Suggested Focus for Research in the IACC Plan
Eileen Nicole Simon, PhD (Biochemistry), RN
conradsimon.org

1. Autism is associated with many different medical conditions [1-79].
2. What vulnerable systems of the brain are impaired by all etiologies?
3. Evidence of auditory processing problems in autism is abundant [80-86].
4. The auditory system has higher blood flow and metabolism than any other area of the brain, and is vulnerable to many insults including oxygen deficiency at birth [87-96].

>>> 5. Loss of speech comprehension results from injury of the midbrain auditory system [97-105]. How much more serious this should be for an infant who has not yet learned to speak. **Shouldn't this mandate investigation of perinatal hazards to this brain area**? I have posted a research proposal at: http://www.inferiorcolliculus.org/proposals.html.

6. Complications at birth are associated with autism [106-111].
7. Statistics for "respiratory depression" and autism prevalence are similar [112, 113].
8. Why is the association of autism with oxygen deficiency at birth not a major focus of research? Can this ethically continue to be ignored?
9. Current obstetric protocol mandates clamping of the umbilical cord immediately at birth, even before the first breath [114]. Is this healthy for any infant?
10. The obstetric profession must be urged to review the teachings of traditional textbooks on transition from placental to pulmonary respiration [115-232]. Preventing any lapse in respiration at birth needs to become an ethical imperative.

REFERENCES, with notes, quotes, and illustrations
(From the bibliography of a work in progress – see www.conradsimon.org)

Environmental conditions associated with autism

Prenatal exposure to alcohol and/or other drugs

1. Nanson JL. Autism in fetal alcohol syndrome: a report of six cases. Alcohol Clin Exp Res. 1992 Jun;16(3):558-65.
2. Harris SR, MacKay LL, Osborn JA. Autistic behaviors in offspring of mothers abusing alcohol and other drugs: a series of case reports. Alcohol Clin Exp Res. 1995 Jun;19(3):660-5.
3. Aronson M, Hagberg B, Gillberg C. Attention deficits and autistic spectrum problems in children exposed to alcohol during gestation: a follow-up study. 1997 Sep;39(9):583-7.
4. Church MW, Eldis F, Blakley BW, Bawle EV. Hearing, language, speech, vestibular, and dentofacial disorders in fetal alcohol syndrome. Alcohol Clin Exp Res. 1997 Apr;21(2):227-37.
5. Christianson AL, Chesler N, and Kromberg JGR Fetal valproate syndrome: clinical and neuro-developmental features in two sibling pairs. Dev Med Child Neurol. 1994 Apr;36(4):361-9.
6. Williams PG, Hersh JH. A male with fetal valproate syndrome and autism. Dev Med Child Neurol. 1997 Sep;39(9):632-4.
7. Williams G, King J, Cunningham M, Stephan M, Kerr B, Hersh JH. Fetal valproate syndrome and autism: additional evidence of an association. Dev Med Child Neurol. 2001 Mar;43(3):202-6.
8. Stromland K, Nordin V, Miller M, Akerstrom B, and Gillberg C (1994) Autism in thalidomide embryopathy: a population study. Developmental Medicine and Child Neurology 36:351-356.

Infectious encephalitis

9. Desmond MM, Montgomery JR, Melnick JL, Cochran GG, Verniaud W. Congenital rubella encephalitis. Effects on growth and early development. Am J Dis Child. 1969 Jul;118(1):30-1.
10. Chess S (1971) Autism in children with congenital rubella. J Autism Child Schizophr. 1971 Jan-Mar;1(1):33-47.
11. Chess S, Fernandez P, Korn S. Behavioral consequences of congenital rubella. J Pediatr. 1978 Oct;93(4):699-703.
12. Townsend JJ, Wolinsky JS, Baringer JR. Progressive rubella panencephalistis: Late onset after congenital rubella. N Engl J Med. 1975 May 8;292(19):990-3.
13. Weil ML, Itabashi H, Cremer NE, Oshiro L, Lennette EH, Carnay L. Chronic progressive panencephalitis due to rubella virus simulating subacute sclerosing panencephalitis. N Engl J Med. 1975 May 8;292(19):994-8.
14. DeLong GR, Bean SC, Brown FR. Acquired reversible autistic syndrome in acute encephalopathic illness in children. Arch Neurol. 1981 Mar;38(3):191-4.
15. Gillberg C. Brief report: onset at age 14 of a typical autistic syndrome. A case report of a girl with herpes simplex encephalitis. J Autism Dev Disord. 1986 Sep;16(3):369-75.
16. Gillberg IC. Autistic syndrome with onset at age 31 years: herpes encephalitis as a possible model for childhood autism. Dev Med Child Neurol. 1991 Oct;33(10):920-4.
17. Ghaziuddin M, Tsai LY, Eilers L, Ghaziuddin N. Brief report: autism and herpes simplex encephalitis. J Autism Dev Disord. 1992 Mar;22(1):107-13.

