hepatitis B) should therefore be recognized as dangerous. The danger is heightened for any infant who has suffered any sign of respiratory depression, and perhaps for all infants subjected to immediate clamping of the umbilical cord [116–66].

The IACC and its research priorities

The Interagency Autism Coordinating Committee (IACC) hosted an Autism Summit Conference in November 2003. I submitted a brief statement urging investigation of umbilical cord clamping as a possible cause of anoxia at birth leading to auditory system impairment. This issue was not included or even mentioned in the subsequent research matrix.

For the meeting held on May 12, 2008 I submitted a partially annotated bibliography similar to the one below, and have posted my submission at http://www.inferiorcolliculus.org/files/IACCMay12Comment.pdf.

Following are summaries of evidence that I will continue to insist should be included in research on autism:

1. Brainstem auditory nuclei are susceptible to impairment by all causes of autism
2. Language is based on information in acoustic signals
3. Language is learned through hearing, and deafness is a serious handicap

4. Aerobic metabolism is highest in the midbrain auditory nuclei (the inferior colliculi)

5. A lapse in aerobic metabolism damages the inferior colliculi

6. Toxic substances disrupt aerobic metabolism in the inferior colliculi

7. The blood brain barrier (BBB) is breached by anoxia and toxic substances

8. Loss of speech comprehension occurs following injury of the inferior colliculi

9. Perinatal hazards and language development

10. Changes in perinatal practices: umbilical cord clamping and vaccinations

Evidence used to understand medical disorders needs to include results from the past. Review of the medical literature is inadequate in too many recent research publications. The bibliography I present here provides evidence (1) of auditory system impairment in autism, (2) how all etiologies of autism may affect this final common pathway in the brain, and (3) that the current protocol for clamping the umbilical cord at birth, followed by neonatal vaccinations, may be the cause of the recent increase in prevalence of autism.

Following are some notes on the ten points listed above.

1. Brainstem auditory nuclei are susceptible to impairment by all causes of autism

Autism is associated with many different medical conditions [167–251]. What vulnerable systems of the brain are impaired by all etiologies? In particular, what impairment in the brain prevents normal language development? Auditory nuclei in the brainstem should be considered. Blood flow and metabolism are higher in the brainstem auditory nuclei than in any other area of the brain [47, 252, 253]. This may go against intuition, but as Fisch (1970) pointed out, the auditory system is the vigilance center of the brain; it is active even while we sleep. Hearing is the sense that keeps us continually aware of environmental events [254].

2. Language is based on information in acoustic signals

Beyond vigilance, awareness, and attention to environmental events, Angelo (1985) noted that the auditory system is an information-seeking system [255]. Language is the pinnacle of information-seeking activities, and while we may think we seek information more through picking up a newspaper, magazine, or surfing for something of interest on the internet, language is inextricably tied to acoustic features:

> "In the past, there has been a distinction between extraction of the auditory parameters of speech and a specialized phonetic speech processor. It was suggested that for the latter, exclusive specialized processing is required by the dominant hemisphere, while the former was handled by the general auditory system shared by both hemispheres. Present research shows that the peculiarity of speech does not lie in its phonologic information but in the acoustic information which the central auditory system processes. It is,

therefore, suggested that specialization for the perceptual process extends to the mechanisms by which the acoustic features of speech are extracted and processed." [255, author's abstract]

3. Language is learned through hearing, and deafness is a serious handicap

Children learn to speak "by ear" unless born deaf, and maturation of the language areas of the cerebral cortex is associated with listening [256]. Young children easily learn to speak more than one language, without accent. Past the first decade of life, detection of syllable and word boundaries in a foreign language becomes more difficult, and for adults to learn to speak a new language without accent is rare. Because of its higher blood flow and metabolism, the auditory system may succumb to aging earlier than other areas of the brain.

Deaf children require early special education to acquire language, and there is little doubt, that cochlear implants for children born deaf are helpful [257–60]. Most children with autism are not deaf. However, evidence of auditory processing problems in autism is abundant, especially aversion to loud noise, or hyperacusis [261–76].

4. Aerobic metabolism is highest in the midbrain auditory nuclei (the inferior colliculi)

The auditory nuclei of the midbrain (the inferior colliculi) have the highest blood flow and metabolism in the brain [47, 252, 253]. This midbrain center is prominently involved in the pattern of symmetric bilateral damage of brainstem nuclei known as Wernicke's encephalopathy, reported for over 100 years in cases of alcoholism, deficiency of vitamin B1 (thiamine), cardiac arrest, and poisoning by toxic substances including antibiotics, pesticides, herbicides, and heavy metals [277–323, 103–15].

5. A lapse in aerobic metabolism damages the inferior colliculi

Symmetric bilateral damage restricted to brainstem nuclei was reported by Wernicke in 1881 in two patients who died following chronic alcohol intoxication, and one who ingested sulfuric acid [277–82]. The same pattern of damage was subsequently described in people who died of beriberi, a neurological disease of the 19th and early 20th centuries that reached epidemic proportions in Asian countries [283–9]. Beriberi was at first thought to be caused by bacterial infection [283], but investigation finally revealed that the disease afflicted people whose dietary staple was rice, after natural brown rice was largely replaced by refined white rice [284–9]. Vitamin B1 (thiamine) had been removed in the refining process.

Thiamine deficiency disrupts aerobic metabolism because thiamine is an essential cofactor for enzymes of the aerobic metabolic pathway [290]. The bilateral symmetric lesions of the brainstem caused by thiamine deficiency have been repeatedly confirmed [291–302]. That this pattern of damage results from disruption of aerobic metabolism has been confirmed in re-

search studies of chemical poisons, thiamine deficiency, and cardiac arrest [111–4, 290, 295, 299, 315, 319–23,].

6. Toxic substances disrupt aerobic metabolism in the inferior colliculi

Alcohol damages the intestinal system, and may therefore prevent absorption of thiamine and other nutrients [308,315]. Alcohol may also be directly toxic to aerobic enzymes. Pyrithiamine is directly toxic by displacing thiamine at its normal site on the enzymes for which it is a cofactor [324–6]. Other substances, including mercury and lead, produce Wernicke-like patterns of damage within the brain, and may also be directly toxic to aerobic enzymes [103–115].

Cardiac arrest and anoxia, if not fatal, also result in Wernicke-like patterns of damage, and the inferior colliculi in the midbrain auditory pathway are most prominently affected by sudden cardiac arrest or total anoxia [54, 67, 68, 70–71, 85–95, 100, 319–23]. Because impairment of auditory function might be expected to interfere with a child's learning to speak, I suggested in 1975 that autism might result from impairment of the inferior colliculi, then in 1990 and 1999 that autism might be a variant of Wernicke's encephalopathy resulting from oxygen deprivation at birth [327–9].

7. The blood brain barrier (BBB) is breached by anoxia and toxic substances

Autism may more accurately be described as a variant of kernicterus [330]. Ranck and Windle (1959) commented that the brainstem lesions caused by asphyxia at birth resembled those found in kernicterus, but lacking the yellow coloration caused by bilirubin [54]. Lucey *et al.* (1964) provided evidence that bilirubin only stains brain nuclei previously injured by asphyxia [100]. Zimmerman and Yannet (1933) had made that observation three decades earlier [99]. Lou *et al.* (1977) injected Evans blue dye into asphyxiated fetal sheep, and found that the dye localized in areas where the blood-brain barrier had been breached [101, 102].

Toxic substances may directly impair the blood-brain barrier in vulnerable nuclei like the inferior colliculi. They may also, like bilirubin, enter vulnerable nuclei as a secondary insult, following injury of the blood-brain barrier by asphyxia [99-102]. Most important is to identify the brain systems affected. The inferior colliculi are most likely to be affected by many insults, and combinations of insults.

8. Loss of speech comprehension following injury of the inferior colliculi

Loss of speech comprehension following injury of the inferior colliculi has been described in at least 13 case reports; five were due to traumatic injury [331, 332, 335, 336, 338], four resulted from cerebrovascular accidents [333, 338, 337, 341], and four from cancerous growths [334, 337, 339, 342]. Traumatic injury was incurred in a skiing accident in one case [336]; the other four resulted from motor vehicle accidents. Vulnerability of the inferior colliculi to impact from the tentorium of the cerebellum was discussed in four of the reports [331, 332, 335, 336]. Injury of the same kind can also occur during a traumatic birth [343–5].

Of the four people injured in automobile accidents, three became disoriented and combative [331, 332, 335]. The patient described by Musiek *et al.* also became combative during early recovery from meningitis [340].

Traumatic Injury: The patient described by Howe *et al.* was alcoholic and intoxicated at the time of her accident [331]. She appeared deaf, not responding to questions or commands, but malingering was considered. On autopsy, punctuate hemorrhages suggestive of Wernicke's encephalopathy were found in the brainstem, including the inferior colliculi and lateral lemiscal tracts of the auditory pathway.

Until pathology in the inferior colliculi was revealed in MRI scans, deafness in the patients of Jani *et al.* and Hu *et al.* was thought to be psychological [332, 335]. Visible injury of the inferior colliculi was confirmed in both patients using gadolinium diethylene-triamine-pentaacetic acid (Gd-DTPA), a substance that only enters the brain at sites where the blood-brain-barrier has been compromised [346–8].

Removal of cancerous growths: Disabilities of patients with cancerous growths of the inferior colliculi are also revealing.

(1) The inferior colliculi were removed in the patient of Meyer *et al.*, and after surgery the patient was unable to understand verbal communication, although nonverbal hearing, reading, writing, and speaking abilities were unimpaired [334]. He could still identify and localize all sources of non-verbal sounds. Furthermore, he also identified correctly pieces of music that he had known before. Pure tone audiogram and brainstem auditory evoked potentials (BAEPs) were normal and identical to those before operation. Speech audiogram performance, however, had dramatically deteriorated to discrimination scores of 10 and 20. Meyer *et al.* suggested that the inferior colliculus may provide a "gating process" that blocks "irrelevant" sensory input, which would be essential for linguistic comprehension.

