# NEONATAL ANESTHESIA – THE ORIGINS OF CONTROVERSY

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## INTRODUCTION

In 1986, the world was shocked when reports of infants undergoing major surgery without anesthesia arose in both the USA and UK. In the USA, mothers of two premature infants wrote letters to the medical journal, BIRTH, protesting the "barbarism of surgery without anesthesia."[i] The first case involved a premature boy, Edward Harrison, who had hydrocephalus – a condition in which the brain enlarges due to fluid build-up in the ventricles. The surgery to correct this condition involves inserting a shunt from the brain into the abdomen to drain the excess fluid. For the surgery, Edward was given only curare, a muscle relaxant that creates paralysis and "although he could not move, cry or react in any way, he could see, hear, and feel as large incisions were cut in his scalp, neck, and abdomen."[ii] The second case involved another premature boy, Jeffrey Lawson, who was similarly paralyzed with curare during an operation to ligate a patent ductus arteriosus (PDA), an aberrant artery in the heart. In both cases, the mothers were told that their children were unable to tolerate powerful anesthetics, too weak to survive anesthesia and that there was no indication that premature babies feel pain.

These letters were quickly picked up by the lay press. From the evening news, to the New York Times, public interest and media turmoil around the cases built quickly and spread fervently.[iii] Accusations against the medical profession were made liberally, equating their actions to the "sanctioned activities of the Third Reich", vivisection, abuse and torture.[iv]

At the same time, a similar debate was raging in the UK. At the 1986 annual meeting of the British Paediatric Association, Kanwal Anand's research group presented their work on using new biochemical methods to detect hormonal changes and measure surgical stress in infants.[v] At the time, the anesthesia provided to infants undergoing surgery consisted of a mixture of nitrous oxide (laughing gas) and curare, as clinical experience suggested that more potent narcotics would increase the risk of cardiorespiratory failure and thus cause more harm than benefit. Going against this belief, the team opted to investigate whether the addition of fentanyl, a potent opioid narcotic, would in fact reduce surgical stress and thus prove more beneficial than harmful. However, there was a misunderstanding with the general public and within weeks of the paper's publication, the British press along with members of parliament condemned the work as "Barbaric pain trials."

The MPs accused the team of paralyzing infants and causing them deliberate agony. Sir Bernard Braine writes, "The trials seemed to us to be even more barbarous when one considers that the babies being tested for pain were given curare, a paralysing drug, so that they would have been unable to kick or struggle even if they were in agony, the obvious intention being to keep them immobile at all costs."[vi] Though the MPs would later deliver a public apology to Anand, and though he would in time, be lauded as a savant and hero in the field of neonatal pain research, at the time his article created a controversy that rivalled the situation in the USA.[vii]

It was in such an environment that the public demanded to know why physicians withheld adequate anesthesia from infants. Or to phrase it less pejoratively: Why did infants not receive anesthesia that was comparable to that received by an adult? In the following years, numerous books and articles were written on the subject. A survey of such literature reveals that the two repeatedly cited reasons were: 1. Infants do not have the capacity to perceive pain. 2. It is too risky to use potent anesthetics on infants, given the risk for cardiorespiratory compromise and death.[viii]

In this regard, the primary aim of this paper will not be to outline the history of neonatal anesthesia, as it is addressed in the existing literature, but to elucidate the origins of the two claims: 1) Infants are insensitive to pain and 2) Light anesthetics are more suitable than potent anesthetics for infants. As such, this paper seeks to explore new factors that need to be considered when discussing the topic of neonatal pain.

## A Brief History of Neonatal Anesthesia

To put later arguments into context, first is a brief history of neonatal anesthesia. William Morton is credited with the first successful public demonstration of ether anesthesia on October 16th 1846. At the Massachusetts General Hospital, he demonstrated the use of ether in the painless removal of a tumour from the jaw of a young printer.[ix] In the years after Morgan's demonstration, the use of anesthesia spread around the world, though its use was quite selective until the late-1800s. The 19th century surgeon was rough, having inherited an attitude of indifference to pain from the days predating anesthesia. It was said that the role of a surgeon was to preserve life and not to prevent the temporary pain of the experience.[x] As such, the use of anesthesia was originally restricted to those considered sensitive, primarily the rich, white and educated women and children.