18. Greer MK, Lyons-Crews M, Mauldin LB, Brown FR 3rd. A case study of the cognitive and behavioral deficits of temporal lobe damage in herpes simplex encephalitis. J Autism Dev Disord. 1989 Jun;19(2):317-26.
19. Domachowske JB, Cunningham CK, Cummings DL, Crosley CJ, Hannan WP, Weiner LB. Acute manifestations and neurologic sequelae of Epstein-Barr virus encephalitis in children. Pediatr Infect Dis J. 1996 Oct;15(10):871-5.
20. Thivierge J. (1986) A case of acquired aphasia in a child. Journal of Autism and Developmental Disorders. 16:507-12.
21. Barak Y, Kimhi R, Stein D, Gutman J, Weizman A. Autistic subjects with comorbid epilepsy: a possible association with viral infections. Child Psychiatry Hum Dev. 1999 Spring;29(3):245-51.
22. Sweeten TL, Posey DJ, McDougle CJ. Brief report: autistic disorder in three children with cytomegalovirus infection. J Autism Dev Disord. 2004 Oct;34(5):583-6.

Lead poisoning
23. Cohen DJ, Johnson WT, Caparulo BK. Pica and elevated blood lead level in autistic and atypical children. Am J Dis Child. 1976 Jan;130(1):47-8
24. Accardo P, Whitman B, Caul J, Rolfe U. Autism and plumbism. A possible association. Clin Pediatr (Phila). 1988 Jan;27(1):41-4.
25. Eppright TD, Sanfacon JA, Horwitz EA. Attention deficit hyperactivity disorder, infantile autism, and elevated blood-lead: a possible relationship. Mo Med. 1996 Mar;93(3):136-8.

Seizure disorder/ neurologic damage
26. Chugani HT, Da Silva E, Chugani DC. Infantile spasms: III. Prognostic implications of bitemporal hypometabolism on positron emission tomography. Ann Neurol. 1996 May;39(5):643-9.
27. daSilva EA, Chugani DC, Muzik O, Chugani HT. Landau-Kleffner syndrome: metabolic abnormalities in temporal lobe are a common feature. J Child Neurol. 1997 Nov;12(8):489-95.

Perinatal complications
28. Lobascher ME, Kingerlee PE, Gubbay SS. Childhood autism: an investigation of aetiological factors in twenty-five cases. Br J Psychiatry. 1970 Nov;117(540):525-9.
29. Levy S, Zoltak B, Saelens T. A comparison of obstetrical records of autistic and nonautistic referrals for psychoeducational evaluations. J Autism Dev Disord. 1988 Dec;18(4):573-81.
30. Steffenburg S, Gillberg C, Hellgren L, Andersson L, Gillberg IC, Jakobsson G, Bohman M. A twin study of autism in Denmark, Finland, Iceland, Norway and Sweden. J Child Psychol Psychiatry. 1989 May;30(3):405-16.
31. Lord C, Mulloy C, Wendelboe M, Schopler E. Pre- and perinatal factors in high-functioning females and males with autism. J Autism Dev Disord. 1991 Jun;21(2):197-209.
32. Ghaziuddin M, Shakal J, Tsai L. Obstetric factors in Asperger syndrome: comparison with high-functioning autism. J Intellect Disabil Res. 1995 Dec;39 (Pt 6):538-43.

33. Bolton PF, Murphy M, Macdonald H, Whitlock B, Pickles A, Rutter M. Obstetric complications in autism: consequences or causes of the condition? J Am Acad Child Adolesc Psychiatry. 1997 Feb;36(2):272-81

34. Matsuishi T, Yamashita Y, Ohtani Y, Ornitz E, Kuriya N, Murakami Y, Fukuda S, Hashimoto T, Yamashita F. Brief report: incidence of and risk factors for autistic disorder in neonatal intensive care unit survivors. J Autism Dev Disord. 1999 Apr;29(2):161-6.

35. Bodier C, Lenoir P, Malvy J, Barthélemy C, Wiss M, Sauvage D. (2001) Autisme et pathologies associées. Étude clinique de 295 cas de troubles envahissants du development [Autism and associated pathologies. Clinical study of 295 cases involving development disorders]. Presse Médicale. 2001 Sep 1;30(24 Pt 1):1199-203.

36. Juul-Dam N, Townsend J, Courchesne E. Prenatal, perinatal, and neonatal factors in autism, pervasive developmental disorder-not otherwise specified, and the general population. Pediatrics. 2001 Apr;107(4):E63.

37. Greenberg DA, Hodge SE, Sowinski J, Nicoll D. Excess of Twins among Affected Sibling Pairs with Autism: Implications for the Etiology of Autism. Am J Hum Genet. 2001 Nov;69(5):1062-7.

38. Wilkerson DS, Volpe AG, Dean RS, Titus JB. Perinatal complications as predictors of infantile autism. Int J Neurosci. 2002 Sep;112(9):1085-98.

39. Hultman CM, Sparen P, Cnattingius S. Perinatal risk factors for infantile autism. Epidemiology. 2002 Jul;13(4):417-23.

40. Zwaigenbaum L, Szatmari P, Jones MB, Bryson SE, MacLean JE, Mahoney WJ, Bartolucci G, Tuff L. Pregnancy and birth complications in autism and liability to the broader autism phenotype. J Am Acad Child Adolesc Psychiatry 2002 May;41(5):572-9.

41. Glasson EJ, Bower C, Petterson B, de Klerk N, Chaney G, Hallmayer JF. Perinatal factors and the development of autism: a population study. Arch Gen Psychiatry. 2004 Jun;61(6):618-27.

42. Larsson HJ, Eaton WW, Madsen KM, Vestergaard M, Olesen AV, Agerbo E, Schendel D, Thorsen P, Mortensen PB. Risk factors for autism: perinatal factors, parental psychiatric history, and socioeconomic status. Am J Epidemiol. 2005 May 15;161(10):916-25; discussion 926-8.