(2) The inferior colliculi were damaged during surgery in the patient of Masuda *et al.* [337]. The patient before onset of her illness was bilingual (Portuguese and Japanese). Immediately after surgery, she complained of bilateral hearing loss with bilateral tinnitus (ringing in the ears). She was unable to understand verbal communications in either Japanese or Portuguese, but she could speak, read, and write in both languages without difficulty and with the same competence as before her surgery. She could identify nonverbal sounds such as the ring of telephone and a baby's cry, and she was able to distinguish some new sounds during the first year after surgery. She also correctly identified pieces of music familiar to her before the surgery, but she could not understand the lyrics.

Meningitis: The patient described by Musiek *et al.* was a 21-year-old college student, who became ill with meningitis [340]. During most of the patient's first week of hospitalization, personnel working with him noted no response to any sound. Toward the end of the week, and for several weeks thereafter, the patient claimed he heard a certain sound, yet other people in the room with him did not hear the sound. MRI revealed that both inferior colliculi were almost totally infarcted. By the third week of his hospital stay, definite improvements in hearing were noted. The patient could hear voices, but he could not understand anything that was being said to him. He stated, "Voices don't sound like voices." He spoke often, but in a monotone voice. Listening was a strain, and fatigued him to the point where he often complained about it. He continued to hear environmental sounds, such as a dish being dropped and water running from a faucet, and he was able to discern loud sounds from soft, but was inconsistent in identification of the sources of environmental sounds. The patient had extreme difficulty listening to people speak whenever background noises were present.

At this point in his recovery, he was able to read slowly, and this skill continued to improve over time. During the fourth week, the patient reported that he felt his hearing was improving. He could hear voices on TV but could not understand what was being said. In general, the patient knew when people were speaking but could not follow speech on a consistent basis. He stated that riding in a car was difficult because everything was too loud.

9. Perinatal hazards and language development

How much more serious impairment of function in the inferior colliculi must be for an infant. How could such a child ever learn to speak? That speech comprehension can be lost following injury of the inferior colliculi should provide the greatest impetus for investigating perinatal impairment of the inferior colliculi as the cause of developmental language disorders.

Gilles (1963) cited the findings by Ranck and Windle (1959) of damage to the inferior colliculi caused by asphyxia at birth, and suggested this should be investigated as a possible cause of childhood aphasia [85, 54]. I have posted a proposal online for use of fMRI to investigate impairment in the inferior colliculi at: http://www.inferiorcolliculus.org/presentation.html.

Every medical condition associated with autism has the potential of disrupting aerobic metabolism in the inferior colliculi. Genetic metabolic conditions are rare. Increased prevalence and/or awareness of autism have come about within the past 20 years. The non-hereditary conditions associated with autism must be considered, especially those that might be related to changes in perinatal care.

10. Changes in perinatal practices: umbilical cord clamping and vaccinations

Vaccinations given to young children have increased since 1970 and are given earlier in infancy [349-352]. Hepatitis B vaccine is given in the immediate neonatal period [352]. Many people view this as dangerous [350, 351]. Vaccination in the first neonatal hours is especially dangerous in view of the obstetric protocol to clamp the umbilical cord immediately at birth, whether or not the infant has taken its first breath.

The danger is that a lapse in respiration at birth will impair the blood-brain-barrier in the brainstem nuclei of high metabolic rate like the inferior colliculi. This will then allow substances such as the thimerosal preservative in vaccines to enter these brain areas.

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[1] Fom`bonne E. Thimerosal disappears but autism remains. Arch Gen Psychiatry. 2008 Jan;65(1):15–6.
[2] Schechter R, Grether JK. Continuing increases in autism reported to California's developmental services system: mercury in retrograde. Arch Gen Psychiatry. 2008 Jan;65(1):19–24.
[3] Baker JP. Mercury, vaccines, and autism: one controversy, three histories. Am J Public Health. 2008 Feb;98(2):244–53.
[4] Offit PA. Vaccines and autism revisited--the Hannah Poling case. N Engl J Med. 2008 May 15;358(20):2089–91.
[5] Young HA, Geier DA, Geier MR. Thimerosal exposure in infants and neurodevelopmental disorders: An assessment of computerized medical records in the Vaccine Safety Datalink. J Neurol Sci. 2008 May 14. [Epub ahead of print]

Umbilical cord blood banking

[6] Dunn PM. Banking umbilical cord blood. Lancet. 1992 Aug 1;340(8814):309.
"The HUC [umbilical cord blood] belongs to the baby, at least until adaptation to extrauterine life has taken place and umbilical pulsation has ceased. It is unethical to rely on permission obtained in advance from the mother to take the blood unless the critical importance of the transitional feto/placental circulation is not only fully explained to her but also is defended in practice by the birth attendants. Unfortunately, in many parts of the world the importance of perinatal feto/placental haemodynamics is poorly understood, as shown by the arbitrary way in which the cord is often triple-clamped at birth to obtain arterial and venous samples for blood gas and acid-base studies. This practice not only abruptly interrupts the umbilical circulation but may also deprive the newly born infant of an amount of blood equivalent to at least a third of its normal circulating volume." [p309]
[7] Díaz-Rossello JL. Early umbilical cord clamping and cord-blood banking. Lancet. 2006 Sep 2;368(9538):840.
"Although there is strong evidence of its adverse effects, and no evidence of its benefits, early clamping is a common practice in modern obstetrics, especially with respect to the harvest of neonatal blood for cord blood banking."
"…Quality standards for cord blood collection are based on ensuring that the largest volume of neonatal blood is retained in the placenta and umbilical cord, which involves clamping the cord as early and as close to the neonate as possible. If complete physiological redistribution of blood from the placenta to the infant's body is allowed to take place, the cord becomes flaccid and pulseless, and the natural residual placental blood volume is insufficient for banking."
"I suggest that the timing (in seconds) of cord clamping should be recorded at every birth, and that cord-blood donors should have a special haematological follow up." [p840]
[8] Royal College of Obstetricians and Gynaecologists. Scientific Advisory Committee opinion paper 2: umbilical cord blood banking. London: Royal College of Obstetricians and Gynaecologists, 2006. http://www.rcog.org.uk/resources/public/pdf/cord_blood_parent_info.pdf (accessed June 20, 2008)

"Some evidence indicates that immediate cord clamping may be harmful to babies. However, delaying cord clamping can prevent a successful cord blood collection." [p5]

[9] ACOG Committee on Obstetric Practice; Committee on Genetics. ACOG committee opinion number 399, February 2008: umbilical cord blood banking. Obstet Gynecol. 2008 Feb;111(2 Pt 1):475-7.

"The collection should not alter routine practice for the timing of umbilical cord clamping." [p476]

But see cord clamping protocol stated in 2006 below [15]. Hopefully a change in the protocol is forthcoming.

Current delivery room protocol—textbook instruction adopted in the 1980s

[10] Hibbard, BM. Principles of Obstetrics. London; Boston: Butterworths, 1988.

"Apgar scores are recorded at 1 minute and again at 5 minutes, timing the observations accurately (see chapter 43, Table 43.1). Also the time to first breath and time to the establishment of regular respirations are recorded."

"Permanent cord clamps or ligatures (Figure 26.27) or special bands are applied to the umbilical cord as soon as possible after birth…" [p470]

"…As soon as possible after suctioning, the cord is clamped…"

"… consequences of a significant shift [of blood volume] toward the infant include polycythemia, circulatory volume overload, and hyperbilirubinemia,and these generally outweigh any potential advantage of augmenting the infant's iron reserve…" [p301, citing Cunningham *et al.*, Williams Obstetrics, 18th ed.]

[11] McGregor Kelly, J. General Care (chapt 22) in Avery GB, Fletcher MA, MacDonald MG, eds . Neonatology, Pathophysiology and Management of the Newborn, Fourth Edition. J.B. Lippincott Company, Philadelphia, 1994.

[12] Cunningham FG, MacDonald PC, Gant NF, Leveno KJ, Gilstrap LC, Hankins GDV, Clark SL, Williams JW, (1997) Williams Obstetrics, Twentieth Edition. Stamford, Conn: Appleton & Lange, pp 336-337.

"Although the theoretical risk of circulatory overloading from gross hypervolemia is formidable, especially in preterm and growth-retarded infants, addition of placental blood to the otherwise normal infant's circulation ordinarily does not cause difficulty. Our policy is to clamp the cord after first thoroughly clearing the infant's airway, all of which usually takes about 30 seconds."

[13] Turrentine, Clinical *Protocols in Obstetrics and Gynecology, Second Edition,* 2003.

(1) Doubly clamp cord segment (10-20 cm) immediately after birth in all deliveries, and place on table.

(2) pH and acid-base determinations indicated for: prematurity, meconium, nuchal cord, low Apgar scores (<7 at 5 minutes), abnormal antepartum fetal heart tracing, any serious problem with delivery or neonate's condition

(3) If unable to obtain cord specimen, aspirate artery on chorionic surface of placenta

(4) Discard cord segment if 5 minute Apgar score satisfactory and newborn stable/vigorous

[14] Cunningham FG, Hauth JC, Leveno KJ, Gilstrap L III, Bloom SL, Wenstrom KD, eds, Williams Obstetrics - Twenty-second edition, New York: McGraw-Hill Medical Publishing Division, 2005.

"... Our policy is to clamp the cord after first thoroughly clearing the airway, all of which usually requires about 30 seconds."

[15] ACOG Committee on Obstetric Practice.ACOG Committee Opinion No. 348, November 2006: Umbilical cord blood gas and acid-base analysis. Obstet Gynecol. 2006 Nov;108(5):1319–22.

"Immediately after the delivery of the neonate, a segment of umbilical cord should be double-clamped, divided, and placed on the delivery table pending assignment of the 5-minute Apgar score. Values from the umbilical cord artery provide the most accurate information regarding fetal and newborn acid-base status. A clamped segment of cord is stable for pH and blood gas assessment for at least 60 minutes, and a cord blood sample in a syringe flushed with heparin is stable for up to 60 minutes (13, 14). If the 5-minute Apgar score is satisfactory and the infant appears stable and vigorous, the segment of umbilical cord can be discarded." [p1321]

History of the current protocol
for clamping the umbilical cord

Early understanding of fetal circulation, respiration, and neonatal transition

[16] Harvey, William. *Anatomical exercitations concerning the generation of living creatures to* which *are added particular discourses of births and of conceptions, &c.* London : Printed by James Young, for Octavian Pulleyn, and are to be sold at his shop at the sign of the Rose in St. Pauls Churchyard, 1653. From Early English Books Online, http://eebo.chadwyck.com/ (accessed 6/28/08).