In fact, one of the early fears around anesthesia, which restricted its uptake, was the frightening possibility that anesthesia did not remove the pain of surgery, but only created paralysis followed by amnesia. Historian Pernick describes it as "a torment worthy of Poe, to feel all the pain but be unable to scream and afterward can not consciously recall the horror."[xi] It is interesting to note here, that even though there was an early fear that anesthesia would provide only amnesia but not pain relief, the later justification given by physicians for withholding anesthesia from infants centered on their supposed inability to recall painful experiences. This seems to indicate a shift in the mentality of physicians, from fearing that amnesia would mask the pain to believing that amnesia itself was sufficient justification for inflicting pain.[xii]

In any sense, up until the 20th century, the decision to administer anesthesia to a neonate to relieve the pain of surgery was inconsistent. Since its inception, infants were observed to be at a higher risk for complications from the anesthetic. They were more likely to suffer from cardiorespiratory compromise leading to heart, lung, kidney failure, and subsequent death.[xiii] The rarity of neonatal surgery beyond the repair of a cleft-lip, compounded by the population's emotional resistance to experimentation on children and the resulting lack of published studies meant that the decision to administer anesthesia to neonates was left in the hands of the individual practitioner.[xiv] When administered, the agents used were comparable to those used in adults – in essence, the deep general anesthetics: chloroform, cyclopropane and ether.

It was only in the early 20$^{th}$ century that the field of neonatal anesthesia started to grow. William Ladd, the father of pediatric surgery, dedicated his career to developing treatments for congenital defects that previously resulted in certain death of the infant.[xv] Spurned on by advances in neonatal cardiac and abdominal surgeries, anesthesia evolved in an effort to provide surgeons with the optimal operating conditions. Charles Robson, a McGill graduate, is considered the first pediatric anesthesiologist. He was the first to describe techniques for administering anesthesia to children and was known to disagree vehemently with his colleagues, who believed that neonates needed no anesthesia [xvi]

The next major advance in neonatal anesthesia arose from the work of Gordon Jackson-Rees, at the University of Liverpool. Arising from the struggle of avoiding cardiorespiratory collapse in neonates when using deep anesthesia, Jackson-Rees proposed the "Liverpool technique" of "light

anesthesia" in the mid-1950s.[xvii] The Liverpool technique consisted of a curare to provide muscle relaxation and nitrous oxide supplemented with low concentrations of other inhalational agents to provide analgesia and amnesia. Soon this became the standard approach for the neonates receiving anesthesia, as it maintained the hemodynamic stability of the infant while producing optimal operating conditions.[xviii]

The standard of "light anesthesia" persisted until 1987, when the combined public outcry against Anand's group and the Harrison and Lawson cases propelled the American Academy of Pediatrics to release a statement on neonatal anesthesia. It stated that the administration of pharmacologic agents (potent anesthetics) to neonates, "is indicated according to the usual guidelines for the administration of anesthesia to high-risk, potentially unstable patients."[xix] In the next decades, research into the understanding of neonatal pain and the finer aspects of neonatal anesthesia would blossom, heavily aided by new advances in technology, from comprehensive cardiorespiratory monitoring to fMRIs.[xx] Neonates would be found to have equal capacity to feel pain as adults and the long-term effects of early exposure to painful stimuli would be elucidated. By the beginning of the 21st century, protocols for neonatal pain assessment and management would be firmly implemented in hospitals across North America.[xxi]

## INFANT INSENSITIVITY TO PAIN

As highlighted previously, one of the two consistently cited reasons for the withholding of anesthesia from neonates was the belief that infants are insensitive to pain. When the American Academy of Pediatrics released its statement on neonatal anesthesia in 1987, it cited the commonly taught rationale that "nerve pathways [in neonates] are not sufficiently myelinated to transmit painful stimuli or that neonates do not have sufficiently integrated cortical function to recall painful experiences."[xxii]

Given this, the question becomes: Where did the principle of neonates not having sufficient myelination or cortical function to experience pain arise? The answer lies largely in the work of Paul Flechsig, a German neuroanatomist. In a series of journal articles and university addresses delivered between 1872-1901, Flechsig stated that there are places in the infant brain where "numerous fibres are devoid of medullary substance even three months after birth" and as a result,