43. Newschaffer CJ, Cole SR. Invited commentary: risk factors for autism--perinatal factors, parental psychiatric history, and socioeconomic status. Am J Epidemiol. 2005 May;161:926-8.

44. McInnes LA, Gonzalez PJ, Manghi ER, Esquivel M, Monge S, Delgado MF, Fournier E, Bondy P, Castelle K. A genetic study of autism in Costa Rica: multiple variables affecting IQ scores observed in a preliminary sample of autistic cases. BMC Psychiatry. 2005 Mar 21;5(1):15.

45. Gillberg C, Cederlund M. Asperger syndrome: familial and pre- and perinatal factors. J Autism Dev Disord. 2005 Apr;35(2):159-66.

46. Badawi N, Novak I, McIntyre S, Edwards K, Raye S, deLacy M, Bevis E, Flett P, van Essen P, Scott H, Tungaraza K, Sealy M, McCann V, Reddihough D, Reid S, Lanigan A, Blair E, de Groot J, Watson L. Autism following a history of newborn encephalopathy: more than a coincidence? Dev Med Child Neurol. 2006 Feb;48(2):85-9.

47. Maimburg RD, Vaeth M. Perinatal risk factors and infantile autism. Acta Psychiatr Scand. 2006 Oct;114(4):257-64.

Genetic/metabolic conditions associated with autism

Neurolipidosis

48. Creak M (1963) Childhood psychosis: A review of 100 cases. British Journal of Psychiatry 109:84-89.
49. Darby JK. Neuropathologic aspects of psychosis in children. J Autism Child Schizophr. 1976 Dec;6(4):339-52.

Tuberous sclerosis

50. Fisher W, Kerbeshian J, Burd L, Kolstoe P. Tuberous sclerosis and autism. Dev Med Child Neurol. 1986 Dec;28(6):814-5.
51. Bolton PF, Griffiths PD (1997) Association of tuberous sclerosis of temporal lobes with autism and atypical autism. Lancet 349(9049):392-395
52. Webb DW, Fryer AE, Osborne JP (1996) Morbidity associated with tuberous sclerosis: a population study. Developmental Medicine and Child Neurology 38:146-55
53. Griffiths PD, Martland TR (1997) Tuberous Sclerosis Complex: the role of neuroradiology. Neuropediatrics 28:244-52.
54. Crino PB, Henske EP (1999) New developments in the neurobiology of the tuberous sclerosis complex. Neurology 53:1384-90.
55. Bolton PF, Park RJ, Higgins JN, Griffiths PD, Pickles A. Neuro-epileptic determinants of autism spectrum disorders in tuberous sclerosis complex. Brain. 2002 Jun;125(Pt 6):1247-55.

Neurofibromatosis

56. Gaffney GR, Kuperman S, Tsai LY, Minchin S. (1989) Forebrain structure in infantile autism. J Am Acad Child Adolesc Psychiatry. 1989 Jul;28(4):534-7.
57. Gaffney GR, Kuperman S, Tsai LY, Minchin S, Hassanein KM (1987a) Midsagittal magnetic resonance imaging of autism. Br J Psychiatry. 1987 Dec;151:831-3.
58. Gaffney GR, Tsai LY, Kuperman S, Minchin S (1987b) Cerebellar structure in autism. Am J Dis Child. 1987 Dec;141(12):1330-2.
59. Gillberg C, Coleman M. Autism and medical disorders: a review of the literature. Dev Med Child Neurol. 1996 Mar;38(3):191-202.

Phenylketonuria (PKU)

60. Lowe TL, Tanaka K, Seashore MR, Young JG, Cohen DJ. Detection of phenylketonuria in autistic and psychotic children. JAMA. 1980 Jan 11;243(2):126-8.
61. Williams RS, Hauser S, Purpura DP, deLong GR, Swisher CN. Autism and mental retardation: Neuropathologic studies performed in four retarded persons with autistic behavior. Arch Neurol. 1980 Dec;37(12):749-53.
62. Chen CH, Hsiao KJ. A Chinese classic phenylketonuria manifested as autism. Br J Psychiatry. 1989 Aug;155:251-3.
63. Miladi N, Larnaout A, Kaabachi N, Helayem M, Ben Hamida M. Phenylketonuria: an underlying etiology of autistic syndrome. A case report. J Child Neurol. 1992 Jan;7(1):22-3.

64. Leuzzi V, Trasimeni G, Gualdi GF, Antonozzi I. Biochemical, clinical and neuroradiological (MRI) correlations in late-detected PKU patients. J Inherit Metab Dis. 1995;18(5):624-34.

Fragile X syndrome
65. Brown WT, Jenkins EC, Friedman E, Brooks J, Wisniewski K, Raguthu S, French J. Autism is associated with the fragile-X syndrome. J Autism Dev Disord. 1982 Sep;12(3):303-8.
66. Folstein SE, Rutter ML Autism: familial aggregation and genetic implications. J Autism Dev Disord. 1988 Mar;18(1):3-30.

Chromosomal disorders
67. Cohen D, Pichard N, Tordjman S, Baumann C, Burglen L, Excoffier E, Lazar G, Mazet P, Pinquier C, Verloes A, Heron D. Specific genetic disorders and autism: clinical contribution towards their identification. J Autism Dev Disord. 2005 Feb;35(1):103-16.