"Moreover, it is a sure way to know whether the Infant that sticketh in the birth be alive, or not, by the pulsation of the Vmbilical Arteries. But most certain it is, that those Arteries are not moved by the virtue or operation of the Mothers, but of his own proper Heart: For they keep a distinct time and pawze, from the Mothers pulse: which is easily experimented, if you lay one hand upon the Mothers wrest, and the other on the Infants Navel-string. Nay in a Casarean Section, when the Embryo's have been yet involved in the membrane called Chorion, I have oftentimes found (even when the Mother was extinct, and stiffe almost with cold) the Vmbilical Arteries beating, and the Foetus himself lusty."

[17] White C (1773) A Treatise on the Management of Pregnant and Lying-In Women. Canton, MA: Science History Publications, 1987. Available from http://www.shpusa.com/bkindex.html (accessed 6/28/08)

"Can it possibly be supposed that this important event, this great change which takes place in the lungs, the heart, and the liver, from the state of a foetus, kept alive by the umbilical cord, to that state when life cannot be carried on without respiration, whereby the lungs must be fully expanded with air, and the whole mass of blood instead of one fourth part be circulated through them, the ductus venosus, foramen ovale, ductus arteriosus, and the umbilical arteries and vein must all be closed, and the mode of circulation in the principal vessels entirely altered - Is it possible that this wonderful alteration in the human machine should be properly brought about in one instant of time, and at the will of a by-stander?" [p45]

[18] Darwin, E *Zoonomia; or, The Laws of Organic Life, Vol 1,* Section XXXVIII. New York: T&J Swords, Faculty of Physic of Columbia College,1796.

"The placenta is an organ for the purpose of giving due oxygenation to the blood of the fetus; which is more necessary, or at least more frequently necessary, than even the supply of food." [p350]

[19] Darwin, E. *Zoonomia,or the laws of organic life, third Edition.* Vol. III. London, J. Johnson, 1801.

Tying of the cord too soon has been a longstanding problem as was recognized by White (1773) above, and Erasmus Darwin (grandfather of Charles) who stated:

"Another thing very injurious to the child, is the tying and cutting of the navel string too soon; which should always be left till the child has not only repeatedly breathed but till all pulsation in the cord ceases. As otherwise the child is much weaker than it ought to be, a portion of the blood being left in the placenta, which ought to have been in the child." [p321]

Textbook instruction on ligation of the cord (to the early 20th century)

Traditional textbooks of midwifery and obstetrics gave explicit instruction not to tie the cord until the infant was breathing, and that it was better to wait for pulsations to cease. Following are quotes from several texts, along with contemporary research findings and opinions:

[20] Meigs C. Professor of Obstetrics and Diseases of Women and Children, Jefferson Medical College. A Philadelphia Practice of Midwifery, 1842

"The head is born: perhaps the cord is turned once, or even more than once around the child's neck, which it encircles so closely as to strangulate it. Let the loop be loosened to enable it to be cast off over the head. …[or] by slipping it down over the shoulders. … If this seems impossible, it should be left alone; and in the great majority of cases, it will not prevent the birth from taking place, after which the cord may be cast off. … Should the child be detained by the tightness of the cord, as does rarely happen, … the funis may be cut … Under such a necessity as this, a due respect for one's own reputation should induce him to explain, to the bys-

tanders, the reasons which rendered so considerable a departure from the ordinary practice so indispensable. I have known an accoucheur's capability called harshly into question upon this very point of practice. I have never felt it necessary to do it but once. … The cord should not be cut until the pulsations have ceased."

[21] Churchill F On the Theory and Practice of Midwifery. London: Henry Renshaw, 1850.

"After birth of the child, the pulsation ceases in about fifteen or twenty minutes, and that portion of the cord which remains attached to the umbilicus dies, and gradually withers, until it falls off, in the majority of cases, on the fifth or sixth day." [p 91 #181 The umbilical cord, funis, or navel string].

"…in ordinary cases, if we find that the cord is twisted around the neck, all we need do is to draw down more of the cord, and either slip the loop over the head or shoulders. If we cannot do this, we must loosen the cord as much as we can, so as to prevent the strangulation of its vessels, and wait for the uterus to expel the child." [p 131]

"If the child be healthy, and not have suffered from pressure, &c. it will
cry as soon as it is born, and when respiration is established, it may be separated from its mother…" [p 132]

[22] Cazeaux P A Theoretical and Practical Treatise on Midwifery. Fifth American from the Seventh French Edition by Wm R Bullock, MD. Philadelphia: Lindsay and Blakiston, 1871.

"…the circulation existing between it [the child] and the placenta is observed to continue for some time… pulsations in the arteries gradually cease, commencing at their placental extremity; and some authors have advised this event to be waited for before cutting the cord…" [p. 406]

[23] Lusk WT The Science and Art of Midwifery. New York: D Appleton and Company, 1882,

"Infants which have had the benefit of late ligation of the cord are red, vigorous, and active, whereas those in which the cord is tied early are apt to be pale and apathetic."

"1. The cord should not be tied until the child has breathed vigorously a few times. When there is no occasion for haste, it is safer to wait until the pulsations of the cord have ceased altogether.

2. Late ligation is not dangerous to the child. The child receives into its system only the amount of blood required to supply the needs created by the opening up of the pulmonary circulation." [pp214–5]

[24] Jellett, Henry. A Manual of Midwifery for Students and Practitioners. New York: William Wood & Company, 1910.

"As soon as the child is born, its eyes are wiped, any mucus in the air passages is removed, and it is placed in a convenient position between the patient's legs. The cord is tied as soon as it has stopped pulsating, and the infant is then removed." [p350]

Introduction of the obstetric clamp (1912)

[25] Wechsler BB. Umbilical clamp. Am J Obstet Dis Women Child 1912; 60:85-6.

"I desire to present to the profession a little device for use on the cord instead of the usual ligature." [p85].

Wechsler reported that on a recent visit to Vienna, he had witnessed the method of clamping and dressing the umbilical cord without ligature in the Schauta Clinic. Wechsler's clamp is pictured and noted to be smaller than the "ordinary Hemostat" used in Vienna. Rationale for use of a clamp was that it lessens the danger of infection. Its use was described as follows:

"Clamping the cord is accomplished in the following way: 1. Wait until pulsation has ceased; 2. Clamp cord about one inch from umbilicus; 3. Cut cord even with clamp.

The infant is then removed by the nurses and the clamp allowed to remain on stump of cord for fifteen minutes, or about the time the placenta has been expelled then the clamp is ready to taken off." [p86]

Obstetric teaching and concurrent research papers (until the 1930s)

[26] Williams JW. (1917) Obstetrics: A Text-Book for the Use of Students and Practitioners, Fourth Edition, New York: Appleton, 1917.

"Immediately after its birth the child usually makes an inspiratory movement and then begins to cry. In such circumstances it should be placed between the patient's legs in such a manner to have the cord lax, and thus avoid traction upon it. "

"Normally the cord should not be ligated until it has ceased to pulsate."
"I have always practiced late ligation of the cord and have seen no injurious effects following it, and therefore recommend its employment, unless some emergency arises which calls for earlier interference." [pp342–3]

More on use of a clamp (a decade after its introduction)

[27] Ziegler CE. Additions to our obstetric armamentarium. Am J Obstet Gynecol 1922; 3:46–53.

"The primary object of ligating or clamping the cord is, of course, to prevent hemorrhage; and while it is true that hemorrhage would rarely occur even were the cord not compressed, especially after the establishment of respiration, the fact is that hemorrhages have occurred and even with fatal termination. In fifteen years I have had two cases of secondary hemorrhage from the cord which were all but fatal. It is likely, therefore, that some form of compression will always be regarded as necessary."

[28] Levy WE, discussant of Dicks JF.Treatment of the umbilical cord by short ligation and the use of a clamp. Am J Obstet Gynecol 1925 Nov; 10(5):706-8. Discussion pp739–40.

"I am rather inclined to disagree with those who advocate the use of a clamp. To me the ligation of the cord is one of the simplest processes in obstetrics, and why complicate what is inherently simple? I quite agree that the cord should be tied as close as possible to the skin margin, but a piece of tape does that just as well as an instrument. The clamp crushes and macerates the tissues, and macerated tissue, as is well known, is prone to develop bacteria. This also holds true of the so-called milking of the cord, which frequently breaks down the outer surface and so favors the entrance of infection." [p740]

[29] von Reuss, August Ritter. The Diseases of the Newborn. New York: William Wood & Co, 1921. (Vienna, January 1914)

"… A compromise is usually adopted, in that the cord is not tied immediately after birth, nor does one wait till the expression of the placenta, but only until the cessation of pulsation in the cord, an average of five to ten minutes." [p419]

[30] Willaims, JW. Obstetrics: A Textbook for the use of Students and Practitioners, Fifth enlarged and revised edition. D. Appleton and Company, New York, 1927

"I have always practiced late ligation of the cord and have seen no injurious effects following it, and therefore recommend its employment, unless some emergency arises which calls for earlier interference…"

[31] DeLee JB. The Principles and Practice of Obstetrics. Philadelphia, WB Saunders, Company, 1930.

"Tying the cord. – After waiting until the pulsation in the exposed umbilical cord has perceptibly weakened or disappeared, the child is severed from its mother. Until the cord is severed the child is still part of its mother and has no legal existence… During the four or eight minutes while waiting to tie the cord the child obtains from 40 to 60 gm. Of the reserve blood of the placenta—a fact that was first shown by Budin. The blood is pressed into the child by the utterine contractions, and part is aspirated by the expanding chest. This extra blood the child needs in its first days of life, and observation has shown that such children lose less in weight and are less subject todisease…" [p330]

[32] Baer JL, in Curtis AH, ed. Obstetrics and Gynecology (3 vols). Philadelphia & London: WB Saunders Company, 1933, Chapt XXIV – The conduct of normal labor pp 702–844.

