
Neonatal Pain Relief and the Helsinki Declaration

Robert S. Van Howe and J. Steven Svoboda

The Helsinki Declaration, first published in 1964, is the universally accepted standard for ethical behavior in research involving human subjects. The Declaration was formulated in response to the abuses of human subjects by the scientists in Nazi Germany and to update the Nuremberg Code. Amended in 1975, 1983, 1989, 1996, and 2000,¹ the Declaration provides the foundation for the United States federal regulations for research involving human subjects.²

To conform to standards developed in the Declaration, a researcher must fulfill the following: (1) respect the autonomy of the individual; (2) promote and safeguard the individual's health; (3) provide informed consent without coercion; (4) take special measures with vulnerable populations; (5) compare new therapies to the best current therapies; (6) have a thorough scientific knowledge of the subject; (7) assess risk versus benefit of the intervention; (8) perform studies that will ultimately benefit the population involved in

the research; (9) accurately report their findings; and (10) fully disclose ethical concerns in their research protocols.

Several placebo-controlled trials have been published in highly respected American medical journals in recent years that attempt to determine the effectiveness of pain relief measures for neonatal circumcision. It is our contention that these trials failed to meet the ethical requirements of the Helsinki Declaration in the key areas listed above. We also contend that the institutional review boards (IRBs) failed their ethical duties by approving these studies and that the journal editors failed their ethical duties by publishing these studies.

Choosing an Ethical Framework

Robert Baker has delineated four potential approaches to bioethical problems: fundamentalism, multiculturalism, postmodernism, and contractarianism. Fundamentalists believe that there exist core moral beliefs that apply to all humans regardless of their culture and when they lived. They believe, for example, that a key element of humanness is the wrongness of inflicting unnecessary pain or suffering. Multiculturalism holds that moral beliefs vary markedly from culture to culture. Multiculturalists believe that moral principles are binding upon a people/culture because they are accepted by those people to whom the moral principles bind. Different cultures in different eras have different moral principles. Thus, what is binding in one culture at one time may not be binding in a different culture at a different time. The postmodernist believes that the dominance of any particular perspective is a function of power, not principle. For example, the conviction of the Nazi physicians at the Nuremberg Tribunal was more a function of Germany's having

Robert S. Van Howe, M.D., M.S., is a general pediatrician, statistician, educator, and researcher with interests in many areas of primary care, with an emphasis on cost-utility analyses. He has been an invited presenter to the American Academy of Pediatrics Task Force on Circumcision and to Centers for Disease Control and Prevention and is currently working on a book on the ethics of genital alteration. **J. Steven Svoboda, J.D., M.S.,** is the Founder and Executive Director of Attorneys for the Rights of the Child (ARC), a section 501(c)(3) educational non-profit organization, this work leading to his receiving the 2002 Human Rights Award of the International Symposium on Human Rights and Modern Society. He has written extensively on the legal and ethical issues surrounding involuntary genital alterations and in 2007 co-authored an Oxford University Press gender studies textbook addressing, among other issues, the connection between gender equity and protecting all children's genital integrity.

lost the war than of the acts attributed to these physicians.³ Consequently, postmodernism is about power rather than ethics and might best be expressed in the idiom, "Might makes right." Baker employs contractarianism to resolve the conflicts and shortcomings of the other three approaches. Simply put, moral order is the result of negotiation between conflicting parties. As Baker puts it:

[M]orality is not a matter of one group imposing its values upon another, but of rendering conflict quiescent by negotiating a set of norms that permits each party to use common resources while respecting the other party's primary areas of nonnegotiability.⁴

infants undergoing the procedure.⁷ Reports by Pedro A. Poma,⁸ Lynne Gershon Maxwell et al.,⁹ Paul S. Williamson and Nolan Donovan Evans,¹⁰ Anthony L. Masciello,¹¹ Richard L. Holve et al.,¹² Paul S. Williamson and Marvel L. Williamson,¹³ and Howard Stang et al.¹⁴ all documented that DPNB positively impacted parameters believed to be associated with neonatal pain prior to 1991. Likewise, Diane Mudge and Janet B. Younger in 1989¹⁵ and Kathleen B. Weatherstone et al. in 1993¹⁶ found topical lidocaine to achieve significant reductions in pain for virtually all subjects. In 1993, Franca Benini and colleagues were also able to reduce pain by applying lidocaine-prilocaine cream (EMLA).¹⁷ Furthermore, ring block was found to have some effect by Masciello in 1990.¹⁸

Several placebo-controlled trials have been published in highly respected American medical journals in recent years that attempt to determine the effectiveness of pain relief measures for neonatal circumcision. It is our contention that these trials failed to meet the ethical requirements of the Helsinki Declaration. We also contend that the institutional review boards failed their ethical duties by approving these studies and that the journal editors failed their ethical duties by publishing these studies.

The Helsinki Declaration evidently was established to protect research subjects from shortcomings of multiculturalism and postmodernism. While the Declaration was negotiated with the aim toward universal acceptability and application, it clearly favors a Kantian approach that treats individuals as ends in themselves rather than means to an end, as opposed to the Utilitarian goal of maximizing the overall good even where that requires sacrificing certain individuals' interests.

The Medical Literature on Pain Relief for Neonatal Circumcision

Until recently the medical literature on pain relief for neonatal circumcision incorporated the startling myth that newborns could not feel pain.⁵ This led many physicians to the belief that pain relief for neonatal circumcision was unnecessary. Unfortunately, newborns not only experience pain, but experience pain more intensely for a given noxious stimulus than do older infants, children, and adults.⁶

The development of pain relief for neonatal circumcision began in 1978 when Christopher Kirya and Milton W. Werthmann used a dorsal penile nerve block (DPNB) to reduce the pain in all but 2 of 52

By the time the 1989 American Academy of Pediatrics (AAP) Task Force on Circumcision report was published, DPNB had been shown to reduce the pain of neonatal circumcision. Indeed the 1989 AAP Task Force report acknowledged that:

Dorsal penile nerve block using no more than 1% lidocaine (without epinephrine) in appropriate doses (3 to 4 mg/kg) may reduce the pain and stress of newborn circumcision.

Despite the wealth of studies showing that the pain of infant circumcision could be safely and effectively reduced, the AAP Task Force surprisingly added:

However, reported experience with local anesthesia in newborn circumcision is limited, and the procedure is not without risk.¹⁹

Details regarding randomized controlled studies of pain relief for neonatal circumcision are given in the appendix.

Helsinki Declaration Applied to Neonatal Circumcision

Application of the ten principles of the revised Helsinki Declaration to the specific case of placebo-controlled trials for neonatal circumcision pain relief clarifies many of the ethical and conceptual difficulties with such studies.

1. *Respect the Autonomy of the Individual*

The clear overriding theme of the Helsinki Declaration is the protection of individual subjects:

In medical research involving human subjects, the well being of the individual research subject must take precedence over all other interests. (Section 6)

for use so that they can market these expanded indications. As will be discussed below, studies of a new therapy in comparison to placebo are more likely to show the newcomer's benefit than a direct comparison to best therapy. More often than not, placebo comparisons are often of little use to clinicians who want to know how new therapies compare to current best therapy rather than placebo. Clearly, a pharmaceutical company with a new product would like a placebo comparison, as it is more likely to boost sales, especially if it is suspected that the new product is of equal or inferior efficacy in comparison to the current best therapy. If a company engages in a placebo-controlled trial, as opposed to an active-controlled trial, primarily or in part to boost sales and company profitability, then the subjects have arguably been exploited. Finally, if a researcher knows that a report of a pla-

Using a substituted judgment approach, one would ask if adult males would volunteer for a research project in which there was a possibility of undergoing a circumcision without any measures for pain relief. The answer is clearly no. If one would not expect any adult volunteers, then one can, therefore, not expect that any newborns would volunteer.