Leber's Congenital Amaurosis
68. Rogers SJ, Newhart-Larson S. Characteristics of infantile autism in five children with Leber's congenital amaurosis. Dev Med Child Neurol. 1989 Oct;31(5):598-608.
69. Malamud N. Heller's disease and childhood schizophrenia. Am J Psychiatry. 1959 Sep;116:215-8.

Adenylosuccinate Lyase Defect
70. Jaeken J, Van den Berghe G. An infantile autistic syndrome characterised by the presence of succinylpurines in body fluids. Lancet. 1984 Nov 10;2(8411):1058-61.
71. Jaeken J, Wadman SK, Duran M, van Sprang FJ, Beemer FA, Holl RA, Theunissen PM, de Cock P, van den Bergh F, Vincent MF, et al. Adenylosuccinase deficiency: an inborn error of purine nucleotide synthesis. Eur J Pediatr. 1988 Nov;148(2):126-31.
72. Barshop BA, Alberts AS, Gruber HE. Kinetic studies of mutant human adenylosuccinase. Biochim Biophys Acta. 1989 Nov 9;999(1):19-23.
73. Van den Berghe G, Vincent MF, Jaeken J. Inborn errors of the purine nucleotide cycle: adenylosuccinase deficiency. J Inherit Metab Dis. 1997 Jun;20(2):193-202.

Lactic Acidosis
74. Coleman M, Blass JP. Autism and lactic acidosis. J Autism Dev Disord. 1985 Mar;15(1):1-8.
75. Philippart M. Clinical recognition of Rett syndrome. Am J Med Genet Suppl. 1986;1:111-8.
76. Lombard J. Autism: a mitochondrial disorder? Med Hypotheses. 1998 Jun;50(6):497-500.

Krebs Cycle (aerobic metabolism) Defects
77. Shaw W, Kassen E, Chaves E. Increased urinary excretion of analogs of Krebs cycle metabolites and arabinose in two brothers with autistic features. Clin Chem. 1995 Aug;41(8 Pt 1):1094-104.

Mitochondrial Disorders

78. Fillano JJ, Goldenthal MJ, Rhodes CH, Marin-Garcia J Mitochondrial dysfunction in patients with hypotonia, epilepsy, autism, and developmental delay: HEADD syndrome. J Child Neurol. 2002 Jun;17(6):435-9.
79. Graf WD, Marin-Garcia J, Gao HG, Pizzo S, Naviaux RK, Markusic D, Barshop BA, Courchesne E, Haas RH. Autism associated with the mitochondrial DNA G8363A transfer RNA(Lys) mutation. J Child Neurol. 2000 Jun;15(6):357-61.

Auditory processing problems

80. Russo N, Larson C, Kraus N. Audio-vocal system regulation in children with autism spectrum disorders. Exp Brain Res. 2008 Mar 18; [Epub ahead of print]
81. Kulesza RJ, Mangunay K. Morphological features of the medial superior olive in autism. Brain Res. 2008 Mar 20;1200C:132-7.
82. Kellerman GR, Fan J, Gorman JM. Auditory abnormalities in autism: toward functional distinctions among findings. CNS Spectr. 2005 Sep;10(9):748-56.
83. Kasai K, Hashimoto O, Kawakubo Y, Yumoto M, Kamio S, Itoh K, Koshida I, Iwanami A, Nakagome K, Fukuda M, Yamasue H, Yamada H, Abe O, Aoki S, Kato N. Delayed automatic detection of change in speech sounds in adults with autism: a magnetoencephalographic study. Clin Neurophysiol. 2005 Jul;116(7):1655-64.
84. Teder-Sälejärvi WA, Pierce KL, Courchesne E, Hillyard SA. Auditory spatial localization and attention deficits in autistic adults. Brain Res Cogn Brain Res. 2005 May;23(2-3):221-34.
85. Oram Cardy JE, Flagg EJ, Roberts W, Roberts TP. Delayed mismatch field for speech and non-speech sounds in children with autism. Neuroreport. 2005 Apr 4;16(5):521-5.
86. Khalfa S, Bruneau N, Rogé B, Georgieff N, Veuillet E, Adrien JL, Barthélémy C, Collet L. Increased perception of loudness in autism. Hear Res. 2004 Dec;198(1-2):87-92.

Measures of blood flow and metabolism

87. Sokoloff L. Localization of functional activity in the central nervous system by measurement of glucose utilization with radioactive deoxyglucose. J Cereb Blood Flow Metab. 1981;1(1):7-36.

88. Kety SS. Regional neurochemistry and its application to brain function. In French, JD, ed, Frontiers in Brain Research. New York: Columbia University Press, 1962. pp 97-120.

89. 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.
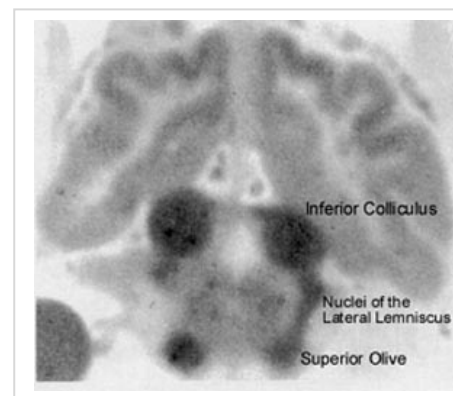
Autoradiograph from Kety (1962) showing greatest blood flow in brainstem auditory nuclei

Vulnerability to disruption of aerobic metabolism by toxic substances

90. Cavanagh JB. Selective vulnerability in acute energy deprivation syndromes. Neuropathol Appl Neurobiol. 1993 Dec;19(6):461-70.