"In most clinics the cord is not tied until pulsation has ceased. This is based on the accepted fact that the delay provides the infant with an additional average of 60 to 90 cc of blood. With premature infants or twins, most of which are usually below the weights of average single infants, this additional blood is a distinct advantage. In full-term infants of normal size the advantage is more theoretical than real." [p828]

[33] DeLee, Joseph B. The Principles and Practice of Obstetrics, Sixth Edition. Philadelphia and London: W.B. Saunders Company, 1936. [earlier editions: 1913, '15, '18, '24, '28, '33 (6th) reprinted in '34 & '36]

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that such children lose less in weight and are less subject to disease. It is an error, on the other hand, to force the blood of the placenta into the child by stripping the cord toward the child. This overloads its blood vessels, causes icterus, melena, even apoplexy …" [p334]

[34] Fitzgibbon, Gibbon. Obstetrics. Browne and Nolan Limited, Dublin, 1937.

"…If the infant has cried and has respired well for about five minutes, there is no advantage in leaving at attached any longer to the placenta. Its pulmonary circulation has been opened up and the pulmonary vessels filled with blood …" [p128]

[35] Frischkorn HB , Rucker MP. The relationship of the time of ligation of the cord to the red blood count of the infant. Am J Ostet Gynecol 1939; 38:592–4.

"If a cord be watched immediately after delivery the umbilical vessels can be seen to pulsate strongly throughout their entire length. In a varying length of time the pulsations cease in the more distal part and as this occurs the umbilical vessels collapse. This process of cessation of pulsation and collapse of the vessels proceeds toward the umbilicus until finally there is no pulsation even at the navel. The vessels are then entirely collapsed. If now the cord be tied and cut very little blood will escape from the placental end." [p 593]

[36] Windle WF (1940) Round table discussion on anemias of infancy (from the proceedings of the tenth annual meeting of the American Academy of Pediatrics) Journal of Pediatrics 18:538–47.

"... The rather common practice of promptly clamping the cord at birth should be condemned. Of course, this will make it impossible to salvage placental blood for 'blood banks.' However, the collection of usable quantities of placental blood robs the newborn infant of blood which belongs to him and which he retrieves under natural conditions...

Immediate clamping of the cord is comparable to submitting the infant to a rather severe hemorrhage." [1, p546]

[37] Read, Grantly Dick. Childbirth Without Fear: The principles and practice of natural childbirth. Harper & Brothers Publishers, New York and London, 1944.

"It is my custom to lift up the crying child, even before the cord is cut …"

"Its first cry remains an indelible memory on the mind of a mother; it is the song which carried her upon its wings to an ecstasy mere man seems quite unable to comprehend." [p95]

Pulmonary oxygenation effects closure of the umbilical arteries

[38] Spivack M. The anatomic peculiarities of the human umbilical cord and their clinical significance. Am J Obstet Gynecol 1946 Sep; 52(3):387–401.

"Oxygenation of the newborn's blood after establishment of its pulmonary respiration is the main factor in bringing about closure of the umbilical arteries…

…Experience since long ago has taught some clinicians that ligation of the cord is not paramount in the care of the stump." [1, p398]

[39] Eisaman JR Jr,, discussant of Ballentine GN. Delayed ligation of the umbilical cord. The Pennsylvania Medical Journal 1947,Apr;50 (7):726–8.

"There seems to be undue haste in severing the umbilical cord immediately after the second stage of labor...

...This practice involves many poorly understood changes in neonatal physiology, i..e., closure of the ductus arteriosus and ductus venosus...

...Not long ago placental blood was recommended for transfusions. The volume so obained was 125 to 250cc, providing immediate ligation of the cord was performed." [p728].

[40] McCausland AM, Homes F, Schumann WR (1949) Management of cord and placental blood and its effect upon the newborn; part I. California Medicine 71(3):190–6.

McCausland *et al.* (1949) sent a questionnaire to 1,900 diplomates of the American Board of Obstetrics and Gynecology to determine the usual practice at that time of handling the umbilical cord at birth. Replies from almost every state numbered 1,198 and revealed that 497 (41.5%) clamped the cord immediately after birth, 400 clamped the cord within five minutes after birth, and only 191 waited for pulsations to cease. However, 455 practiced stripping of the cord.

McCausland *et al.* recommended stripping of the cord, especially for premature infants, whom they described as not only underdeveloped, but often in varying degrees of shock.

[41] Eastman HJ. Williams Obstetrics, Tenth Edition, New York, Appleton-Century-Crofts, 1950.

"Whenever possible, clamping or ligating the umbilical cord should be deferred until its pulsations wane or, at least, for one or two minutes…

…. There has been a tendency of late, for a number of reasons, to ignore this precept. In the first place the widespread use of analgesic drugs in labor has resulted in a number of infants whose respiratory efforts are sluggish at birth and whom the obstetrician wishes to turn over immediately to an assistant for aspiration of mucus, and if necessary, resuscitation. This readily leads to the habit of clamping all cords promptly." [pp397–8]

[42] Landau DB, Goodrich HB, Francka WF, Burns FR Death of cesarean infants: a theory as to its cause and a method of prevention. Journal of Pediatrics 1950; 36:421–6.

"Usually at the time of cesarean section as soon as the uterus is opened the operator delivers the infant as rapidly as is consistent with the infant's safety. The cord is clamped and cut immediately and the infant is handed to the waiting assistant...

...This is in marked contrast to the procedure during normal or vaginal delivery. At this time the cord is not clamped and severed until pulsations have ceased."

[43] Greenhill JP. Principles and Practice of Obstetrics; originally by Joseph B. DeLee, M.D., Tenth Edition. W.B. Saunders Company, Philadelphia and London, 1951.

"After waiting until the pulsation in the exposed umbilical cord has ceased, the child is severed from its mother."

"DeMarsh, Alt, Windle and Hillis [The effect of depriving the infant of its placental blood; on the blood picture during the first week of life. JAMA 1941; 116:2568–73] showed that those infants whose cords were not clamped until the placenta had separated from the uterus had on average 0.556 million more erythrocytes per cubic millimeter and 2.6 gm more hemoglobin per 100cc during the first week than those whose cords were clamped immediately. These authors maintained that early clamping of the umbilical cord is equivalent to submitting the child to a hemorrhage at birth. Wilson, Windle and Alt [Deprivation of placental blood as a cause of iron deficiency in infants. Am J Dis Child 1941; 62:320–7.] found that infants whose umbilical cords were clamped immediately after birth had a lower mean corpuscular hemoglobin at eight and ten months of age than those whose cords were clamped after the placenta began to descend into the vagina. It was suggested then that early clamping of the cord may lead to an iron deficiency during the first year of life."

"McCausland, Holmes and Schumann [Management of cord and placental blood and its effect upon the newborn; part I. California Medicine 1949; 71(3):190–6.] advise stripping the cord and placental blood into the infant because it is harmless if done gently and because term babies receive about 100cc of extra blood in this way. These authors claim that babies receiving this blood had higher erythrocyte counts, higher hemoglobin values, higher initial weights and less initial weight losses." [p.251]

From Apgar onward (and concurrent research)

[44] Apgar V (1953) A proposal for a new method of evaluation of the newborn infant. Current Researches in Anesthesia and Analgesia 32:260-267. Online at: http://apgar.net/virginia/Apgar_Paper.html (accessed 6/28/08)

This was Apgar's first paper on scoring the condition of infants during the minutes following birth. Apgar attributed failure of an infant to breathe right away at birth as the result of too much anesthesia given the mother during childbirth, and she stated: "It is common for an infant to breathe once, but then become apneic for many minutes. A satisfactory cry is sometimes not established even when the infant leaves the delivery room."

But should any newborn leave the delivery room, or his connection to his mother before breathing is established?

In a report five years later, Apgar *et al.* (1958) reported that they clamped the cord within the first minute after birth to preserve the "sterile field" and to transfer the baby to neonatal specialists. See citation 148 below.

Meanwhile, many obstetricians continued to follow the instruction of textbooks to wait for pulsations of the cord to cease.

Research on expansion of the lungs at birth

[45] Jäykkä S. A new theory concerning the mechanism of the initiation of respiration in the newborn; a preliminary report. Acta Paediatr. 1954 Sep;43(5):399–410.

     Jäykkä proposed his theory that filling of the capillary bed surrounding the alveoli was the stimulus for initiating lung expansion and the first breath of the newborn.

1955 Greenhill's textbook review of evidence

[46] Greenhill, JP Obstetrics Eleventh Edition WB Saunders Company, Philadelphia and London, 1955

     "Immediately after the baby is delivered it should be held well below the level of the vulva for a few minutes or placed in a warm container the level of which is considerably below the mothers' buttocks (Fig 279). The purpose of keeping the baby at this level is to permit the blood in the placenta to get to the baby. Dieckmann and associates maintain that this procedure will add from 50 to 75 percent of the blood in the placenta and cord to the newborn child [Dieckmann, WJ, Forman JB, and Philips GW: Effects of Intravenous Injections of Ergonovine and Solution of Posterior Pituitary Extract on the Postpartum Patient. Am. J. Obst. & Gynec 60:655 (Sept) 1950].

     If the placenta separates while waiting, expressing it from the uterus and holding it elevated for two or three minutes will accomplish the same purpose. The cord is cut after about three minutes or after it collapses. If the baby is in a special container, it is left in until after the cord is cut. As soon as possible after delivery any mucus in the air passages must be removed with a soft rubber bulb or a tracheal catheter.