At the very minimum, subjects must not be exploited. Even strong critics of the Declaration, such as Franklin G. Miller and Howard Brody, who propose reducing the ethical responsibilities of clinical investigators to the bare minimum, concede that exploitation of subjects is unethical.²⁰ While all research subjects are used toward the advancement of medical knowledge, exploitation entails "unfair use." Fair use requires fully informed consent, research that has a reasonable chance of answering a clinically important question, and a proper consideration of the subjects' interests in the context of the proposed research. Unfair use entails using subjects as means to an end with little or no regard for the welfare of the subjects. For example, children are vulnerable to exploitation because they are unable to meaningfully consent and dependent on others to protect their best interests. The poor are at risk because of limited access to health care outside a research setting.²¹

Exploitation of experimental subjects can arise when research is deliberately performed in a way that may conceal part of the truth or may be primarily aimed at effectively marketing a product rather than seeking a scientifically useful result. For example, pharmaceutical companies fund and perform clinical research on their products in hopes of developing indications

cebo-controlled trial is more likely to be published than an active-treatment trial, then the subjects may have been exploited to advance the researcher's career through successful publications.

This potential pitfall is exemplified by the study by Anna Taddio and colleagues published in the *New England Journal of Medicine*.²² In a study funded by drug manufacturer Astra, EMLA was compared to placebo, which resulted in an immediate boost in EMLA usage for this indication. However, subsequent studies found that EMLA is inferior to DPNB and only marginally better than placebo.²³ Despite its inferiority, EMLA is often listed as one of the mainstays of therapy, primarily as the result of publication of this placebo-controlled trial. We believe both the subjects who received placebo and to a lesser extent those receiving EMLA, who underwent an inferior form of pain relief, were exploited by Astra and the investigators by being recruited and enrolled in a study that *by deliberate design* was not seeking useful medical knowledge but rather the promotion of their own product.

2. *Promote and Safeguard the Individual's Health*

Sections 3 and 4 of the Declaration speak of the duty of the physician to "promote and safeguard the health

of the people” with the health of the patient being the physician’s “first consideration.” In the placebo-controlled pain relief studies under consideration, two criteria apply in interpreting this duty. The first is whether the interventions being scrutinized promote the subjects’ health. While the expected reduction in the pain of neonatal circumcision would promote health, the use of placebo controls when known effective therapy existed fails to fully safeguard the subjects’ health.

The second criterion encompasses the broader question of whether research on aspects of unproven interventions comply with the Helsinki Declaration. A hypothetical example would be a study analyzing the efficacy of adding a new, untested chemotherapy agent to tumor debulking relative to tumor debulking alone, given that the pervasive practice of tumor debulking has never been shown to improve outcomes and may worsen prognosis. By retaining tumor debulking in the protocol, we would contend that the study of the new chemotherapy agent is unethical because it exposes the subjects to the unnecessary risks of an unproven intervention. The same logic would apply to neonatal circumcision, as the consensus of medical organizations is that it does not promote or safeguard health.²⁴ Since it has not been shown that neonatal circumcision is “necessary to promote the health of the population represented,” this group (neonates) should not have been included in the research. From a fundamentalist’s perspective, all unnecessary suffering is unallowable. Clearly the infants in the placebo arms suffered unnecessarily. One could also extend this to make a cogent argument that all of the participants in the trials suffered unnecessarily.

3. *Informed Consent*

Section 24 of the Declaration calls for volunteer participants whose informed consent has been obtained through a process satisfying specific criteria:

In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potentials risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. (Section 24)

An infant obviously cannot provide informed consent for himself. Instead, someone else must provide consent on his behalf. This is often referred to as parental permission because it is usually the parent who grants permission, but it can also be a guardian other than the parents.²⁵ Many authors, wishing to avoid a prolonged explanation, use “informed consent” to encompass informed consent in competent subjects, parental permission, and a child’s assent. The most important aspects of parental permission on behalf of an infant are the infant’s inability to consent or assent and the duty of the parent (or guardian) to protect the interests and rights of the infant. Permitting parents (or guardians) to make decisions on behalf of the infant relies on the bedrock assumption that the decision maker will make decisions that are in the infant’s best interest. Regrettably, this is not always the case. There is an unfortunate history of children being treated as property, rather than as citizens with the full complement of rights.²⁶ Some have questioned, given the perinatal emotional upheaval, whether parental permission can ever be truly free and informed in the neonatal context.²⁷ The informed consent process also needs to include a discussion in which the investigators inform the parents of potential subjects of the availability of interventions known to be effective (such as DPNB), but that within the study, the possibilities were only interventions of unknown effectiveness or placebo, which is not effective. Based on the publications arising from the placebo-controlled trials, there is no indication that such information was given as part of the informed consent process. If this information were provided, then we can only speculate how many parents approached to include their sons in the research would decline for this reason. Only one of the published studies indicated that the parents of three infants refused to give consent.²⁸ The rest of the studies are silent on this point. Disturbingly, in two of the studies, untreated non-randomized control groups were included in the studies without parental permission.²⁹

4. *Vulnerable Populations*

The researcher also must assure that consent has not been coerced as potential research subjects are often vulnerable (Section 9) or in a dependent relationship (Section 26). Additional requirements apply where subjects belong to particularly vulnerable populations:

For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a

research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden. (Section 27)

As noted in Sections 3-4, the proxy decision maker is charged with protecting the infant's interests and health. Two approaches have been advocated for accomplishing this. The first is to determine what is in the newborn's best interests. This can take the form of a risk-benefit or cost-utility analysis. If the risks outweigh the benefit, then proxy consent should not be given. The second approach is known as substituted judgment. Using this approach, the decision maker asks what the newborn would decide for himself if legally competent.³⁰ Newborns about to undergo cir-

5. Compare New Therapies to the Best Current Therapy

Section 32 may be the Declaration's most controversial. It previously read as follows:

The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists. (Former Section 32, previously numbered as Section 29)

While the language is clear, many have tried to twist the meaning of this section to justify placebo-controlled trials in situations where their justification is problematic. The controversy attracted the most attention with studies in Africa in which low-dose

One could successfully argue that, even with pain relief, the inherent risks and burdens of the circumcision, including loss of the functions of the foreskin, outweigh any benefits. Given the unfavorable risks and losses associated with the underlying procedure, one could easily conclude that the procedure itself is unethical, and therefore any study of neonatal circumcision must also be unethical.

cumcision have no power to say no. They may have a right to say no, but because of their powerlessness, they are unable to exercise this right.³¹ Because the newborn is dependent on both the parents and the physician, the Declaration calls for a higher standard of protection for neonates, who are necessarily unable to consent to being research subjects. Consequently, the physician/researcher must take special steps to protect the child's best interests.

Section 8 affirms, "In medical practice and in medical research, most interventions involve risks and burdens. Using a substituted judgment approach to weighing risks against benefits, one would ask if adult males would volunteer for a research project in which there was a possibility of undergoing a circumcision without any measures for pain relief. The answer is clearly no.³² If one would not expect any adult volunteers, then one can, therefore, not expect that any newborns would volunteer.