"the remainder of the cortex is not myelinated, and constitutes the association centres as yet unprepared for function." From this, he postulated that, "upon anatomical grounds, a child at birth may have a simple sensation."[xxiii] In this same time period, Darwin published his observations on an infant, in which he wrote that in the first seven days of their life infants are only capable of "reflex actions" such as "sucking and screaming" as opposed to conscious or voluntary thought. As such, any perceived response to pain "must be considered as a reflex or an instinctive action" rather than "that of the seat of will."[xxiv]

In 1941, this theory would be further entrenched in the minds of the medical community via Myrtle McGraw's work. Building on the Flechsig's work, she determined that "the preponderance of evidence from cited histological studies indicates that the function of the cerebral cortex at the time of birth is problematical" and as such, "the sensori-motor experiences of the newborn infant do not extend beyond the subcortical or thalamic level." From this, she concluded that "prior to the onset of cortical control there occurs a period [of] diminished sensory experience."[xxv] Then, in 1960, David Levy's work would serve to compound the belief that neonates lack the ability to recall painful experiences. Levy observed the behaviours of 800 infants as they received routine vaccinations and concluded that "until the age of eight months, not one infant in our series gave any evidence of remembering a previous inoculation."[xxvi] As such, the rationale that neonates are insensitive to pain due to insufficient myelination and lack of cortical recall was established in the medical community.

Given this, a relevant avenue to explore, is the idea of whether the notion that babies are insensitive to pain existed before Flechsig's work and thus, before the established pool of scientific knowledge existed. Naturally, one could ask any new mother whether they believe their infant feels pain, and the reflexive response is a resounding yes – a fact needlessly demonstrated through the cases of Harrison and Lawson.[xxvii] Historians such as Pernick and Chamberlain claim that the notion existed at the formation of the medical establishment, as evidenced by the writing of Bigelow in the first volume of the Transactions of the American Medical Association in 1848, the journal that would later become the prestigious JAMA.[xxviii] Bigelow contended that the ability to experience pain was related to mental capacity and that, as infants had "neither the anticipation nor remembrance of suffering, however severe," narcotism was unnecessary. [xxix]

Yet, evidence exists to the contrary. In 1852, Pierson, a surgeon writing on the prudence of early operation for cleft-lips and the ability of infants to tolerate pain, states that "it was formerly generally believed that the earliest infancy was the period when the system was most liable to convulsions."[xxx] Though Pierson disagreed with the "maxim" that the nervous system was more sensitive at birth, his statement in itself demonstrates that the dogma of the day was that infants were indeed more sensitive to pain. This is further supported by the commentary of Michael Underwood, the father of pediatrics, who in 1827 highlighted the "great irritability of infants' nervous systems."[xxxi] As such, it can be postulated that the 1800s was a time of change with respect to neonatal pain, rather than a fixed point in the story of neonatal insensitivity to pain – A change that was perhaps propelled by surgeons with an inherited attitude of indifference to pain and a relative insensitivity to the mews of an infant compared to the screams of a grown man.

## THE DANGERS OF DEEP ANESTHESIA

Looking back on the arguments raised by physicians in favour of withholding anesthesia from infants, the second prominently cited justification is that "some neonates undergoing surgery are often so unstable that the risk of an anesthetic agent is too great."[xxxii] To put this view into context, from the first trials with inhaled anesthetics it quickly became apparent that infants were more susceptible to the deadly risks and side effects of narcotics. It was not uncommon to have an infant suffer cardiac arrest or severe post-operative hypotension leading to multiple organ failure and death.[xxxiii]

This risk became especially pronounced in the early-1900s, when the evolving specialty of pediatric surgery was expanding their reach beyond cleft-lips to the field of life threatening congenital anomalies including esophageal atresia, tetralogy of Fallot and diaphragmatic hernia.[xxxiv] For these cases, the surgeons required a significantly deeper level of anesthesia in order to achieve the muscle relaxation necessary to obtain satisfactory operating conditions. A surgeon writes, "unless the patient is deeply under the influence of chloroform, there is risk of protrusion of the intestine and rapidity of operating becomes a matter of great difficulty."[xxxv] As such, the anesthesiologists were constantly working at the limits of the therapeutic indices of chloroform and cyclopropane.