     Tying the Cord. After waiting until the pulsation in the exposed cord has ceased, using dull scissors, the child is severed from its mother. With a piece of linen bobbin, coarse silk, rubber band or any sterile strong string, the cord is ligated close to the cutaneous margin of the umbilicus, making sure that there is no umbilical hernia which might allow a loop of intestine to be caught in the grasp of the ligature. It is important to leave as little as possible of the cord to be cast off except when a baby has erythroblastosis…"

     "DeMarsh, Alt, Windle, and Hillis showed that infants whose cords were not clamped until the placenta had separated from the uterus had an average of 0.56 million more erythrocytes per cubic millimeter and 2.6 gm. More hemoglobin per 100 ml. during the first week than those whose cords were clamped immediately. These authors maintained that early clamping of the cord is equivalent to submitting the child to a hemorrhage at birth. Wilson, Windle, and Alt found that infants whose umbilical cords were clamped immediately after birth had a lower mean corpuscular hemoglobin at 8 and 10 months of age than those whose cords were clamped after the placenta began to descend into the vagina. Thus early clamping of the cord may lead to an iron deficiency during the first year of life.

     McCausland, Holmes and Schumann advise stripping the cord and placental blood into the infant because it is harmless if done gently and because term babies receive about 100 ml of extra blood in this way. Babies receiving this blood have higher erythrocyte counts, higher hemoglobin values, higher initial weights and less initial weight losses." [pp280–2]

     "After waiting until the pulsation in the exposed cord has ceased, using dull scissors, the child is severed from its mother." [p281]

     Citing the work of Landau *et al.* [Landau DB *et al.* J Pediat 36:421, April 1950.]: "In attempting to account for the death of babies delivered by cesarean section, Landau and associates concluded that blood loss to the child incurred by immediate clamping of the cord amounted to 90 ml, a quantity of definite significance, especially in preterm infants. Improvement was noted in the condition of babies when drainage of blood from the placenta, after its removal, was facilitated by suspending it in a towel above the child for six to ten minutes or until the cord vessels collapsed." [p283]

Blood flow is found to be higher in the auditory system than anywhere else in the brain

[47] Landau WM, Freygang WH, Rowland LP, Sokoloff L, Kety SS. The local circulation of the living brain; values in the unanesthetized and anesthetized cat. Trans Am Neurol Assoc. 1955-1956;(80th Meeting):125–9.

     This was the first report on blood flow measurements using a radioactive tracer. That nuclei of the brainstem auditory pathway are the sites of

highest blood flow came as a surprise, but also predicted the pattern of damage found by Ranck and Windle (1959) in monkeys subjected to asphyxia at birth.

Weight gain from placental transfusion

[48] Gunther M. The transfer of blood between baby and placenta in the minutes after birth. Lancet. 1957 Jun 22;272(6982):1277–80.

     Measurements of weight change at birth following placental transfusion. Gunther reconfirmed results of research from 1875 to 1930 published in French and German journals.

Human assisted delivery of thoroughbred foals and the convulsive foal syndrome

[49] Mahaffey LW, Rossdale PD (1957) On the newborn infant's oxygen supply. Lancet 1957 Jul 13, ii:95.

     Mahaffey and Rossdale (responding to the article above by Gunther) described a convulsive syndrome affecting about 2 percent of thoroughbred foals delivered with human assistance.

     "For a considerable time we have been greatly concerned with the possibility that the syndromes are associated with very early severance of the umbilical cord."

     "It seems more than a coincidence that, as far as we can verify, the syndromes do not occur in thoroughbred foals which are born unattended in open paddocks in Australia, but are well known in France and Italy, where the cord is always severed by attendants within seconds of birth. Further, in Europe the disease seems to be unknown in breeds of horses other than thoroughbreds and these generally foal without human 'interference.' Other domestic species which give birth to their young alone, and 'naturally,' are similarly unaffected."

Transfer of placental blood to the alveolar capillaries opens the lungs

[50] Jäykkä S. Capillary erection and lung expansion; an experimental study of the effect of liquid pressure applied to the capillary network of excised fetal lung. Acta Paediatr Suppl. 1957 Jan;46(suppl 112):1–91.

     Jäykkä provided evidence in support of the theory he proposed in 1954 that expansion of the lungs after birth results from fluid filling the capillary network surrounding the alveoli.

Textbooks continue to promote placental transfusion

[51] Willson JR, Beecham CF, Forman I, Carrington ER. Obstetrics and Gynecology. The CV Mosby Company, St. Louis, 1958.

     "The baby is held with its head downward for a few seconds while the cord is stripped from the introitus toward the infant several times. This adds 75 or more ml of blood, which would otherwise be discarded with the placenta, to the infant's vascular system." [p337]

     "The blood in the fetal circulation is distributed between the vessels in the infant's body and those in the placenta …"

     "…At the end of the second trimester about half the total blood is in the placenta, but as the baby grows larger relatively more is contained in the infant itself. The blood volume of the newly born baby is only about 250 ml. Consequently as much as possible must be preserved. If clamping and ligation of the cord are delayed for several minutes after the baby is born, as much as 100 ml of blood will be transferred from the placenta to the baby. The same result can be obtained by stripping the cord from the vulva toward the infant repeatedly until no more blood enters the vessels from the placental end." [p373]

Apgar *et al.* promote clamping of the cord within one minute after birth

[52] Apgar V, Holaday DA, James LS, Weisbrot IM. Evaluation of the newborn infant – second report. JAMA 1958; 168(15):1985–9.

     In 1958, Apgar (and her colleagues) wrote that scoring at one minute was done because this represented the time of most severe depression:

     "In the Sloane Hospital the cord has been cut by this time, and the infant is in the hands of an individual other than the obstetrician. In many hospitals, such is not the case. Those obstetricians who practice slow delivery and delayed clamping of the cord until pulsations of the umbilical ar-

tery cease still have the infant in the sterile field. However, if the obstetrician is reminded of the passage of time by another observer, he may assign a score even though the cord is still attached." [p1987]

Thus the Apgar score devised over 50 years ago reflected the perceived need to remove the newborn from the "sterile field" for repair of the episiotomy, manage delivery of the placenta, and to give the infant to neonatal specialists, often for resuscitation.

Apgar *et al.* also wrote in the 1958 paper: "All infants with a score of 8, 9,or 10 are vigorous and have breathed within seconds of delivery. In this group, scores of 8 or 9 reflect a lower score for color. The infants with a score of 4 or less are blue and limp and have failed to establish respiration by one minute." [p1987]

The Apgar score is all about how well a newborn establishes respiration. In contrast to the opinion expressed by White in 1773, Apgar and her colleages expected that the transition from fetal to neonatal respiration should take place within seconds of delivery.

Apgar *et al.* (1958) noted that many obstetricians at that time still practiced "slow delivery," waiting for pulsations of the cord to cease, and they suggested that a score could still be assigned, obtaining the heart-rate of the infant by palpating the umbilical cord.

Transfer of placental blood to the alveolar capillaries opens the lungs

[53] Jäykkä S. Capillary erection and the structural appearance of fetal and neonatal lungs. Acta Paediatr. 1958 Sep;47(5):484–500.

Jäykkä demonstrated that expansion of the lungs results from filling of the capillary bed surrounding the alveoli. Ventilation of non-inflated lungs led to patchy non-uniform opening of the alveoli. Respiration is exchange of carbon dioxide for oxygen via hemoglobin in the lungs or placenta, and of oxygen for carbon dioxide in other organs. Pulmonary respiration cannot begin until blood (laden with carbon dioxide) fills the capillaries that supply the alveoli. An initial exhalation may precede the first breath.

Newborn monkeys subjected to clamping of the umbilical cord and suffocation

[54] Ranck JB, Windle WF. Brain damage in the monkey, Macaca mulatta, by asphyxia neonatorum. Exp Neurol. 1959 Jun;1(2):130-54.

This was the first report of symmetrical bilateral brainstem damage found in monkeys subjected to experimental asphyxia at birth, and that this pattern of damage bore a close resemblance to that seen in kernicterus: "The human neuropathologic entity most closely resembling the effects of asphyxia neonatorum in the monkey is kernicterus. There are similarities in the distribution and type of nerve cell changes in both conditions. Major differences between the findings in the monkey and those in human infants with kernicterus are absence in the former of the usual history of erythroblastosis fetalis, lack of clinical jaundice, lack of pigment in the lesions, frequent presence of neuroglia cell damage, and presence of marked astrocytic and phagocytic reactions." [p153]

More on the convulsive foal syndrome

[55] Mahaffey LW, Rossdale PD (1959) A convulsive syndrome in newborn foals resembling pulmonary syndrome in the newborn infant. Lancet. 1959 Jun 13;1(7085):1223–5.

"Variable degrees of traction are usually practised by attendants when the head and forelegs are emerging from the vulva. The amnion is prematurely ruptured by hand, the legs are grasped and a pull is exerted upon them... the umbilical cord is ruptured with such haste that the newborn foal (weighing 100-120 lb.) is deprived of an average of 1020 ml. of blood and often 1500 ml.—probably about 30% of its potential blood-volume.

Under normal conditions a mare usually rests for period of up to half an hour after parturition, during which the foal also is inactive. The cord remains intact and is not broken until the mare (sometimes the foal) attempts to get to its feet. Meanwhile virtually all the blood in the placenta has passed back into the circulation of the foal, and it is difficult to collect even 50 ml. of blood when the cord ruptures at this stage."

Respiratory distress and continuing pulsation of the umbilical cord stump

[56] Desmond MM, Kay JL, Megarity AL (1959) The phases of "transitional distress"occurring in neonates in association with prolonged postnatal umbilical cordpulsations. Journal of Pediatrics 55:131–51.

"More recent experience with distressed infants revealed that certain of these infants show disturbances in the closure of umbilical vessels after birth.

…The umbilical arteries normally cease to pulsate within a short period after the infant has been delivered."

… While ligation of the umbilical cord immediately after birth is a tradition in modern obstetrics, the danger of hemorrhage from cords left unligated is not great." [p131]

"Forty-one infants manifested prolonged pulsation of the cord after delivery. The mean duration of cord pulsation was 5 hours, with a range of from 40 minutes to 13 hours after birth." [1, p132]

"Seventy-three per cent of the infants had either fetal distress prior to delivery or difficulty with the onset of respiration on delivery." [p145]

Apgar's colleague on respiratory distress and delay in onset of respiration

[57] James LS. Physiology of respiration in newborn infants and in the respiratory distress syndrome. Pediatrics. 1959 Dec;24:1069–101.