AZT and placebo were randomly given to pregnant women after it had been proven that high-dose AZT effectively reduced maternal-fetal transmission of HIV. While the editor of the *New England Journal of Medicine* interpreted Section 32 of the Declaration literally and called the studies unethical,³³ apologists for the studies put an interesting spin on the language in the section. Instead of "best current prophylactic, diagnostic, and therapeutic methods," the apologists asserted that Section 32 really meant to say "standard practice." Standard practice in developing countries is often limited by economic factors, and high-dose AZT therapy for pregnant women in Africa would never economically be an option. For this reason, researchers, such as Robert J. Levine, believed they could use "standard practice" as the comparison group; in Africa, this meant no treatment.³⁴ A heated debate thus ensued and led to a modification of the Helsinki Declaration in October 2000:

The benefits, risks, burdens and effectiveness of a new intervention must be tested against

those of the best current proven intervention, except in the following circumstances:

- The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
- Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option. (Section 32)

It is notable that the latest version of the Declaration has added the strongly worded final sentence about “extreme care to avoid abuse.” Although many of the placebo-controlled trials involving neonatal circumci-

For example, if the study of EMLA versus placebo by Taddio et al. had compared EMLA to DPNB, then EMLA would have been shown to be inferior to DPNB, as the investigators evidently knew.³⁵ This would have made the study less likely to gain publication, especially in a journal as prestigious as the *New England Journal of Medicine*. More importantly, the failure of EMLA would have hampered sales, something Astra, as the manufacturer of EMLA and the sponsor of the study, did not want to happen.

A distinction exists between common practice and standard of care. These terms are far from coterminous; in fact, it is possible for a practice to be extremely pervasive and yet out of line with the latest medical knowledge and/or the official guidance of pertinent specialty medical bodies. For example, when a new therapeutic approach is found, such as laparoscopic cholecystectomy or antibiotics for recurrent peptic ulcer disease, there can be a time when older therapies are still widely employed, despite their inadequa-

The studies assessing pain relief for neonatal circumcision often relied on only a few indirect measures of pain. This reliance on limited response data, knowing it will provide an incomplete picture, can effectively invalidate the reported results. We contend that it is unethical to expose an infant to a protocol that fails to collect easily obtainable data that would decrease bias in the research outcome.

sion were performed before this revision, we will apply the revised recommendations. Why would investigators want to use a placebo rather than the best current methods? Consider the following reasons.

1. Use of a placebo makes it more likely that an intervention will be shown “effective,” though such a result may be clinically irrelevant.
2. Showing “effectiveness” makes it more likely that a study will get published, thus advancing the careers of the investigators.
3. Showing “effectiveness” will increase the popularity or sales of the intervention studied.
4. Using placebo controls keeps the new therapy from going head to head with established therapy and being shown inferior, which would decrease the likelihood of being published, advancing the careers of the investigators, or making money for the company financing the study.

cies, as the result of inertia. In the example under discussion, the majority of neonatal circumcisions are performed without anesthesia, so the erroneous conflation of common practice with standard of care would lead to a conclusion that circumcision with no anesthetic is the standard of care in North America. Irrespective of common practice, the standard of care based on pertinent studies and the American Academy of Pediatrics’s (AAP) position should mandate its universal use. In 1987, the AAP released a position paper on pain relief in neonates recommending that “the decision to withhold such [pain] medication should be based on the same medical criteria used for older patients.”³⁶ Most physicians who fail to apply or inject an anesthetic for neonatal circumcision do so either out of ignorance or time considerations.³⁷ In short, instead of relying solely or primarily on local or common practice as a standard, researchers should also take into serious account whatever standards may have been established by medical specialties.

As mentioned above, the AAP's position paper mandates application of the same standards regarding pain medication to infants and older patients.³⁸ Nevertheless, infants continue to undergo circumcisions without the benefit of pain relief, while older children and adults receive dorsal penile nerve block and topical anesthesia as adjunctive post-operative pain relievers, and general anesthesia is used during the procedure.³⁹ The level of pain these neonates experience is clearly greater than those who have the procedure performed under general anesthesia.⁴⁰ The newborn is inexperienced in filtering noxious stimuli, so the full impact of pain, without adaptive measures, is delivered. In older children and adults, pain is attenuated by filters developed with experience by the nervous system.

emphasizes that treatment considerations need to be attended to in concert with research issues. Research subjects have given up certain freedoms to be in the trial, thereby increasing their vulnerability, and therefore should be awarded higher levels of protection. Again, these concerns become even more critical in the case of newborn infants. Instead, the opposite took place in these studies. As pointed out by Christopher J. Cold, the unanesthetized surgery permitted on these newborns would not have been allowed on laboratory animals.⁴³

In what situations would a placebo-controlled trial have been ethically acceptable? Consider the following.

Given that a method of providing adequate anesthesia, short of general anesthesia, has not been demonstrated, it may be prudent to call for a moratorium on neonatal circumcision until adequate anesthesia becomes available.

This difference in our perception may be explained by older boys and men who can articulate their level of pain, whereas infants are reduced to screams that the circumcising physician may ignore. The AAP's policy recommendation regarding pain relief has been incorporated into the statement issued by the Australasian Association of Paediatric Surgeons, which recommend delaying circumcision until six months of age when an experienced surgeon and a pediatric anesthesiologist are available and general anesthesia can be safely delivered.⁴¹

An additional repudiation of using "common practice" as a synonym for "standard of care" is contained in Section 31 of the Declaration, which states:

They physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects. (Section 31)

While Miller and Brody argue that researchers do not have an ethical obligation to care for the medical needs of research subjects,⁴² this is clearly contrary to the intent of the Helsinki Declaration, which

1. The Helsinki Declaration would allow a placebo-controlled trial if there were no effective treatment available; however, in this case, effective treatment was known and often referred to in the published papers.
2. The revised Declaration would allow a placebo-controlled trial for "compelling and scientifically sound methodological reasons." As will be discussed later, none of the reasons given for performing a placebo-controlled trial meets this criterion.
3. The revised Declaration would allow a placebo-controlled trial if "the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm." As discussed below, short-term, severe pain provides sufficient risk to negate placebo use.

Disturbingly, a number of studies explicitly or implicitly recognized that failure to use pain relief could not satisfy the standard of care but employed a no-treatment group anyway.⁴⁴ For example, C. G. Mohan et al. admit, "Circumcision in the newborn is a simple but significantly painful surgical procedure, which requires pain intervention," yet included a non-randomized, unconsented control group who received no pain intervention.⁴⁵ Further, Peter S. Kurtis and associates note, "There is a broad body of informa-

tion now available on techniques that are believed to reduce the pain associated with circumcision,” yet had two control groups that did not receive pain relief. Additionally, in their discussion section they state, “[W]e no longer feel that using nonanesthetized controls for research is ethical.”⁴⁶ Similarly, Frederick C. Kass and John R. Holman acknowledge, “Previous studies have demonstrated dorsal penile nerve block (DPNB), subcutaneous ring block, and some topical anesthetic formulations (eg, eutectic mixture of local anesthetics cream) to be effective,” yet used a placebo control group.⁴⁷

Marguerite Herschel et al. state that “DPNB can be considered the standard for pain relief during circumcision,” yet used a no-treatment control.⁴⁸ Equally problematic, the authors spend most of their ink com-

in our neonatal intensive care unit (NICU) is to provide anesthesia during neonatal circumcision, we did not feel justified in randomizing any infant to no anesthesia,” yet they included a non-randomized control group of infants who had circumcisions performed without anesthesia or analgesia at another institution but did not “consent” either directly or through proxy to be in the study. Amazingly, this was approved by their IRB!