91. 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.

92. 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.

Vulnerability to anoxia at birth

93. 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.

94. 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.

Damage in the inferior colliculi in a human infant – bottom right. From Leech & Alvord (1977)

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

96. Windle WF. Brain damage by asphyxia at birth. Sci Am. 1969 Oct;221(4):76-84.

**Loss of speech comprehension following injury of the inferior colliculi**

97. Pan CL, Kuo MF, Hsieh ST. Auditory agnosia caused by a tectal germinoma. Neurology. 2004 Dec 28;63(12):2387-9.

98. Kimiskidis VK, Lalaki P, Papagiannopoulos S, Tsitouridis I, Tolika T, Serasli E, Kazis D, Tsara V, Tsalighopoulos MG, Kazis A. Sensorineural hearing loss and word deafness

caused by a mesencephalic lesion: clinicoelectrophysiologic correlations. Otol Neurotol. 2004 Mar;25(2):178-82.

99. Musiek FE, Charette L, Morse D, Baran JA. Central deafness associated with a midbrain lesion. J Am Acad Audiol 2004 Feb;15(2):133-51.
100. Hoistad DL, Hain TC. Central hearing loss with a bilateral inferior colliculus lesion. Audiol Neurootol 2003 Mar-Apr; 8(2):111-223.
101. Vitte E, Tankéré F, Bernat I, Zouaoui A, Lamas G, Soudant J. Midbrain deafness with normal brainstem auditory evoked potentials. Neurology 2002;58:970–973.
102. Masuda S, Takeuchi K, Tsuruoka H, Ukai K, Sakakura Y. Word deafness after resection of a pineal body tumor in the presence of normal wave latencies of the auditory brain stem response. Ann Otol Rhinol Laryngol. 2000 Dec;109(12 Pt 1):1107-12.
103. Johkura K, Matsumoto S, Hasegawa O, Kuroiwa Y. Defective auditory recognition after small hemorrhage in the inferior colliculi. J Neurol Sci. 1998 Nov 26;161(1):91-6.

Traumatic injury of the inferior colliculi, incurred in a skiing accident, that resulted in loss of speech comprehension.
From Johkura et al. (1998)
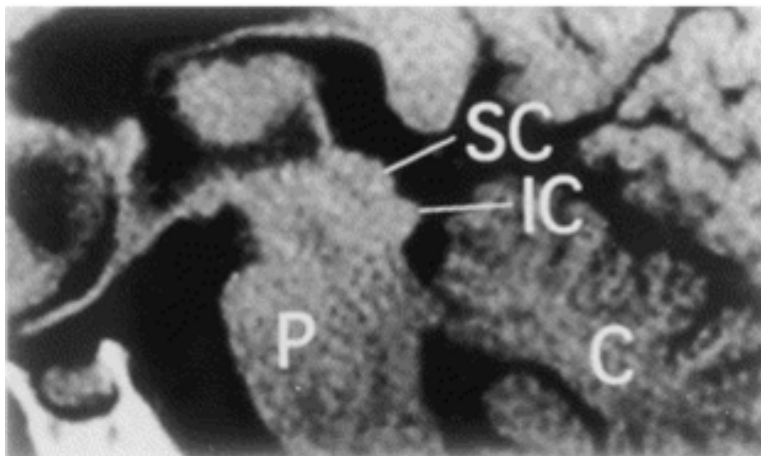
104. Meyer B, Kral T, Zentner J. Pure word deafness after resection of a tectal plate glioma with preservation of wave V of brain stem auditory evoked potentials. J Neurol Neurosurg Psychiatry. 1996 Oct;61(4):423-4.
105. Howe JR, Miller CA. Midbrain deafness following head injury. Neurology. 1975 Mar;25(3):286-9.

Perinatal risk associated with autism

106. Limperopoulos C, Bassan H, Sullivan NR, Soul JS, Robertson RL Jr, Moore M, Ringer SA, Volpe JJ, du Plessis AJ. Positive screening for autism in ex-preterm infants: prevalence and risk factors. Pediatrics. 2008 Apr;121(4):758-65.
107. Kolevzon A, Gross R, Reichenberg A.Prenatal and perinatal risk factors for autism: a review and integration of findings. Arch Pediatr Adolesc Med. 2007 Apr;161(4):326-33.
108. Badawi N, Novak I, McIntyre S, Edwards K, Raye S, deLacy M, Bevis E, Flett P, van Essen P, Scott H, Tungaraza K, Sealy M, McCann V, Reddihough D, Reid S, Lanigan A, Blair E, de Groot J, Watson L. Autism following a history of newborn encephalopathy: more than a coincidence? Dev Med Child Neurol. 2006 Feb;48(2):85-9.
109. Larsson HJ, Eaton WW, Madsen KM, Vestergaard M, Olesen AV, Agerbo E, Schendel D, Thorsen P, Mortensen PB. Risk factors for autism: perinatal factors, parental psychiatric history, and socioeconomic status. Am J Epidemiol. 2005 May 15;161(10):916-25; discussion 926-8.
110. Glasson EJ, Bower C, Petterson B, de Klerk N, Chaney G, Hallmayer JF. Perinatal factors and the development of autism: a population study. Arch Gen Psychiatry. 2004 Jun;61(6):618-27.
111. Hultman CM, Sparen P, Cnattingius S. Perinatal risk factors for infantile autism. Epidemiology. 2002 Jul;13(4):417-23.