James (1959) was co-author with Apgar in 1958 of the paper in which they explained that at the Sloane Hospital (at Columbia University) the umbilical cord was cut within the first minute after birth to preserve the "sterile field," and that all infants with Apgar scores of 8, 9, or 10 had breathed within seconds of delivery. In this paper on respiratory distress a year later, he cites delay in onset of respiration at birth as the primary etiologic factor: "A review of the obstetrical histories in infants who show a rising respiratory rate has indicated that delayed respiration at birth, even for 2 minutes, seemed to affect markedly both the incidence of abnormal breathing and subsequent." [p1089]

More on respiratory distress syndrome

[58] Moss AJ, Duffie ER Jr, Fagan LM. Respiratory distress syndrome in the newborn. Study on the association of cord clamping and the pathogenesis of distress. JAMA. 1963 Apr 6;184:48–50.

Reports of respiratory distress syndrome appear to have increased with more and more widespread clamping of the umbilical cord sooner and sooner after birth.

Moss *et al.* pointed out that pulsations in the cord become progressively weaker and finally cease after the transition from placental to pulmonary respiration is complete. This represents a gradual change-over with only minor alterations in systemic blood flow, but with sudden occlusion of the cord before expansion of the alveolar vascular bed, systemic pressure may cause rupture of capillaries in the lungs, brain, and other organs. They concluded their paper with the following comment: "The carefree manner in which the newly born infant is 'disconnected' from his 'oxygenator' without any assurance that respirations will ever begin is in sharp contrast to the meticulous care with which the thoracic surgeon separaes his patient from the pump-oxygenator." [p50]

1960s textbooks continue to teaching waiting for pulsations of the cord to cease

[59] Greenhill JP. Obstetrics: Froim the original text of Joseph B. DeLee, MD. 13th ed. W.B. Saunders Company, Philadelphia & London, 1965.

"After pulsation in the exposed cord has ceased, using dull scissors, the child is separated from its mother." [p376]

Postnatal placental circulation

[60] Stembera ZK, Hodr J, Janda J. Umbilical blood flow in healthy newborn infants during the first minutes after birth. Am J Obstet Gynecol. 1965 Feb 15;91:568–74.

In earlier research (published in German and Czech journals) Stembera *et al.* found that the placenta begins to separate from the wall of the uterus

at about 2 minutes after birth, and that the concentration of oxygen in the umbilical arteries begins to decline only 60 to 90 seconds after the first breath. They thus concluded:

"After inclusion of all of our previous data with those in the present communication, it would appear that the first 100 seconds after birth is a period during which the flow and metabolic conditions in the maternal-placental-fetal system continue essentially in a manner similar to that in utero." [p573]

Transfer of blood from placenta to lungs with onset of pulmonary respiration

[61] Redmond A, Isana S, Ingall D. Relation of onset of respiration to placental transfusion. Lancet. 1965 Feb 6;1:283–5.

Redmond *et al.* measured residual placental blood as an estimate of placental transfusion before and after onset of respiration. In 55 infants, the cord was clamped before onset of respiration, and in 97 after the onset of respiration. The plot of residual blood to onset of respiration from the paper by Redmond *et al.* shows a dramatic drop in residual blood in cases where the cord was clamped after onset of respiration.

"Our data, obtained from normal uncomplicated pregnancies, clearly demonstrated that a placental transfusion is an inevitable physiological consequence of initial pulmonary expansion, over which obstetricians and paediatricians have little, if any, control."

"The tendency for some obstetricians to deliver the head, aspirate the nose and mouth, and slowly extract the remainder of the baby probably aids the transmission of placental blood to the infant." [p284]

[62] Taylor, E. Stewart. Beck's Obstetrical Practice, 8th ed. The Williams & Wilkins company, Baltimore, 1966.

"After delivering the child, the obstetrician suspends it by its feet … During this time the fluid within the tracheobronchial tree may be expelled by gravity. Most infants take their first extrauterine gasp at this time, and it is well to have the trachea clear."

"If the obstetrician waits until the cord stops pulsating, the child receives considerable amount of blood (up to 100 ml). This procedure is harmless to the normal infant and may be beneficial. However, the extra blood volume from the placenta may be detrimental in some pathological conditions of the infant. The most notable of these are maternal-fetal blood group incompatibilities, anomalies of the infant cardiovascular system, or severe fetal asphyxia."

"In normal full-term deliveries, the cord is clamped with two hematostats as soon as the cord stops pulsating." [p202]

[63] Fitzpatrick E, Eastman NJ, Reeder SR. Maternity Nursing, Eleventh Edition, JB Lippincott Company, Philadelphia, Toronto, 1966. [1929, 33, 34, 37, 40, Zabriskie's Handbook of Obstetrics, 1st to 6th editions by Louise Zabriskie; 1943, 48, 52, 7th to 9th editions, Zabriskie's Obstetrics for Nurses, 10th ed., 1960, by Elise Fitzpatrick & Nicholson J. Eastman]

"…The infant usually cries immediately, and the lungs become expanded; about this time the pulsations in the umbilical cord begin to diminish. The physician usually will defer clamping the cord until this occurs, or for a minute or so if practicable, because of the marked benefit of the additional blood to the infant." [p268]

"Emergency delivery… There is no hurry to cut the cord, so this should be delayed until proper equipment is available. It is a good plan to clamp the cord after pulsations cease (but not imperative at the moment) and to wait for the physician to cut the cord after he arrives." [p288]

Transfer of respiratory function from placenta to lungs

[64] Dunn PM. Postnatal placental respiration. Dev Med Child Neurol. 1966 Oct; 8(5): 607–8.

"The transfer of respiratory function from the placenta to the lungs at birth stands out as the most dramatic, complex and important event in our lives. How does this transfer take place? We know that there is often a delay after delivery before breathing commences and that a further interval must pass before pulmonary respiration meets the requirements of the newborn infant [2]. What of the placenta during this time? Does its respiratory function cease at the moment of delivery, or is it maintained until the lungs have assumed their new responsibility?" [p607]

[65] Moss AJ, Monset-Couchard M. Placental transfusion: early versus late clamping of the umbilical cord. Pediatrics. 1967 Jul;40(1):109–26.

"Iatrogenic interruption of the placental circulation at birth has, in most cases, become an automatic procedure with little or no regard for the phy-

siologic alterations evoked or for their subsequent effect upon the fetus." [p109]

A safe period of anoxia?

[66] James LS. Resuscitation of the newborn, in DE Reid and TC Barton, eds, Controversy in Obstetrics and Gynecology. Philadelphia, London, Toronto: WB Saunders Company, 1969.

Apgar's colleague discussed problems of C-section as result of loss of uterine contractions, not of cutting the umbilical cord prematurely: "In infants delivered by cesarean section, hemoglobin, hematocrit value, and blood pressure have frequently been found to be lower than in infants delivered per vaginum … due to a loss of blood into the placenta, since the uterus is not contracting."

James' interpretation of the effects of asphyxia on newborn monkeys suggests he regarded a short episode of oxygen insufficiency as safe, not that he and Apgar should revise their practice of clamping the cord within one minute after birth: "Asphyxiated newborn monkeys resuscitated before the last gasp show little or no cerebral damage. On the other hand prolongation of asphyxia for as short a period as four minutes after the last gasp is accompanied by widespread tissue damage and abnormal behavior in the surviving animals. Thus for the newborn monkey the 'safe' period of anoxia is short if functional integrity is to be maintained." [pp220–1]

Disruption of brain maturation in monkeys asphyxiated at birth

[67] Faro MD, Windle WF. Transneuronal degeneration in brains of monkeys asphyxiated at birth. Exp Neurol. 1969 May;24(1):38–53.

Abstract: "Brain damage occurring from 10 months to 8 years 9 months after neonatal asphyxiation for 11.5-17 min was assessed histologically in 12 rhesus monkeys. Comparison was made with brains of ten monkeys asphyxiated for brief periods or living shorter times and with those of five nonasphyxiated controls. Very slight damage occurred after 6-7 min of asphyxia; major destruction of relay nuclei in afferent input systems and parts of the basal ganglia, after 11.5-17 min. In the course of time, beginning about 10 months after birth, secondary transneuronal degeneration became evident. This was most clearly seen in the parts of the cerebral cortex which had received projections from the thalamic nuclei destroyed during the asphyxia; also in other thalamic nuclei and the brain-stem reticular formation. Gradual improvement in physical status and in behavioral responses to environment occurred while brain structure deteriorated."

[68] Windle WF. Brain damage by asphyxia at birth. Sci Am. 1969 Oct; 221(4):76–84.

"…in any delivery it is important to keep the umbilical cord intact until the placenta has been delivered. To clamp the cord immediately is equivalent to subjecting the infant to a massive hemorrhage, because almost a fourth of the fetal blood is in the placental circuit at birth." [p78]

"The monkey experiments described in this article have taught us that birth asphyxia lasting long enough to make resuscitation necessary always damages the brain." [p84]

1970s bilirubin and other uncertainties

[69] Saigal S, O'Neill A, Surainder Y, Chua LB, Usher R. Placental transfusion and hyperbilirubinemia in the premature. Pediatrics. 1972 Mar;49(3):406–19.

Is it safe to allow a placental transfusion? By the 1970s the practice of clamping the cord was so widespread, at least in obstetric practice associated with academic institutions, that whether a placental transfusion should be allowed became a major topic for research. Thus the opening comment of this highly influential report states: "In full-term infants placental transfusion increases the blood volume of the newborn by 40% to 60% within 5 minutes of birth. Most of the excess blood volume is eliminated within 4 hours by an extravasation of plasma from the circulation. For the remainder of the neonatal period, such infants retain a 50% larger red cell volume dispersed through a slightly enlarged blood volume, with higher hematocrit values than are found in infants whose umbilical cords are clamped immediately at birth." [p406]

"If delayed cord clamping is adopted as a means to reduce the incidence of respiratory distress syndrome in premature births, there will be accompanying augmentation of hyperbilirubinemia to deal with." [p418]

This paper, with its single focus on bilirubin danger, has been one of the most influential in adopting immediate clamping of the umbilical cord at birth as a standard protocol.