Similarly, in response to a letter to the editor calling for pain relief for circumcised newborns,⁵⁴ Taddio and Gideon Koren acknowledge the importance of pain relief in this context: “In our view, the pain and suffering of infants who are circumcised should not be ignored because many believe that the procedure should not be performed. These infants, like all

When the IRBs were presented with the protocols for these placebo-controlled trials, did they consider performing medically unnecessary surgery on children problematic? Did they fail to recognize a problem with withholding effective pain interventions for a procedure known to be extremely painful? Did they not appreciate that the selected study designs would fail to demonstrate whether these interventions provided adequate anesthesia? Were they unaware that the interventions proposed fell below the standard established by the AAP for pain relief in neonates?

paring sucrose to placebo, while comparisons to DPNB, which proved markedly better than either sucrose or placebo, were cursory. Janice Lander and colleagues based their misleadingly titled work on the primary hypothesis that “[n]ewborns receiving placebo will have greater distress during and following circumcision than newborns receiving EMLA, dorsal penile nerve block, or ring block.”⁴⁹ This violates the concept of equipoise — “a state of genuine uncertainty on the part of the clinical investigator regarding the comparative therapeutic merits of each arm in a trial” — that provides the foundation of ethical clinical research.⁵⁰ The study by Marvel L. Williamson tried to play it both ways. The study employed placebo controls, but used a ratio of DPNB to no treatment of 2:1, to minimize the number of subjects given no pain relief. Taddio et al. note that previous work from Benini⁵¹ had already demonstrated that EMLA was superior to placebo, and that DPNB was superior to EMLA.⁵² Once again, equipoise was not present when the study was designed. Perhaps the most bizarre twist occurred in the study by Meggan Butler-O’Hara and associates.⁵³ The investigators admit, “Because the current practice

infants, should have the benefit of pain relief.”⁵⁵ However, their stated position did not prevent them from providing only placebo to some newborns in their previous studies.⁵⁶

6. Thorough Scientific Knowledge

Section 12 of the Declaration requires that research involving humans be “based on a thorough knowledge of the scientific literature.” Investigators cannot bury their heads in the sand and ignore the research that has gone before them. In most of these studies researchers cited the literature that documented effectiveness of DPNB, only to ignore this science when designing their studies.

7. Risk versus Benefit

Sections 18 to 20 of the Declaration are adamant about the impermissibility of placing human subjects at unreasonable risk.

Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the

individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation. (Section 18)

Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results. (Section 20)

Here, the investigators failed again. By having a placebo arm, they knowingly exposed half of their newborn subjects to a painful, medically unnecessary procedure without any attempt at pain relief. Even such strong advocates for placebo-controlled trials as Miller and Brody — while willing to allow such studies to proceed even when established effective therapies exist — nevertheless concede that the use of placebo should be precluded when excessive risks exist, including a risk of “short-lived but severe discomfort.”⁵⁷ Robert Levine, citing the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research publication on *Research Involving Children*, suggests that an ethical review by a national organization may be required if the risk for subjects in research involving children exceeds that normally encountered in daily life, such as routine medical or psychological examinations.⁵⁸ Clearly, a painful procedure in a study setting in which no anesthetic was provided would require review, but, unfortunately, such a national review mechanism has never been established.

The risk-benefit analysis should also extend past a selection of acceptable research options to determine whether the risks of neonatal circumcision outweigh the benefits. One could successfully argue that, even with pain relief, the inherent risks and burdens of the circumcision, including loss of the functions of the foreskin, outweigh any benefits.⁵⁹ Given the unfavorable risks and losses associated with the underlying procedure, one could easily conclude that the procedure itself is unethical, and therefore any study of neonatal circumcision must also be unethical.

Researchers cannot credibly claim ignorance of the procedure’s risks and losses, given the pervasiveness of pertinent information. Ironically, two studies that linked neonatal circumcision to long-term alterations in how infants perceive pain⁶⁰ were carried out by one

of the teams that also performed a placebo-controlled trial.⁶¹

8. *Ultimately Benefit the Population*

Section 21 of the Declaration speaks to the necessity for a reasonable likelihood of benefits able to justify the underlying research:

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects. (Section 21)

Charles Kowalski provides a couple important caveats regarding this principle, pointing out that “clinical relevance is a necessary but not sufficient condition for ethical acceptability.”⁶² Although it may be of minimal clinical interest that an intervention is better than placebo, the most clinically relevant information is whether the new therapy is equivalent or better than best therapy. Regrettably, this question was not answered by the studies that failed to include a group using best-known therapy.

Kowalski also notes that a poorly designed study is always unethical.⁶³ The design used in these studies is suspect on two levels. First of all, a serious question exists whether these studies adequately measured what they intended to measure: pain response. While infants are not able to directly express their level of pain, a variety of easily measured indirect measures of pain and stress have been developed. The most evident expression of pain and stress in the newborn is crying. The duration and pitch of the cry can give an indication of the degree of pain and stress.⁶⁴ Facial expressions have also been found to reliably measure distress. Easily measured vital signs, such as heart rate, blood pressure, and oxygenation levels also change with pain and stress.

Electrophysiological measurement of cardiac activity as a measure of vagal tone is a very sensitive measure of stress.⁶⁵ Likewise, cortisol levels, which now can be measured in the saliva, assess the hypothalamic-pituitary-adrenocortical response to pain and stress.⁶⁶ Changes in the amount and type of sleep and the latency to sleep are also indicative of stress. Because it is not uncommon to encounter inconsistent results between two different pain parameters,⁶⁷ omitting any of these parameters will give a less than complete picture of neonatal stress reactivity.⁶⁸

The studies assessing pain relief for neonatal circumcision often relied on only a few indirect measures of pain (see Appendix). This reliance on limited response data, knowing it will provide an incomplete picture, can effectively invalidate the reported results.

We contend that it is unethical to expose an infant to a protocol that fails to collect easily obtainable data that would decrease bias in the research outcome.

A study of pain relief for neonatal circumcision can answer one of two questions: (1) Does agent A provide better pain relief during circumcision than agent B? or (2) Does agent A provide adequate pain relief during circumcision? A major design flaw is the failure to address this second and more crucial question by not including controls in which the procedure was not performed. In keeping with the intent of the position paper issued by the Australasian Association of Paediatric Surgeons, if agent A provides better pain relief during circumcision than agent B, but neither agent provides adequate pain relief (which appears to be the case based on the side-by-side comparisons published so far), then clinically, one would be ethically compelled to forgo circumcision until adequate pain relief could be afforded. To date, none of the studies has included

issues introduce systematic bias. Researchers are asking a lot of their human subjects; the least they can do is design a study that eliminates as much bias as is feasible.

9. *Accurately Report Findings*

The Declaration imposes a duty on researchers to report their results carefully and precisely, regardless of whether the results were desired or expected:

Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. (Section 30)

The investigators know the most about their research and are responsible for every aspect of their research. Responsibility for the ethical aspects of the research is no different. While these individuals may feel bolstered by their IRB's approval or the publication of their study, it is the investigators who, during the study's design phase, decided to use placebo controls rather than either of the more ethically acceptable alternatives: active controls using DPNB or newborns who did not undergo the surgery.

controls in which the surgery was not performed. The reasons may mimic why placebo controls are so popular, such as increased likelihood of a positive finding leading to publication, and the fear of discovering an intervention's shortcomings. We contend that failing to use this proper control group renders the study findings clinically useless, which in turn would make these studies unethical. Given that a method of providing adequate anesthesia, short of general anesthesia, has not been demonstrated, it may be prudent to call for a moratorium on neonatal circumcision until adequate anesthesia becomes available.

Other serious study design flaws pervade the studies, including the lack of randomization of subjects and the small numbers of subjects in the study by Mark E. Holton,⁶⁹ the predictable assignment scheme used by Williamson,⁷⁰ the non-randomized non-consented control group from a different institution in the study by Butler-O'Hara and associates,⁷¹ and the non-randomized, non-consented control group in the study by Mohan and colleagues.⁷² All of these design

Some of the authors in question may have presented their results and/or interpreted them in a biased fashion. The most striking example of this may be the study comparing EMLA to placebo published by Taddio et al.⁷³ The authors report their findings simply as:

During surgery, the scores were lower in the lidocaine-prilocain group than the placebo group (P=0.01).⁷⁴

Interestingly, when the data is closely examined, all of the indicators of pain substantially exceed the levels measured before the procedure began, indicating that circumcision was painful regardless of the intervention used. The clinical importance of this result is never mentioned, let alone analyzed in detail. The data from Taddio and colleagues also indicate that EMLA was better than placebo during only 4 of the 13 stages of the procedure. So during 69% of the procedure, using EMLA was equivalent to using noth-

ing at all. This clinically important observation was not mentioned by the investigators. Finally, the most effective method of reducing the pain of circumcision — avoidance of the procedure — has never been mentioned in any of the studies.