It was in such an environment that in 1958 Jackson-Rees advocated the use of the Liverpool technique of "light anesthesia" in infants. It was found that this technique produced optimal operating conditions while avoiding the complications of deep anesthesia, and as such, it became the standard of care.[xxxvi] As mentioned above, the Liverpool technique, as Jackson-Rees first proposed it consisted of a "50% mixture of nitrous oxide and oxygen, if necessary supplemented by pethidine or ether, to produce analgesia and a paralysant drug to attain relaxation and initiate the control of respiration."[xxxvii]

In recent years, historians have singled out the invention and popularity of the Liverpool technique as the cause for why infants were operated on "without analgesics or with very small, clearly subtherapeutic doses of analgesics."[xxxviii] Yet, this is not entirely correct for two reasons. First, the Liverpool technique, as it was first described by Jackson-Rees, clearly includes the use of an analgesic agent, nitrous oxide supplemented by an additional inhalational anesthetic if needed. To equivocate the use of a muscle paralysant alone without analgesia, with the Liverpool technique is incorrect. Jackson-Rees' aim in creating the Liverpool technique was to achieve a balance in which the different aspects of anesthesia (analgesia, amnesia and paralysis) would be met, while avoiding the dangers of deep anesthesia.[xxxix] Though later clinicians might have elected to use a muscle paralysant alone, such as in the Harrison and Lawson cases, this is a perversion of the Liverpool technique and should be considered as such.[xl] To pin the inhuman treatment of infants on the Liverpool technique is to hold Pasteur and the germ theory accountable for biological warfare.

The second issue that needs to be addressed is the pervasive belief that the Liverpool technique was invented for infants and that it was clearly subtherapeutic.[xli] In fact, the technique was used for nearly a decade in adults, before Jackson-Rees advocated its use in infants.[xlii] This leads into the question of whether it was known to be subtherapeutic. Adults, unlike infants, are able to express their complaints verbally after the surgery. Yet, in the published reports of the time, there was "no evidence of 'awareness' during the operative procedure" when the technique was used in the adult population.[xliii] Given this, it is incorrect to suggest that the technique was known to be subtherapeutic at the time, as the available evidence indicated that it was a safe and effective form of anesthesia.

## CONCLUDING REMARKS

To surmise, the issue of neonatal anesthesia is not simply one of negligence or ignorance of the medical profession, as the public was lead to believe, but quite possibly simply one of equipoise. In a situation where the benefits and harms of opioid anesthesia were unknown, the controversial work of Anand provided the long-sought answer. Though, it can also be said that the public outcry served to engender reflection in the medical community and begot the multitude of studies that are available today. In addition, this paper proposes that, in the discussion of neonatal anesthesia, it is important to consider the exact origins of neonatal insensitivity to pain, rather than accepting that the idea has existed since the origin of medicine. In this sense, it is possible that two paradigm shifts occurred: first the shift to neonatal insensitivity to pain in the mid-1800s and then the shift back to sensitivity in the late-1900s. Finally, it is important to reconsider the role of the Liverpool technique in the history of neonatal anesthesia – not as the bane of an infant's existence, but rather, as a technique that made neonatal surgery possible.

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[i] (Harrison and Lawson 1986)
[ii] Ibid
[iii] (Lawson 1988), (Rovner 1987), (Boffey 1987)
[iv] (Shearer, Surgery on the Paralyzed, Unanesthetized Newborn 1986), (Harrison and Lawson 1986)
[v] (Anand, et al. 1985), (Anand, Sippel and Aynsley-Green 1987)
[vi] (British Paediatric Association 1987)
[vii] (Bernard 1988)
[viii] (Shearer, Newborn Surgery Without Anesthesia: Is the Problem Solved? 1988), (British Paediatric Association 1987), (Butler 1989), (Chamberlain 1991), (American Academy of Pediatrics 1987)
[ix] (Mai and Cote 2012)
[x] (Pernick, A Calculus of Suffering 1985)
[xi] (Pernick, A Calculus of Suffering 1985, 36-37)
[xii] (Shearer, Newborn Surgery Without Anesthesia: Is the Problem Solved? 1988)
[xiii] (Costarino and Downes 2005), (Pernick, A Calculus of Suffering 1985)
[xiv] (Smith 1975)
[xv] (Rowe and Rowe 2000)
[xvi] (Costarino and Downes 2005)
[xvii] Ibid
[xviii] (Steward 2015)
[xix] (American Academy of Pediatrics 1987)
[xx] (Goksan, et al. 2015), (Fitzgerald 2015)
[xxi] (Edwards 2011), (Roofthooft, et al. 2014)