Statistics for respiratory depression at birth

112. 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.
113. 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.

Current delivery room protocol

114. 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]

How many prospective parents are aware of this procedure?

History of the current protocol

Understanding of fetal circulation, respiration, and neonatal transition

115. 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 Church-yard, 1653. From Early English Books Online, http://eebo.chadwyck.com/

"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."

116. 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

"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]

117. 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. Online from: The American Antiquarian Society/ NewsBank, Early American Imprints, Series 1(1639-1800).

"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]

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

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

"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]

119. 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 bystanders, 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."

120. 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 lop 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]

121. 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]

122. 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." [pp214-215]

123. 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)

124. 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 without ligature in the Schauta Clinic. The clamp is pictured and
noted to be smaller than the "ordinary Hemostat" used in Vienna. The 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 research (until mid 20th century)

125. Williams JW. (1917) Obstetrics: A Text-Book for the Use of Students and Practitioners, Fourth Edition, 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." [pp342-343]

126. 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."

127. 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 simples processes in obstetrics, and why complicate whqat 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]

128. 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]

129. Willaims, J. Whitridge. Obstetrics: A Textbook for the use of Students and Practitioners, Fifth enlarged and revised edition. D. Appleton and Company, New York/London, 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…"

130. 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 uttering 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]

131. 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]

132. Zimmerman HM, Yannet H. Kernicterus: jaundice of the nuclear masses of the brain. American Journal of Diseases of Children 1933 Apr; 45:740-759.

     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.

133. 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]

     "After waiting until the pulsation in the exposed umbilical cord has perceptibly weakened or disappeared, the child is severed from its mother."

     "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 uterine 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 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]

134. 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]

135. 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; 38:592-594.

"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]

136. 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 18:538-547.

"... The rather common practice of promptly clamping the cord at birth should be condemned. Of course, this will make it imposible 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]

137. 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]

138. 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]

139. Eisaman JR Jr,, discussant of Ballentine GN. Delayed ligation of the umbilical cord. The Pennsylvania Medical Journal 1947,Apr;50 (7):726-728.

    "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].

140. 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):190-196.

    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.

141. Eastman HJ (1950) Williams Obstetrics, Tenth Edition,

    "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." [pp397-398]

142. 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; 36:421-426.

    "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."

143. 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.

     p 281 – "After waiting until the pulsation in the exposed cord has ceased, using dull scissors, the child is severed from its mother."

     P 832 – "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." [pp280-282]

     Landau DB et al. (1950) J. Pediat 36:421, April 1950. (see citation 142 above)

144. Greenhill JP (1951) 25.A.1951.2) 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 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 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 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

145. 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

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.

146. Greenhill, JP (1955) WQ 100 G812p 1955 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. 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 extr blood in this way. Babies receiving this
blood have higher erythrocyte counts, higher hemoglobin valuies, higher
initial weights and less initial weight losses."

147. 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. See the illustration (autoradiogram) from citation 88 above. 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.

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

Mahaffey and Rossdale 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 unkown 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."

149. 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.

150. 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]

151. 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 artery 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.

152. 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."

153. Desmond MM, Kay JL, Megarity AL (1959) The phases of "transitional distress" occurring in neonates in association with prolonged postnatal umbilical cord pulsations. Journal of Pediatrics 55:131-151.

"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]

154. 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]

155. 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]

156. 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]

157. 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 appears to break down 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." [132, p757]

158. Greenhill JP. Obstetrics: Froim the original text of Joseph B. DeLee, MD. Thirteenth Edition. 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]

159. 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]

The work of Stembera et al. confirms White's (1773) statement nearly 200 years earlier, that the changes that must take place in the transition from fetal to neonatal circulation cannot be expected to take place within an instant of time, and at the will of a bystander.

That most infants appear unharmed by immediate clamping off of ongoing postnatal placental support reflects the ability of the very young to recover and heal quickly.

160. 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]

161. Taylor, E. Stewart. Beck's Obstetrical Practice, Eight Edition. 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 a 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]

162. 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, Tenth Edition, 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]

163. 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]

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

165. Mossakowski MJ, Long DM, Myers RE, DeCuret HR, Klatzo I. The early histochemical and ultrastructural changes in perinatal asphyxia. J Neuropathol Exp Neurol. 1968 Jul;27(3):500-516.

166. 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.

"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."

"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." [pp220-221]

167. 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."

Bilirubin and other uncertainties

168. 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.

169. 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.

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

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

171. 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]

172. 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 1 1/2 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.

173. 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 pathological 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. (1968) 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 [3]. 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]

If a baby does not breathe right away at birth, should the umbilical cord be clamped off right away? Respiratory depression in infants born alive is a current concern and topic for research [4, 5]. If an infant is born alive, it has been receiving oxygen through the umbilical cord up to the time of birth. Shouldn't that lifeline be left intact until the lungs become functional?

Breakdown of the blood brain barrier by asphyxia has been shown to allow bilirubin and other
substances in the circulation to enter the brain. High levels of bilirubin won't affect the brain if the blood-brain barrier has not been breached. Immediate clamping has been too long defended as a means to avoid circulatory overload and hyperbilirubinemia.

Lou et al. (1979) reported results of more research on the vulnerability of the blood-brain barrier to circulatory insufficiency in fetal lambs [6].