10. Full Disclosure of Ethical Concerns

Section 14 of the Declaration requires that ethical considerations be enumerated and complied with:

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. (Section 14)

While we do not have access to the information provided to the IRBs or to the parents of prospective subjects, we believe that, if the investigators had been forthcoming about the ethical considerations of their protocols, then the IRBs should have not approved them. With the exception of the article by Barbara Brady-Fryer et al.⁷⁵ and the study by Butler-O'Hara et al.,⁷⁶ there is no indication that investigators were aware of any ethical dilemmas. This lack of insight, however, does not decrease the investigators' accountability.

Investigational Review Board Responsibility

Section 15 of the Declaration requires that all study protocols be approved by an independent "research ethics committee," which constitutes IRBs in the United States.

When the IRBs were presented with the protocols for these placebo-controlled trials, did they consider performing medically unnecessary surgery on children problematic? Did they fail to recognize a problem with withholding effective pain interventions for a procedure known to be extremely painful? Did they not appreciate that the selected study designs would fail to demonstrate whether these interventions provided adequate anesthesia? Were they unaware that the interventions proposed fell below the standard established by the AAP for pain relief in neonates?

Without knowing more details about the information provided to the IRB, it is hard to delineate its level of responsibility. Investigators are charged with the responsibility to provide background to the IRB regarding best-known therapy. Still, for these research applications to have succeeded, the members of the IRB either failed to do their homework or were deceived by the investigators.

Medical Journal Responsibility

Section 30 of the Declaration delineates the medical journals' responsibility to only publish ethically and scientifically suitable research:

Reports of research not in accordance with the principles of this Declaration should not be accepted for publication. (Section 30)

The *New England Journal of Medicine* provides a piquant example of discord between their stated positions and actual behavior. In response to studies of AZT in pregnant women in Africa that included a placebo arm, its editor Marcia Angell strongly attacked inappropriate placebo-controlled trials:

When effective treatment exists, a placebo may not be used. Instead, subjects in the control group of the study must receive the best known treatment.

Even informed consent, important though it is, is not protection enough, because of the asymmetry in knowledge and authority between researchers and their subjects. An approval by an institutional review board, though also important, is highly variable in its responsiveness to patients' interests when they conflict with the interests of researchers.

The Journal has taken the position that it will not publish reports of unethical research, regardless of their scientific merit.⁷⁷

We do not want a scientifically neat study if it is ethically flawed. [internal citations omitted]⁷⁸

Ironically, it was the *New England Journal of Medicine* that published the study by Taddio et al. comparing EMLA to placebo in which the best known and most effective therapy was not given. Instead of commenting on the study's clear ethical violations, the *Journal* recruited Thomas Wiswell, one of circumcision's foremost promoters, to provide a strongly biased opinion piece.⁷⁹ Without a reasonable alternative hypothesis, we believe the clear ethical violations were overlooked by the editorial staff in order to advance a more important goal: the promotion of neonatal circumcision. In keeping with their promotional policy, the *New England Journal of Medicine* subsequently published another study favoring circumcision that relied on methodology that ought to have provided grounds for immediate rejection.⁸⁰ In that study, data from discordant studies from four continents were combined using an inappropriate statistical

approach to give marginally significant findings favoring circumcision.

Editors of several other well-respected journals have also failed to identify the obvious ethical problems with these studies. While they may have seen promoting the use of anesthesia for neonatal circumcision as more important than pain relief for newborns in the research protocols, these studies do not necessarily enhance the chances of pain relief being used for circumcision so much as they enhance the probability of one particular *form* of pain relief being employed. To its credit, in 1999 the *Archives of Pediatrics and Ado-*

Placebo Controls Defended

The strongest argument in favor of a placebo-controlled trial when effective treatment exists is put forth by Robert Temple and Susan S. Ellenberg. Their argument is based on experience suggesting that the “equivalence” of a new therapy to an established therapy as shown by active-control equivalence trials does not necessarily mean that both therapies were effective; rather, it could mean that both therapies are ineffective. When using an active control, the researcher makes the assumption that the active control will be effective in that particular study and that, if placebo

In a culture that does not recognize the value of children and does not recognize children as possessing the same rights and protections as adults, the infant research subject will be treated differently than an adult research subject. The infant research subject will be unable to meaningfully express his dissatisfaction with the research, and the researcher, not valuing the input of the infant subject, will not actively pursue evidence of discontent. This attitude toward children, not uncommon in North America, results in the interests of infant research subjects being ignored.

lescent Medicine published an editorial calling for an end of placebo-controlled studies of local anesthetic for neonatal circumcision.⁸¹ We believe this editorial was published a decade too late.

It may be unfair to place all of the blame on the editorial staffs of journals. Editors often rely heavily on comments generated in the peer-review process, though at the same time they have discretion over which reviewers are assigned to particular articles.

Circumcision’s continued persistence, despite universal agreement on the lack of medical justification for the procedure, depends in part on the publication of as many articles as possible showing assertedly effective interventions for the pain it causes. The most superficially persuasive studies, due to the opportunity for apparently more impressive numbers, are those using placebo controls, so the ethical problems pervasive in these studies could be conveniently overlooked to allow the perpetuation of the practice.

Once unethically obtained study results are obtained and published, it is arguable that we cannot ethically use these results. At minimum, we believe the studies’ results should be referenced in something like the following manner: “In the clearly unethical study by Taddio et al. comparing EMLA to placebo...”

were included, it would have been inferior to the active control. The researcher makes this assumption based on information external to the trial, similar to a historically controlled trial. If previous trials of similar design between the active control and placebo have shown a large effect size with little between-study variability and few instances of unexplained failures, then there is little need for placebo controls. Temple and Ellensberg exhort researchers to review previous placebo-controlled trials for this evidence as well as any elements of study design that could reduce or eliminate the active control-placebo difference, such as select study populations.⁸²

Brady-Fryer alludes to this defense of her study group’s action by suggesting that the effectiveness of topical and local anesthetics had not been adequately evaluated, but did not take this defense any further. To justify the use of a placebo-control using Temple and Ellensberg’s criteria, one would need to successfully demonstrate that previously published trials comparing DPNB and placebo did not have a large effect size, had substantial between-study variability, had clear study design differences or flaws, and had unexplained study failures. However, none of the studies makes an attempt at such demonstrations. Instead, the reviews of the literature appearing in many of the studies confirmed that DPNB repeatedly and consistently had

been shown to be superior to placebo in reducing the pain associated with neonatal circumcision.

Using an alternative approach, Robert Veatch analyzes the point of subject indifference between entering a study offering new therapy versus placebo and getting best current therapy outside of a study.⁸³ The point at which the potential subject is indifferent between these choices, according to Veatch, allows researchers to depart from using best current therapy as part of the research protocol.

Several problems prevent this reasoning from fair applicability to circumcision pain studies. First, a serious question arises whether the Veatch approach can ethically be extended to the case of incompetent research subjects. Secondly, as will be discussed in more detail in the next section, the indifference point of a proxy decision maker may not be a valid gauge of the infant's own views or best interests.