Neuropathology of foals born with human assistance found similar to that in monkeys

[70] Palmer AC, Rossdale PD. (1975) Neuropathology of the convulsive foal syndrome. J Reprod Fertil Suppl. 1975 Oct;(23):691–4.

[71] Palmer AC, Rossdale PD. (1976) Neuropathological changes associated with the neonatal maladjustment syndrome in the thoroughbred foal. Res Vet Sci. 1976 May;20(3):267–75.

Palmer and Rossdale found brain damage in thoroughbred foals delivered with human assistance similar to that found in monkeys subjected to asphyxia at birth.

Continuing fear of elevated bilirubin

[72] Beischer, Norman A & MacKay Eric V. Obstetrics and The Newborn: For midwives and medical students. W.B. Saunders: Philadelphia, 1976.

"The optimal time for clamping (or tying) the cord is not known for certain. Late clamping of the cord results in an additional volume of blood reaching the infant. This is harmful in premature and erythroblastotic infants.

In the asphyxiated infant, early clamping allows rapid transfer of the child for resuscitation purposes. In other patients, the cord is clamped when pulsations cease." [p395]

[73] Saigal S, Usher RH. Symptomatic neonatal plethora. Biol Neonate. 1977;32(1-2):62–72

In this paper Saigal and Usher (1977) described "symptomatic neonatal plethora" in 8 premature and 3 full-term infants with the suggestion that these conditions were caused by "large placental transfusions associated with delayed clamping of the umbilical cord" [p62]. Saigal and Usher stated implications of their findings as follows. "After many years of controversy, the question of when to clamp the umbilical cord seems to be resolving towards a middle course. Excessive delay (more than 2 min) in cord clamping produces hyperbilirubinemia and sometimes symptomatic hypervolemia or polycythemia. Immediate cord clamping in premature infants tends to increase mortality from respiratory distress syndrome. It seems advisable, therefore, to delay cord clamping for 1 to 1½ min in premature infants, with less delay in full-term infants." [2, p70]

Clamping the cord soon after delivery had become the norm. There seemed to be no memory of the traditional teaching of textbooks, or research from less than 20 years earlier [3]. Treatment of mothers in premature labor with betamethasone, and neonatal use of surfactant were being used to prevent respiratory distress syndrome and hyaline membrane disease of the lungs. The association of lung pathology with clamping of the umbilical cord had become irrelevant, and placental transfusion was now regarded as a potential hazard.

1980s textbook teachings, from tradition to confusion and change

[74] Bodyazhina V. Textbook of Obstetrics: Translated from the Russian by Alexander Rosinkin (revised from the 1980 ed.). Mir Publishers, Moscow, 1983.

"The umbilical cord should be tied up after its vessels stop pulsating, which occurs in 2-3 min following the delivery of the infant. In the course of a few minutes that the umbilical cord pulsates, from 50 to 100 ml of the blood is delivered into the vascular system of the foetus from the placenta. As soon as the pulsation discontinues, the cord should be cut off and tied up in aseptic conditions." [p156]

[75] Beischer NA, MacKay EV (1986) Obstetrics and the Newborn: An illustrated textbook, Second Edition. WB Saunders Company, Philadelphia, 1986.

"The optimum time of clamping is 30-60 seconds after birth: This will provide some 80 ml of extra blood to the baby. Excess blood volume in the baby can be a disadvantage, producing polycythemia and hyperviscosity, with such attendant problems as respiratory distress, heart failure, jaundice, convulsions and apathy." [p381]

"Apgar scores are recorded at 1 minute and again at 5 minutes, timing the observations accurately... Also the time to first breath and time to the establishment of regular respirations are recorded.

… Permanent cord clamps or ligatures (Figure 26.27) or special bands are applied to the umbilical cord as soon as possible after birth…" [p470]

"The optimal time for clamping (or tying) the cord is not known for certain. Late clamping of the cord results in an additional volume of blood reaching the infant. This may result in hyperviscosity, jaundice and cardiorespiratory, neurological and renal problems. The extra blood specifically aggravates jaundice in premature infants and in those with erythroblastosis, so early clamping of the cord is advised in such infants." [p546]

"Q: What is the significance of continued pulsation of the arteries in the umbilical cord at birth?

A: It means that respiration has not commenced. The physiological stimulus causing closure of umbilical arteries (and ductus arteriosus) is an increase in oxygen saturation of the blood which occurs when the lungs expand with air." [p710]

"Routine practices concerning the time for clamping the umbilical cord vary. If the child's condition is satisfactory cord clamping and severing can be delayed until pulsation has stopped and the infant is position at or below the level of the mother. The additional blood transfused from the placenta can be as much as 100 ml. The benefits of this are not fully evaluated but the additional volume may be harmful in preterm infants. Early clamping facilitates prompt resuscitation, if required, and transfer to the mother's arms…" [pp734–5]

[76] Kraybill, EN. Needs of the term infant, In GB Avery, MA Fletcher, & MG MacDonald, eds. Neonatology. Pathophysiology and Manangement of the Newborn, Third Edition. JB Lippincott, Philadelphia, 1987.

"… with present information it seems reasonable to avoid the extremes of immediate and of very late clamping. The first 30 to 60 seconds after delivery are well spent in suctioning the airway … The normal newborn invariably cries during this interval …" [p258]

Continuing respect for nature's plan

[77] Dunn PM. Stress failure of pulmonary capillaries at birth. Lancet. 1993 Jan 9;341(8837):120.

"My own interest stems from studies (1960-73) on fetal adaption to extrauterine life. These results showed that preterm infants delivered by caesarean section were much less likely to develop and die from RDS [respiratory distress syndrome] if pulmonary respiration was established while the umbilical circulation was still intact and if positive-pressure ventilation, when required, was gentle with the aim of evacuating lung fluid through the lymphatic system, rather than of inflating the lungs. I argued that sudden occlusion of the vigorously pulsating cord of an apnoeic infant would, by cutting off the low-resistance placental circulation, lead to a sharp transitory rise in systemic blood pressure. This, in turn would lead to transitory heart failure and a raised venous pressure, especially if acute placental transfusion hypervolaemia was also present. At the same time the rise in systemic blood pressure would be transmitted through the patent ductus arteriosus to the pulmonary arteries, just as lung expansion was leading to a sudden fall in pulmonary vascular resistance."

[78] Mercer JS, Skovgaard RL. Neonatal transitional physiology: a new paradigm. J Perinat Neonatal Nurs. 2002 Mar;15(4):56–75.

Mercer and Skovgaard brought attention to Jäykkä's research in their analysis of blood volume redistribution required by all body organs following birth.

"The hypothesis proposed is that a successful neonatal transition is dependent upon a newborn having an adequate blood volume to recruit the lung for respiratory function through capillary erection and an adequate *red cell* volume to provide enough oxygen delivery to stimulate and maintain respiration." [p59]

Statistics for respiratory depression at birth

[79] Milsom I, Ladfors L, Thiringer K, Niklasson A, Odeback A, Thornberg E. Influence of maternal, obstetric and fetal risk factors on the prevalence of birth asphyxia at term in a Swedish urban population. Acta Obstet Gynecol Scand. 2002 Oct;81(10):909–17.

"During the 7-year period 1985–91, the incidences of low Apgar score (<7 at 5 min), pure birth asphyxia and birth asphyxia with HIE in this population were 6.9, 5.4 and 1.8 per 1000 live born infants, respectively." [p911]

[80] Baskett TF, Allen VM, O'Connell CM, Allen AC. Predictors of respiratory depression at birth in the term infant. BJOG. 2006 Jul;113(7):769–74.

"Overall, the rate of respiratory depression at birth was low (6.2/1000) and the rate of the serious manifestation of seizures was less than 1 in 1000." [p772]

Autism prevalence

[81] Chakrabarti S, Fombonne E. Pervasive developmental disorders in pre-school children: confirmation of high prevalence. Am J Psychiatry. 2005 Jun;162(6):1133–41.

"Sixty-four children (85.9% boys) were diagnosed with pervasive developmental disorders. The prevalence was 58.7 per 10,000." [p1133]

[82] Nicholas JS, Charles JM, Carpenter LA, King LB, Jenner W, Spratt EG. Prevalence and characteristics of children with autism-spectrum disorders. Ann Epidemiol. 2007 Sep; 17(9):747-8. 2008 Feb;18(2):130–6.

"Cases from the first two study years (2000 and 2002) have been combined for this analysis. RESULTS: A total of 296 children met criteria for ASD, yielding a prevalence of 6.2 per 1000." [2007, p748]

Cases from South Carolina… surveillance of 47,726 children who are 8 years of age… 295 children met criteria for ASD… "CONCLUSIONS: Results indicate that ASDs affect 1 in 162 children 8 years of age in South Carolina." [2008, abstract]

[83] Center for Disease Control updates http://www.cdc.gov/ncbddd/autism/ (accessed 6/28/08)

[84] Park A. How safe are vaccines? Time Magazine. 2008 Jun 2;171(22):36–41.

"Autism 1 in 150: The prevalence of autism among 8-year-olds in the U.S. Autism rates have not declined, even though thimerosal, which some believe contributes to the disease, was removed from vaccines in 2001." [p38]

Symmetric bilateral damage of brainstem nuclei

[85] Gilles FH. Selective symmetrical neuronal necrosis of certain brain stem tegmental nuclei in temporary cardiac standstill [Abstract of presentation at the American Association of Neuropathologists: 38th Annual Meeting. Atlantic City. New Jersey]. J Neuropathol Exp Neurol 1963 Apr; 22(2):318.

Gilles reported pathology similar to that observed by Ranck & Windle in an 18-month-old infant who died a few weeks following resuscitation from drowning. He also suggested that the brainstem pattern of damage with prominent involvement of the inferior colliculi (in the midbrain auditory pathway) might lead to developmental language delay.