174. Bodyazhina V. Textbook of Obstetrics: Translated from the Russian by Alexander Rosinkin (revised from the 1980 edition). 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 asceptic conditions." [p156]

175. 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]

176. 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]

177. 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]

178. 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.

"…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.]

179. 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."

180. 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

181. 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."

Correction in progress

182. Peltonen T. Placental transfusion--advantage and disadvantage. Eur J Pediatr. 1981 Oct;137(2):141-6.

183. 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.

184. Hohmann M. [Early or late cord clamping? A question of optimal time] Wien Klin Wochenschr. 1985 May 24;97(11):497-500. German.

185. Hofmeyr GJ, Bolton KD, Bowen DC, Govan JJ. Periventricular/intraventricular haemorrhage and umbilical cord clamping. Findings and hypothesis. S Afr Med J. 1988 Jan 23;73(2):104-6.

186. Hofmeyr GJ, Bex PJ, Skapinker R, Delahunt T. Hasty clamping of the umbilical cord may initiate neonatal intraventricular hemorrhage. Med Hypotheses. 1989 May;29(1):5-6.

187. [No authors listed] A study of the relationship between the delivery to cord clamping interval and the time of cord separation. Oxford Midwives Research Group. Midwifery. 1991 Dec;7(4):167-76.

188. Linderkamp O, Nelle M, Kraus M, Zilow EP. The effect of early and late cord-clamping on blood viscosity and other hemorheological parameters in full-term neonates. Acta Paediatr. 1992 Oct;81(10):745-50.

189. Kinmond S, Aitchison TC, Holland BM, Jones JG, Turner TL, Wardrop CA. Umbilical cord clamping and preterm infants: a randomised trial. BMJ. 1993 Jan 16;306(6871):172-5.

190. Grajeda R, Pérez-Escamilla R, Dewey KG. Delayed clamping of the umbilical cord improves hematologic status of Guatemalan infants at 2 mo of age. Am J Clin Nutr. 1997 Feb;65(2):425-31.

191. McDonnell M, Henderson-Smart DJ. Delayed umbilical cord clamping in preterm infants: a feasibility study. J Paediatr Child Health. 1997 Aug;33(4):308-10.

192. Papagno L. Umbilical cord clamping. An analysis of a usual neonatological conduct. Acta Physiol Pharmacol Ther Latinoam. 1998;48(4):224-7.

193. Morley GM. Cord closure: Can hasty clamping injure the newborn? OBG Management, July 1998: 29-36.

194. 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.

195. Ibrahim HM, Krouskop RW, Lewis DF, Dhanireddy R. Placental transfusion: umbilical cord clamping and preterm infants. J Perinatol. 2000 Sep;20(6):351-4.

196. Rabe H, Wacker A, Hülskamp G, Hörnig-Franz I, Schulze-Everding A, Harms E, Cirkel U, Louwen F, Witteler R, Schneider HP. A randomised controlled trial of delayed cord clamping in very low birth weight preterm infants. Eur J Pediatr. 2000 Oct;159(10):775-7.

197. Mercer JS. Current best evidence: a review of the literature on umbilical cord clamping. J Midwifery Womens Health. 2001 Nov-Dec;46(6):402-14.

198. Gupta R, Ramji S. Effect of delayed cord clamping on iron stores in infants born to anemic mothers: a randomized controlled trial. Indian Pediatr. 2002 Feb;39(2):130-5.

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

200. Buckley S. A natural approach to the third stage of labour. A look at early cord clamping, cord blood harvesting, and other medical interference. Midwifery Today Int Midwife. 2001 Fall;(59):33-6.

201. Mercer JS, McGrath MM, Hensman A, Silver H, Oh W. Immediate and delayed cord clamping in infants born between 24 and 32 weeks: a pilot randomized controlled trial. J Perinatol. 2003 Sep;23(6):466-72.

202. van Rheenen P, Brabin BJ. Late umbilical cord-clamping as an intervention for reducing iron deficiency anaemia in term infants in developing and industrialised countries: a systematic review. Ann Trop Paediatr. 2004 Mar;24(1):3-16.

203. Rabe H, Reynolds G, Diaz-Rossello J. Early versus delayed umbilical cord clamping in preterm infants. Cochrane Database Syst Rev. 2004 Oct 18;(4):CD003248.

204. Hutchon DJ. Epidemiology of preterm birth: delayed cord clamping used to be taught and practised. BMJ. 2004 Nov 27;329(7477):1287; author reply 1287.

205. Philip AGS, Saigal S. When should we clamp the umbilical cord? *Neoreviews*. 2004; 5: 142-154. http://neoreviews.aappublications.org/cgi/reprint/5/4/e142.

206. Mercer JS, Skovgaard RL, Peareara-Eaves J, Bowman TA. Nuchal cord management and nurse-midwifery practice. J Midwifery Womens Health. 2005 Sep-Oct;50(5):373-9.

207. Aladangady N, McHugh S, Aitchison TC, Wardrop CA, Holland BM. Infants' blood volume in a controlled trial of placental transfusion at preterm delivery. Pediatrics. 2006 Jan;117(1):93-8.

208. Ceriani Cernadas JM, Carroli G, Pellegrini L, Otaño L, Ferreira M, Ricci C, Casas O, Giordano D, Lardizábal J. The effect of timing of cord clamping on neonatal venous hematocrit values and clinical outcome at term: a randomized, controlled trial. Pediatrics. 2006 Apr;117(4):e779-86.