Third, where a proxy decision maker is involved, it is problematic for a researcher to fail to offer current best therapy even when the proxy's assent is obtained. While some would release researchers from their ethi-

not adequately evaluated topical and local anesthetics' effectiveness in reducing the pain of neonatal circumcision; (2) no anesthetic use was "standard treatment"; (3) there was some doubt as to whether the interventions studied were better than placebo; and (4) a placebo group was necessary in order to convince more doctors to begin using topical and local anesthetics for neonatal circumcision.⁸⁶

We have already addressed the "standard treatment" issue and whether DPNB has shown superiority over placebo. The final claim, using a placebo-controlled trial to convince physicians to begin using anesthetics for neonatal circumcision, has been cited by others.⁸⁷ Nowhere does the Helsinki Declaration allow for the use of placebo controls as a promotional tool. To compensate for her colleagues' failings, Brady-Fryer relies on the well-worn utilitarian justification that, if a study using placebo controls was successful in converting more physicians to using an anesthetic, then the unnecessary suffering of the placebo group infants would not have been in vain. Knowing what we know now about the impact of unanesthetized circumcision

Perhaps the investigators, IRB members, and medical journal editors were conditioned not to question the quirks that surround the procedure, and instead viewed not following the guidelines of the Helsinki Declaration as just another of the many exceptions to standard practice that are made for neonatal circumcision.

cal obligation to do what is best for the patient, others would see the physician as having to protect patients from doing what is not in their best interests. As discussed above in Sections 3 and 4, the Declaration clearly expects investigators to place a priority on the subjects' best interests. The specifics of this duty for infants has been laid out by the American Academy of Pediatrics (AAP), who state that physicians need to protect their patients — i.e., the child — from parental decisions that threaten the child's health, such as unwarranted surgeries.⁸⁴

Attempted Justifications

Several of these investigators have addressed concerns regarding whether their studies were ethical. Only two did so without being prompted by a letter to the editor. Barbara Brady-Fryer, one of the investigators in a study published in the *Journal of the American Medical Association*,⁸⁵ published an article defending their actions on four grounds: (1) previous studies had

on the newborn's brain, such reasoning provides little consolation to placebo-receiving subjects. We also doubt whether the study's political intentions were disclosed to parents providing proxy consent. Taken at face value, the infant subjects were used as a means to a political ends, rather than as ends in themselves, and thus were exploited. So rather than providing a justification, this fourth justification further indicts their study as unethical.

Other research has exhibited similarly alarming ethical violations and inconsistencies. In their study of ring block versus no anesthesia, Susan Hardwick-Smith and colleagues did not use a saline injection as a control because they believed subjecting a newborn to an unnecessary injection was unethical. For similar reasons, they relied on noninvasive monitoring methods.⁸⁸ Inexplicably, the authors considered an injection of saline unethical, but circumcision without anesthesia, especially after they stated that DPNB was the standard of care, did not pose an ethical problem.

Much more entertaining are the responses investigators have made to ethical challenges raised in letters to the editor. The most common diversion of responsibility was to hide behind the IRB's approval of the research.⁸⁹ The Declaration is clear on this point and reiterated several times in the document. Research investigators need to know the ethical, legal, and regulatory requirements in their countries (Section 9) and they have a duty to protect "the life, health, privacy, and dignity of the human subject" (Section 10 quoted and 15). It is ultimately the responsibility of the investigator to perform an ethical study. The IRB serves just as an *advisory* role and can only work with the information it is provided. Finally, the IRB can make mistakes. The Declaration clearly provides that if the IRB commits an error, the investigators are not absolved of their responsibilities. The investigators know the most about their research and are responsible for every aspect of their research. Responsibility for the ethical aspects of the research is no different. Research investigators need to know the ethical, legal, and regulatory requirements in their countries (Section 10), and they have a duty to protect "the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects" (Section 11 quoted and 16).

Other responses may fairly be characterized as pathetic, and in some cases bordering on bizarre. When directly asked whether they had clinical equipoise at the onset of their study,⁹⁰ Taddio and Koren failed to address the question, but rather referred to the standard practice of providing no pain relief and the studies "approved by ethics boards all over the world." Following a later study, Taddio and Koren responded defensively to a letter to the editor questioning whether their studies were merely promotional pieces for EMLA.⁹¹ Rather than answering the question, they personally attacked the letter writer by stating, "Hill's claim that we are more interested in the promotion of EMLA reflects his bias against circumcision and any products that may be associated with it."⁹² In response to the question of why their study had not included a control group in which no surgery was performed, Taddio and Koren responded, "It is unimaginable to consider asking parents (or ethics boards) to agree to have infants participate in a study where they would be restrained solely for the purpose of research."⁹³ If that is unethical, which we doubt since it involves minimal harm, then how could it possibly be ethical to physically restrain a newborn boy and cut off his foreskin without anesthesia and without his consent? Finally, Taddio and Koren dismiss concerns that they did not measure serum cortisol without providing any supporting references, stating that it "has

been demonstrated to be an unreliable indicator of the efficacy of analgesia during circumcision."⁹⁴ Many in this field have long considered cortisol levels to be the most valid indirect measure of pain in newborns.⁹⁵

Perhaps the most outrageous response to a letter to the editor questioning the use of placebo control group⁹⁶ came from Butler-O'Hara, who replied:

We do not endorse unanesthetized surgery. Unanesthetized surgery was not part of the study design and would certainly not be condoned by our Institutional Review Board. We specifically stated that we did not feel it was ethical to include such a group as part of our study, but rather quantified the reactions of the infants whose circumcisions were performed by physicians who do not routinely use local anesthesia.⁹⁷

If unanesthetized surgery was not part of the study and such surgery would not be condoned by their IRB, then how did a control group of 20 unanesthetized circumcisions end up in their study?

Potential Justifications for Unethical Research

Unethical human researchers have relied on a limited repertoire of excuses. In the Nuremberg trials of Nazi physicians who had performed often grossly inhumane experiments on the inhabitants of concentration camps, the physicians based their defense in part on the absence of any ethical standards, which was probably not the case, and that they were only following orders. The widely distributed, clear international guidelines provided in the Helsinki Declaration, as well as other documents, eliminates this defense for today's researcher.

Robert Baker suggests that a more compelling defense of the Nazi physicians would derive from the designation of inhabitants of concentrations camps, Jew in particular, as *Untermenschen*. Or more simply put, the German doctors' subjects were at that time considered in their culture to be something less than human and thus not subject to ethical research standards developed for research involving humans. Baker points out that Germany had at that point developed strong laws limiting the types of research to which animals could be subjected. Since very little research could be performed on humans or animals, the *Untermenschen* provided ethically defensible subjects for research.⁹⁸ In the studies under discussion, Baker's argument may apply in the sense that children, especially newborns, are often treated as if they are sub-human or not fully human. This lack of importance

given to children is evident in recommendations for elective surgery in children sooner rather than later,⁹⁹ and in the failure to insist on pain relief that would be mandatory for the same procedure in older children, adults,¹⁰⁰ and sometimes even animals.¹⁰¹ Ironically, many of these investigators were pediatricians, a profession that champions children's rights. Their inability to treat these newborns as fully human contradicts this advocacy.

The next excuse — one relied upon in the defense of American researchers involved in the Cold War radiation experiments — is to claim “moral ignorance” and/or “cultural blindness.” The Advisory Committee on Human Radiation Experiments appointed by former President Clinton developed this rationale:

*ignorance only exculpates the agent; it does not make wrong acts right.*¹⁰²

For investigators to be exculpated, one would need to demonstrate cultural factors that mediated their blindness to their wrong acts. In a culture that does not recognize the value of children and does not recognize children as possessing the same rights and protections as adults, the infant research subject will be treated differently than an adult research subject. The infant research subject will be unable to meaningfully express his dissatisfaction with the research, and the researcher, not valuing the input of the infant subject, will not actively pursue evidence of discontent. This attitude toward children, not uncommon in North

The Helsinki Declaration was developed to keep the most vulnerable research subjects from being exploited and harmed. Unfortunately for the infants enrolled in these studies, the system put in place to protect them was unable to do so as the investigators, the members of the IRBs, and journal editors failed to uphold the guidelines laid down in the Declaration.