[86] Gilles FH. Hypotensive brain stem necrosis. Selective symmetrical necrosis of tegmental neuronal aggregates following cardiac arrest. Arch Pathol. 1969 Jul;88(1):32–41.

[87] Myers RE. Two patterns of perinatal brain damage and their conditions of occurrence. Am J Obstet Gynecol. 1972 Jan 15;112(2):246–76.

In more experiments with monkeys, Myers confirmed that the symmetric bilateral pattern of brainstem damage is caused by eight or more minutes of total oxygen cutoff at birth, and that prolonged partial hypoxia in utero results in the pattern of cortical damage associated with cerebral palsy.

[88] Norman MG (1972) Antenatal neuronal loss and gliosis of the reticular formation, thalamus, and hypothalamus. A report of three cases. Neurology. 1972 Sep;22(9):910–6.

[89] Griffiths AD, Laurence KM. The effect of hypoxia and hypoglycaemia on the brain of the newborn human infant.Dev Med Child Neurol. 1974 Jun;16(3):308–19.

[90] Grunnet ML, Curless RG, Bray PF, Jung AL. Brain changes in newborns from an intensive care unit. Dev Med Child Neurol. 1974 Jun;16(3):320–8.

[91] Schneider H, Ballowitz L, Schachinger H, Hanefield F, Droeszus J-U. Anoxic encephalopathy with predominant involvement of basal ganglia, brain stem and spinal cord in the perinatal period. Report on seven newborns. Acta Neuropathol. 1975 Oct 1;32(4):287–98.

[92] Smith JF, Rodeck C. Multiple cystic and focal encephalomalacia in infancy and childhood with brain stem damage. J Neurol Sci. 1975 Jul;25(3):377–88.

[93] Leech RW, Alvord EC Jr. Anoxic-ischemic encephalopathy in the human neonatal period, the significance of brain stem involvement. Arch Neurol. 1977 Feb;34(2):109–13.

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[95] Natsume J, Watanabe K, Kuno K, Hayakawa F, Hashizume Y. Clinical, neurophysiologic, and neuropathological features of an infant with brain damage of total asphyxia type (Myers). Pediatr Neurol. 1995 Jul;13(1):61–4.

Disrupted brain maturation in autism

[96] Bauman ML, Kemper TL. Neuroanatomic observations of the brain in autism: a review and future directions. Int J Dev Neurosci. 2005 Apr-May;23(2-3):183–7.

[97] Müller RA. The study of autism as a distributed disorder. Ment Retard Dev Disabil Res Rev. 2007;13(1):85-95. Review. Erratum in: Ment Retard Dev Disabil Res Rev. 2007;13(2):195.

[98] Amaral DG, Schumann CM, Nordahl CW. Neuroanatomy of autism. Trends Neurosci. 2008 Mar;31(3):137–45.

What causes kernicterus (jaundice of subcortical brain nuclei)?

[99] Zimmerman HM, Yannet H. Kernicterus: jaundice of the nuclear masses of the brain. American Journal of Diseases of Children 1933 Apr; 45:740–59.

Before discovery of Rh factor sensitivity, Zimmerman and Yannet in 1933 summarized a large number of case reports of kernicterus. They concluded that kernicterus was caused by bilirubin staining of subcortical nuclei already injured by sepsis or oxygen deprivation. They further commented, "This differs in no way from the well known fact that any intravital dye will localize in zones of injury and will leave unstained tissues which are not damaged." [p757]

Fear of elevated bilirubin levels became a prime reason 40 years later for advocating immediate clamping of the umbilical cord at birth – to minimize placental transfusion.

Effects of asphyxia on the brain, and asphyxia plus circulating toxins

[100] Lucey JF, Hibbard E, Behrman RE, Esquival FO, Windle WF. Kernicterus in asphyxiated newborn monkeys. Exp Neurol 1964 Jan; 9(1):43-58.

Lucey et al. induced hyperbiliruninemia in fourteen newborn monkeys by injecting a solution of bilirubin into the bloodstream every six hours. Bilirubin levels of 20 to 35 mg were maintained for up to 96 hours.

Then, "Six healthy full-term monkeys were asphyxiated at birth. A rubber bag filled with saline solution was placed over the fetal head as it was delivered from the uterus before the first breath. The umbilical cord was then clamped and asphyxiation carried out for 10 or 12 minutes." [p45] Hyperbilirubinemia was then induced in the asphyxiated monkeys as in the fourteen control animals.

Lucey et al. described the monkeys made hyperbilirubinemic as showing marked yellow coloration of skin and mucous membranes. Those not asphyxiated became slightly lethargic but none developed signs of neurological impairment. Monkeys subjected to asphyxia before induction of hyperbilirubinemia developed tremors, seizures, and prolonged periods of opisthotonus (a postural state with arched back and neck).

"Hyperbilirubinemia alone did not result in selective staining of nuclei in the brain, such as is associated with human kernicterus … the brains had a diffuse, faint to moderate, yellow color, but no extravascular bilirubin was seen." [p50]

Bilirubin is not directly toxic to the brain. Asphyxia causes breakdown of the blood-brain barrier, which then allows bilirubin to get into neural cells. As Zimmerman and Yannet noted in 1933, "any intravital dye will localize in zones of injury and will leave unstained tissues which are not damaged." [39, p757]

[101] Lou HC, Tweed WA, Johnson G, Jones M, Lassen NA. Breakdown of blood/brain barrier in kernicterus. Lancet. 1977 May 14;1(8020):1062-3.

Lou et al. (1977) addressed what appeared to be the primary concern over "delayed" cord clamping allowing placental transfusion [1]. Citing the paper by Lucey et al. (1964) [2] they stated: "Asphyxiated infants are especially susceptible to kernicterus, even if their plasma-bilirubin levels are low.' Furthermore, it is very difficult to produce clinical and patho-

logical signs of kernicterus by injection of bilirubin intravenously in normal infant monkeys, while kernicterus was readily produced in previously asphyxiated monkeys." [1, p1062]

Mossakowski *et al.* The early histochemical and ultrastructural changes in perinatal asphyxia. J Neuropathol Exp Neurol. 1968 Jul;27(3):500-516] used Evans blue dye to investigate the blood-brain barrier in newborn monkeys subjected to asphyxia by clamping the umbilical cord and obstructing the airway [69]. Lou *et al.* also used Evans blue dye in fetal lambs subjected to oxygen insufficiency for 1-2 hours: "The fetuses were asphyxiated by partially inflating a cuff around the umbilical cord. Asphyxia developed over a period of 1-2 h (pH about 690)." [1, p1062]

The initial response of the fetal lambs was a slowing of heart rate and increased blood pressure during the first half- to one-hour period of umbilical cord blood flow restriction. After that the blood pressure declined and remained low. Twinning is frequent in lambs, and Lou *et al.* used the twin as a control for the fate of Evans blue dye, and reported:

"We have found, in experimental asphyxia lasting 1-2 h, a striking discoloration throughout cortex and basal ganglia after intravenous injection of 3 ml/kg of a 2% solution of Evans blue in eight non-exteriorised fetal lambs, in contrast to the uncoloured brain tissue in non-asphyxiated twins acting as controls." [1, p1062]

In conclusion they commented: "We suggest that the breakdown of the fetal blood/brain barrier to albumin is due to a combination of the initial moderate hypertension and severe vasodilation during asphyxia.7 The permeability of the blood/brain barrier to albumin in asphyxiated babies would facilitate the transport of bilirubin from plasma to neurones and thus explain the increased susceptibility to kernicterus." [1, p1063]

[102] Lou HC, Lassen NA, Tweed WA, Johnson G, Jones M, Palahniuk RJ. Pressure passive cerebral blood flow and breakdown of the blood-brain barrier in experimental fetal asphyxia. Acta Paediatr Scand. 1979 Jan;68(1):57–63.

Symmetric bilateral brainstem damage caused by toxic substances

[103] Bini L and Bollea G (1947). Fatal poisoning by lead-benzine (a clinico-pathologic study). Journal of Neuropathology and Experimental Neurology 1947; 6:271–85.
[104] Franken L Étude anatomique d'un cas d'intoxication par le bromure de méthyle. [Anatomical study of a case of methylbromide poisoning. Acta Neurol Psychiatr Belg. 1959 Mar;59(3):375–83.
[105] von Rogulja P, Kovac W, Schmid H. Metronidazol-Encephalopathie der Ratte. Acta Neuropathol. 1973 Jun 26;25(1):36–45.
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[107] Dunn PM, Stewart-Brown S, Peel R. Metronidazole and the fetal alcohol syndrome. Lancet. 1979 Jul 21;2(8134):144.
[108] Bertoni JM, Sprenkle PM. Lead acutely reduces glucose utilization in the rat brain especially in higher auditory centers. Neurotoxicology. 1988 Summer;9(2):235–42.
[109] Oyanagi K, Ohama E, Ikuta F. The auditory system in methyl mercurial intoxication: a neuropathological investigation on 14 autopsy cases in Niigata, Japan. Acta Neuropathol. 1989;77(6):561–8.
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receptive fields, and plasticity in rat primary auditory cortex. Proc Natl Acad Sci U S A. 2007 May 1;104(18):7646–51.

Accumulating evidence of error—why are any more randomized controlled trials needed?

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[117] Künzel W. [Cord clamping at birth - considerations for choosing the right time (author's transl)] Z Geburtshilfe Perinatol. 1982 Apr-May;186(2):59–64. German.
[118] Hohmann M. [Early or late cord clamping? A question of optimal time] Wien Klin Wochenschr. 1985 May 24;97(11):497–500. German.
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[128] Mercer JS, Nelson CC, Skovgaard RL. Umbilical cord clamping: beliefs and practices of American nurse-midwives. J Midwifery Womens Health. 2000 Jan-Feb;45(1):58–66.
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Vulnerability of the auditory system to disruption of aerobic metabolism

Wernicke's encephalopathy

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Beriberi, and discovery of thiamine and other vitamin deficiencies

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This paper from over 100 years ago provides a good example of a wrong idea based on the understanding at that time of infectious diseases as causes of epidemics. That a diet based on refined white rice deficient in thiamine was later discovered to be responsible for the epidemic of beriberi.

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