[xxii] (American Academy of Pediatrics 1987), (Hatch 1987)
[xxiii] (Flechsig 1901), (Bourke 2014, 214-218), (Cope 1988)
[xxiv] (Darwin 1877)
[xxv] (McGraw 1941)
[xxvi] (Levy 1960)
[xxvii] (Harrison and Lawson 1986)
[xxviii] (Pernick, A Calculus of Suffering 1985), (Chamberlain 1991)
[xxix] (Bigelow 1848)
[xxx] (Peirson 1852)
[xxxi] (Bourke 2014)
[xxxii] (American Academy of Pediatrics 1987)
[xxxiii] (Pernick, A Calculus of Suffering 1985), (Costarino and Downes 2005)
[xxxiv] (Swenson 1948), (Steward 2015)
[xxxv] (Cautley and Dent 1902)
[xxxvi] (Stead 1955), (Rees 1958)
[xxxvii] (Gray and Rees 1952)
[xxxviii] (Paola, Walker and Nixon 2010, 275), (Mayock and Gleason 2011, 429)
[xxxix] (Gray and Rees 1952)
[xl] (Lippmann, et al. 1976), (Harrison and Lawson 1986)
[xli] (Paola, Walker and Nixon 2010, 275), (Mayock and Gleason 2011, 429), (Steward 2015)
[xlii] (Gray and Rees 1952)
[xliii] (Brice, Hetherington and Utting 1970), (Taub and Eisenberg 1975), (Keenan 1972)

## Works Cited


American Academy of Pediatrics. "Neonatal Anesthesia." *Pediatrics* 80, no. 3 (1987): 446.

Anand, K.J.S, M.J. Brown, R.C. Causon, N.D. Christofides, S.R. Bloom, and A. Aynsley-Green. "Can the human neonate mount an endocrine and metabolic response to surgery?" *Journal of Pediatric Surgery* 20, no. 1 (February 1985): 41-48.

Anand, K.J.S., W.G. Sippel, and A. Aynsley-Green. "Randomised trial of fentanyl anesthesia in preterm babies undergoing surgery: effects on the stress response." *Lancet* I (1987): 243-248.

Bernard, Braine. "MP apologises." *British Medical Journal* 297 (October 1988): 865.

Bigelow, H.J. "Anesthetic symptoms considered separately." *Transactions of the American Medical Association* 1, no. 1 (1848): 206-214.

Boffey, Philip M. "Infants' sense of pain is recognized, finally. ." *New York Times*, Nov 1987.

Bourke, Joanna. *The Story of Pain: from prayers to painkillers.* Oxford: OUP Oxford, 2014.

Brice, D.D., R.R. Hetherington, and J.E. Utting. "A simple study of awareness and dreaming during anesthesia." *British Journal of Anesthesia* 42 (1970): 535-542.

British Paediatric Association. "Medicine and the Media." *British Medical Journal* 295 (September 1987): 659-660.

Butler, Nance Cunningham. "Infants, pain and what health care professionals should want to know now - an issue of epistemology and ethics." *Bioethics* 3, no. 3 (1989): 181-199.

Cautley, E., and C.T. Dent. "Congenital hypertrophic stenosis of the pylorus and its treatment by pyloroplasty." *Lancet*, 1902: 1679-1685.

Chamberlain, David B. "Babies don't feel pain: a century of denial in medicine." *The Second International Symposium on Circumcision* . San Francisco, 1991.

Cope, Doris K. "Neonatal Pain: The Evolution of an Idea." *The American Association of Anesthesiologists Newsletter.* September 1988. www.asahq.org/Newsletters/1998/09_98/Neonatal_0998.html (accessed September 29, 2016).

Costarino, Andrew T., and John J. Downes. "Pediatric Anesthesia Historical Perspective." *Anesthesiology Clin N Am* 23 (2005): 573-595.

Darwin, Charles R. "A biographical sketch of an infant." *Mind. A Quarterly Review of Psychology and Philosophy* 2, no. 7 (1877): 285-294.