Sometimes cultural factors can prevent individuals from discerning what they are morally required to do and can therefore mitigate the blame we would otherwise place on individuals for failing to do what they ought to do.... An individual may...be *morally* ignorant. Because of features of his or her deeply enculturated beliefs, the individual may be unable to recognize, for example, that certain people (such as members of another race) deserve equal respect or even that they are people with rights.... In extreme cases, a culture may instill a moral ignorance so profound that we may speak of *cultural moral blindness*.... Some of those committed to the ideology of slavery may have been morally blind in just this way, and their culture may have induced this blindness.

Only if an agent could not be reasonably expected to remedy his or her culturally induced moral ignorance would such ignorance exculpate his conduct. But even in cases in which the individual could not be blamed for persisting in ignorance, this would do nothing to show that the actions...resulting from his or her ignorance was not wrong. *Nonculpable moral*

America, results in the interests of infant research subjects being ignored. As mentioned above, one would have expected these researchers to have been more sympathetic toward their infant subjects.

The second source of cultural blindness comes from the historical ties of neonatal circumcision to religion. Even though a substantial percentage of Jews and Muslims do not perform circumcisions, and even though most circumcisions of Jews are not in compliance with the religious requirements,¹⁰³ many adherents of Judaism and Islam believe circumcision is a required religious rite. In the United States, medicalized circumcision, through imprecise thinking, continues to be conflated with the Jewish ritual, leading doctors to view circumcision as different from other medical procedures. Such associations unfortunately lead physicians to view the traditional methods of preputioectomy, which do not encompass the use of anesthesia, as sacrosanct. However, this excuse is not compelling considering that non-religious circumcision was the focus of the research and one would expect that only a few of the investigators, IRB members, and journal editors adhere to faiths in which circumcision is a duty. Notwithstanding, religion can be a sensitive issue, so it is possible that IRB members and journal editors were unwilling to challenge the ethics of unanesthetized circumcision for fear of upsetting individuals of those faiths that require circumcision.

Stronger evidence of our cultural blindness is how the medical culture treats the procedure as an exceptional practice. Neonatal circumcision is the most common medical surgical procedure in the United States, and yet is not recommended by any domestic or international medical association.¹⁰⁴ Neonatal circumcision is the only medically unnecessary procedure that is routinely solicited. Neonatal circumcision is the only situation in which physicians perform a procedure on other physicians' patients without obtaining the latter's permission first. Neonatal circumcision is one of the only situations in which amputated tissue is not sent for pathologic evaluation. (This may be because the prepuce has little or no value in the American medical culture. In many American medical textbooks, the prepuce is merely described as the portion of the penis removed by circumcision.¹⁰⁵ Its complex structure, including the high density of fine touch neuroreceptors, has only found its way into journals accessible to American physicians in the past decade.¹⁰⁶) Neonatal circumcision is one of the only situations in which the elements of informed consent are routinely overridden.¹⁰⁷ Neonatal circumcision is so ingrained in both our general and medical cultures that these anomalies are accepted without question. If these behaviors were extended to other procedures, such as routine tonsillectomy, then they would not be tolerated. Perhaps the investigators, IRB members, and medical journal editors were conditioned not to question the quirks that surround the procedure, and instead viewed not following the guidelines of the Helsinki Declaration as just another of the many exceptions to standard practice that are made for neonatal circumcision. The most plausible explanation for this irrational behavior has been put forth by Sarah Waldeck, who notes that social modifiers act as multipliers that influence behavior by coloring the manner in which individuals understand information. In the case of circumcision, social modifiers cause individuals to overemphasize the procedure's positive consequences and underemphasize its negative consequences, thus leading them to a distorted perception that is inconsistent with the facts.¹⁰⁸

While "moral ignorance," "cultural blindness," and "social norm multipliers" may help explain the actions of the investigators, IRB members, and journal editors, they are not legitimate excuses. Some of the researchers acknowledged that their actions were ethically questionable, but decided to proceed with the unethical studies anyway.

Not Every Study Employs Placebo Controls

Not every study of pain relief for neonatal circumcision used placebo controls. In a study that took place

between February 1995 and May 1997, Charles W. Newton et al. compared plain and buffered lidocaine in DPNB for neonatal circumcision without using a placebo group. In their discussion section they state, "A placebo group was not used in our study, because it is considered unethical to withhold a known beneficial anesthetic agent for a painful procedure." James G. Lenhart and associates also did not include a placebo group in their study published in 1997. They stated:

If circumcisions are to be performed as humanely as possible, it is incumbent that investigations be conducted to determine which technique is most effective in eliminating the associated pain.¹⁰⁹

As DPNB has become more acceptable to physicians, studies have increasingly shied away from using placebo control groups. Taddio et al. published a study in 2000 (dates of the actual study were not provided) that was not funded by a pharmaceutical company, comparing the following: (1) use of the Mogen clamp with a combination of DPNB, EMLA, acetaminophen, and sugar-coated gauze dipped in grape juice with (2) use of the Gomco clamp with EMLA.¹¹⁰ In 1999, Cynthia R. Howard et al. published a study comparing EMLA and DPNB without a placebo group (dates of the actual study were also not provided). The study protocol was approved by the Clinical Investigation Committee of Rochester General Hospital, and parental informed permission was obtained. The authors noted that "pain control for the procedure is increasingly recognized as a standard of care." As reasons for not including unanesthetized controls in their study, they cited the pain of unanesthetized controls as well as the effectiveness of DPNB and EMLA.¹¹¹ In addition to coining a new oxymoron ("humane circumcision") in their study from 1993 to 1994, Howard Stang and Leonard Snellman et al. used DPNB alone as its control group because it has repeatedly been shown to be safe and efficacious.¹¹² In a 2002 study comparing the Mogen clamp to the PlastiBell, all subjects received a DPNB.¹¹³ We find it refreshing to know that some circumcision pain researchers carefully consider the ethical implications of their actions.

Conclusion: How Did This Happen?

Why have so many studies of questionable ethics been undertaken and published on this one narrow subject?

One possible factor is a carryover effect stemming from the myth that newborns feel no pain. Inertia allowed researchers to posit the "standard of care" defense while delaying institution of practice changes

that would have made providing pain relief during neonatal circumcision the standard of care. Collectively we appear to suffer from cultural blindness to the pain suffered by infants. Pain in neonates has long been ignored with a turnaround only beginning with the highly publicized article by Kanwaljeet J. S. Anand and P. R. Hickey in 1987.¹¹⁴

This may be symptomatic of a larger lack of empathy we have as a society for infants. Children are too often treated as chattel, which makes it acceptable for them to be treated as a means to an end, rather than an end in themselves. Unfortunately, this sub-human status is assigned to a group that is especially vulnerable to exploitation, especially in the hands of those subscribing to the postmodernism “might makes right” system of bioethics. The Helsinki Declaration was developed to keep the most vulnerable research subjects from being exploited and harmed. Unfortunately for the infants enrolled in these studies, the system put in place to protect them was unable to do so as the investigators, the members of the IRBs, and journal editors failed to uphold the guidelines laid down in the Declaration.