209. Mercer JS, Vohr BR, McGrath MM, Padbury JF, Wallach M, Oh W. Delayed cord clamping in very preterm infants reduces the incidence of intraventricular hemorrhage and late-onset sepsis: a randomized, controlled trial. Pediatrics. 2006 Apr;117(4):1235-42.

210. Philip AG. Delayed cord clamping in preterm infants. Pediatrics. 2006 Apr;117(4):1434-5.

211. Chaparro CM, Neufeld LM, Tena Alavez G, Eguia-Líz Cedillo R, Dewey KG. Effect of timing of umbilical cord clamping on iron status in Mexican infants: a randomised controlled trial. Lancet. 2006 Jun 17;367(9527):1997-2004.

212. Mercer J, Erickson-Owens D. Delayed cord clamping increases infants' iron stores. Lancet. 2006 Jun 17;367(9527):1956-8.

213. van Rheenen PF, Gruschke S, Brabin BJ. Delayed umbilical cord clamping for reducing anaemia in low birthweight infants: implications for developing countries. Ann Trop Paediatr. 2006 Sep;26(3):157-67.

214. Levy T, Blickstein I. Timing of cord clamping revisited. J Perinat Med. 2006;34(4):293-7.

215. van Rheenen PF, Brabin BJ. Effect of timing of cord clamping on neonatal venous hematocrit values and clinical outcome at term: a randomized, controlled trial. Pediatrics. 2006 Sep;118(3):1317-8; author reply 1318-9.

216. Hutchon D, Ononeze B. Preterm birth: effect of corticosteroids or immediate cord clamping? PLoS Med. 2006 Oct;3(10):e462.

217. van Rheenen PF, Brabin BJ. A practical approach to timing cord clamping in resource poor settings. BMJ. 2006 Nov 4;333(7575):954-8.

218. Hutchon DJ. Delayed cord clamping may also be beneficial in rich settings. BMJ. 2006 Nov 18;333(7577):1073.

219. Hosono S, Mugishima H, Fujita H, Hosono A, Minato M, Okada T, Takahashi S, Harada K. Umbilical cord milking reduces the need for red cell transfusions and improves neonatal adaptation in infants born at less than 29 weeks' gestation: a randomised controlled trial. Arch Dis Child Fetal Neonatal Ed. 2008 Jan;93(1):F14-9.

220. Ultee CA, van der Deure J, Swart J, Lasham C, van Baar AL. Delayed cord clamping in preterm infants delivered at 34 36 weeks' gestation: a randomised controlled trial. Arch Dis Child Fetal Neonatal Ed. 2008 Jan;93(1):F20-3.

221. Baenziger O, Stolkin F, Keel M, von Siebenthal K, Fauchere JC, Das Kundu S, Dietz V, Bucher HU, Wolf M. The influence of the timing of cord clamping on postnatal cerebral oxygenation in preterm neonates: a randomized, controlled trial. Pediatrics. 2007 Mar;119(3):455-9.

222. Hutton EK, Hassan ES. Late vs early clamping of the umbilical cord in full-term neonates: systematic review and meta-analysis of controlled trials. JAMA. 2007 Mar 21;297(11):1241-52.

223. van Rheenen P, de Moor L, Eschbach S, de Grooth H, Brabin B. Delayed cord clamping and haemoglobin levels in infancy: a randomised controlled trial in term babies. Trop Med Int Health. 2007 May;12(5):603-16.

224. Mercer JS, Erickson-Owens DA, Graves B, Haley MM. Evidence-based practices for the fetal to newborn transition. J Midwifery Womens Health. 2007 May-Jun;52(3):262-72.

225. Kugelman A, Borenstein-Levin L, Riskin A, Chistyakov I, Ohel G, Gonen R, Bader D. Immediate versus delayed umbilical cord clamping in premature neonates born < 35 weeks: a prospective, randomized, controlled study. Am J Perinatol. 2007 May;24(5):307-15.

226. Dewey KG, Chaparro CM. Session 4: Mineral metabolism and body composition iron status of breast-fed infants. Proc Nutr Soc. 2007 Aug;66(3):412-22.

227. Weeks A Umbilical cord clamping after birth. BMJ. 2007 Aug 18;335(7615):312-3.

228. Rabe H, Reynolds G, Diaz-Rossello J.A systematic review and meta-analysis of a brief delay in clamping the umbilical cord of preterm infants. Neonatology. 2008;93(2):138-44.

229. Chaparro CM, Fornes R, Neufeld LM, Tena Alavez G, Eguía-Líz Cedillo R, Dewey KG. Early umbilical cord clamping contributes to elevated blood lead levels among infants with higher lead exposure. J Pediatr. 2007 Nov;151(5):506-12.

230. Strauss RG, Mock DM, Johnson KJ, Cress GA, Burmeister LF, Zimmerman MB, Bell EF, Rijhsinghani A. A randomized clinical trial comparing immediate versus delayed clamping of the umbilical cord in preterm infants: short-term clinical and laboratory endpoints. Transfusion. 2008 Apr;48(4):658-65.

231. Wiberg N, Källén K, Olofsson P. Delayed umbilical cord clamping at birth has effects on arterial and venous blood gases and lactate concentrations. BJOG. 2008 May;115(6):697-703.

232. McDonald SJ, Middleton P Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes. Cochrane Database Syst Rev. 2008 Apr 16;(2):CD004074.