Eger II, Edmond I., Rod N. Westhorpe, and Lawrence J. Saidman. "1910-1950: Anesthesia before, during and after two world wars." In *The Wondrous Story of Anesthesia*, by Edmond I. Eger II, Lawrence J. Saidman and Rod N. Westhorpe, 51-71. New York: Springer Science & Business Media, 2013.

Fitzgerald, Maria. "What do we really know about newborn infant pain?" *Experimental Physiology* 100, no. 12 (2015): 1451-1457.

Flechsig, Paul. "The cerebral cortex in the human subject." *The Lancet*, October 1901: 1027-1029.

Goksan, Sezgi, et al. "fMRI reveals neural activity overlap between adult and infant pain." *eLife*, no. 4 (2015).

Gray, T.C., and G.J. Rees. "The role of apnoea in anesthesia for major surgery." *British Medical Journal*, October 1952: 891-892.

Harrison, Helen, and Jill Lawson. "Letters." *BIRTH* 13, no. 2 (1986): 124-125.
Hatch, D.J. "Analgesia in the neonate." *British Medical Journal* 294 (April 1987): 920.
Keenan, Richard L. "Nitrous oxide-curare anesthesia: reappraisal." *MCV Quarterly* 8, no. 2 (1972): 142-147.
Lawson, Jill. "More on Newborn Surgery Without Anesthesia." *BIRTH* 15, no. 1 (March 1988): 36.
Levy, David M. "The infant's earliest memory of inoculation: a contribution to public health procedures." *The Journal of Genetic Psychology* 96 (1960): 3-46.
Lippmann, M., R.J. Nelson, G.C. Emmanouilides, J. Diskin, and D.W. Thibeault. "Ligation of patent ductus arteriosus in premature infants." *British Journal of Anesthesia* 48 (1976): 365-369.
Mai, Christine L., and Charles J. Cote. "A history of pediatric anesthesia: a tale of pioneers and equipment." *Pediatric Anesthesia* 22 (2012): 511-520.
Mayock, Dennis E., and Christine A. Gleason. "Neonatal pain and stress: assessment and management." In *Avery's Diseases of the Newborn*, by Christine A. Gleason and Sandra E. Juul, 429-444. Philadelphia, PA: Elsevier Health Sciences, 2011.
McGraw, Myrtle B. "Neural maturation as exemplified in the changing reactions of the infant to pin prick." *Child Development* 12, no. 1 (March 1941): 31-42.
Paola, Frederic A., Robert Walker, and Lois L. Nixon. *Medical ethics and humanities.* Burlington: Jones & Bartlett Learning, 2010.
Peirson, A.L. "Early Operation for Harelip." *American Intelligence*, October 1852: 576.
Pernick, Martin S. *A Calculus of Suffering.* New York City: Columbia University Press, 1985.
Rees, Jackson G. "Neonatal Anesthesia." *British Medical Bulletin* 14, no. 1 (1958): 38-41.
Rovner, S. "Sparing infants the agony of surgery." *Washington Post*, Nov 1987.
Rowe, Marc I., and Stephen A. Rowe. "The last fifty years of neonatal surgical management." *The American Journal of Surgery* 180 (November 2000): 345-352.
Shearer, Madeleine H. "Newborn Surgery Without Anesthesia: Is the Problem Solved?" *BIRTH* 15, no. 1 (March 1988): 36-38.
Shearer, Madeleine H. "Surgery on the Paralyzed, Unanesthetized Newborn." *BIRTH* 13, no. 2 (June 1986): 79.
Smith, Robert M. "The Pediatric Anesthetist, 1950-1974." *Anesthesiology* 43, no. 2 (1975): 144-155.
Snow, John. "Part I." *Lancet*, 1855: 361-363.
Stead, Alan L. "The response of the newborn infant to muscle relaxants." *British Journal of Anaesthesia* 27 (1955): 124-130.
Steward, David J. "The History of Neonatal Anesthesia." In *Neonatal Anesthesia*, by Jerrold Lerman, 1-15. New York City: Springer-Verlag New York, 2015.
Swenson, Orvar. "The diagnosis and treatment of atresia of the esophagus and tracheo-esophageal fistula." *Pediatrics* 1 (1948): 195-204.
Taub, Harvey A., and louis Eisenberg. "A comparison of memory under three methods of anesthesia with nitrous oxide and curare." *Canadian Anesthesiologists' Society Journal* 22, no. 3 (May 1975): 298-306.