Circumcision is a lightning rod issue in the United States, raising a host of potentially explosive issues involving religion, sexuality, social conformity, and potential defensiveness among those who have undergone it and/or performed it, all of which it should be noted are not medical issues. Were it not for the occasional rogue physician who envisions physicians as “cultural brokers” regarding medicalized circumcision,¹¹⁵ it should be obvious that factors unrelated to medicine and public health should play no more than a exceedingly peripheral role in medical decision making. However, the issue becomes incomparably more compelling when we consider the needless and medically unjustified, even contraindicated issues of suffering, tissue amputation, and violation of human and civil rights. Add to this the harm to individual autonomy, health, principles of consent, the violations of the Helsinki Declaration, and the unmet responsibilities of medical journals and investigational review boards. Once all factors are revealed, it is impossible to consider circumcision a minor issue, but rather circumcision comes to symbolize one of the greatest ongoing systemic ethical violations for which modern medicine has been responsible. We can only reiterate our collective commitment to respect for the physical integrity of all human beings, faithful adherence to our profession’s ethical requirements, and observance of the primal dictum, “First, do no harm.”

Appendix: Characteristics of Placebo-Controlled Trials for Pain Relief during Neonatal Circumcision

Herschel et al.¹¹⁶

Patients: 119, randomized equally (shuffled opaque unmarked envelopes). **Setting:** March and April 1997, University of Chicago Hospitals. **Interventions:** No treatment, DPNB, oral sucrose. **Outcome measures:** Heart rate, pulse oximetry. **Informed consent:** “informed written consent both for circumcision and for participation in the study.” **IRB:** “The protocol was approved by the Institutional Review Board of the University of Chicago Hospitals.”

Holliday et al.¹¹⁷

Patients: 50 neonates, birthweight 1600 to 2500 grams. **Setting:** May 1994 to June 1995, Georgetown University Medical Center. **Interventions:** DPNB, EMLA, control (placebo cream). **Outcome measures:** Heart rate, blood pressure, pulse oximetry, respiratory rate, behavioral scores. **Informed consent:** “informed consent was obtained from the parents of each patient enrolled in the study.” **IRB:** “The protocol was approved by the Georgetown University Medical Center institutional review board.”

Lander et al.¹¹⁸

Patients: 52 healthy, full-term, male newborns. **Setting:** September 1994 to October 1996, location not disclosed. **Interventions:** Ring block, DPNB, EMLA, topical placebo. **Outcome measures:** Heart rate, cry, methemoglobin level, respiratory rate, pulse oximetry, palmar sweat, facial expressions. **Informed consent:** “Parents who requested circumcision for their newborn sons were asked for informed consent to participate.” **IRB:** “University and hospital institutional review boards approved the study protocol.”

M. E. Holton¹¹⁹

Patients: 91 patients circumcised (8 with DPNB), 97 calcaneal punctures. **Setting:** “4-month period at a community hospital.” **Interventions:** DPNB, no DPNB, calcaneal puncture. **Outcome measures:** Behavioral scores based on crying, screaming, agitation, and level of activity based on Gronigen Distress Scale and the Children’s Hospital of Eastern Ontario Pain Scale. **Informed consent:** “Parental consent was obtained under guidelines of the Texas Medical Disclosure Panel for Informed Consent. **IRB approval:** Not documented.

M. L. Williamson¹²⁰

Patients: 30 newborn males. Setting: Not documented. Interventions: DPNB, no treatment (ratio 2:1). Outcome measures: Crying (duration and type), pulse oximetry, blood pressure, respiratory rate, heart rate, cardiac rhythm, vomiting, gagging, breath holding, jitteriness. Informed consent: "Consent for participation in the study was obtained from parents who had already decided to have their sons circumcised. The anesthetic procedure was explained and questions were answered about circumcision. Parents were told they could not choose whether their sons would have the DPNB or remained unanesthetized." IRB: "clearance for the study from the medical staff, the nursing staff, and the Humane Subjects Review Board."

Butler-O'Hara et al.¹²¹

Patients: 50 infants over 34 1/2 weeks gestation, randomized only to EMLA and DPNB. "A third, nonrandomized group of full-term infants (n=20), who were circumcised by an obstetrician without any anesthesia, were also circumcised with the Stuart Surgical circumcision tray and the Hollister PlastiBell." Setting: No dates given, tertiary referral, neonatal intensive care nursery in a university teaching hospital, [Assumed to be University of Rochester Medical Center]. Interventions: DPNB, EMLA, no treatment. Outcome measures: Neonatal Infant Pain Scale (NIPS) score, heart rate, respiratory rate. Informed consent: "Informed parental consent was obtained for circumcision and enrollment into the study." IRB: "The protocol was approved by the Institutional Review Board." Additional comment: "Because the current practice in our neonatal intensive care unit (NICU) is to provide anesthesia during neonatal circumcision, we did not feel justified in randomizing any infant to no anesthesia. For comparison purposes, data on infants circumcised without anesthesia or analgesia were obtained from 20 infants circumcised by two obstetricians who followed their usual practice."

P. J. Woodman¹²²

Patients: 61 neonates randomized into the three groups, computer-generated random list. Setting: Between October 1995 and September 1996 [Assumed to be Genesys Regional Medical Center, Flint, Michigan]. Interventions: EMLA, 30% lidocaine cream, placebo. Outcome measures: Heart rate, pulse oximetry, crying time, blood pressure. Informed consent: "Written informed consent was obtained from the parents requesting circumcision for their sons." IRB: "Research approval was obtained from the Institutional Review Board and Departments of Pediatrics and Obstetrics and Gynecology at the hospital where the study

was conducted. Study protocols were in accordance with the ethical standards for human experimentation established by the revised Declaration of Helsinki (1983)." Additional comment: "Five percent lidocaine-prilocaine was donated by Astra USA, Inc."

Taddio et al. (New England Journal of Medicine)¹²³

Patients: 68 full-term 38 assigned to EMLA, 30 to placebo. Setting: Dates not given [Assumed to be the Women's College Hospital, Toronto]. Interventions: EMLA, placebo. Outcome measures: Facial activity, time spent crying, heart rate, blood pressure. Informed consent: "the parents gave written informed consent for their infants to participate." IRB: "The protocol was approved by the ethics boards of the Hospital for Sick Children and Women's College Hospital." Additional comment: "Supported by Astra Pharm Inc., Canada, and by a grant from the Medical Research Council of Canada-Pharmaceutical Manufacturers Association of Canada."

Hardwick-Smith et al.¹²⁴

Patients: 40 healthy male newborns, randomly assigned. Setting: Dates not given [Assumed to be the University of Texas Health Science Center at Houston, Houston, Texas]. Interventions: Ring block, no anesthesia. Outcome measures: Crying time, behavioral state, pulse oximetry, heart rate, respiratory rate. Informed consent: Not documented. IRB approval: Not documented.

Mohan et al.¹²⁵

Patients: 80 male infants, "Control-group infants [20 infants] were monitored according to the study protocol but before initiation of the randomized trial in which the different forms of analgesia were used." Setting: Dates not given, [Assume to be The Brooklyn Medical Center]. Interventions: EMLA, sucrose-dipped pacifier, sucrose and EMLA, control (water dipped pacifier). Outcome measures: Heart rate, pulse oximetry, blood pressure, crying time. Informed consent: "The next 60 newborn male infants for whom parental consent could be obtained were randomly assigned to one of three groups." (This indicates that informed consent was not obtained for the control group.) IRB approval: No documentation.

Kurtis et al.¹²⁶

Patients: 48 healthy, full-term infants randomized into one of four groups. Setting: Dates not given [Assumed to be either St. Francis Hospital and Medical Center, Hartford, or University of Connecticut School of Medicine, Farmington, Connecticut]. Interventions: Gomco versus Mogen clamp, with and with-

out DPNB. **Outcome measures:** Heart rate, respiratory rate, pulse oximetry, duration of crying, salivary cortisol levels, facial expression. **Informed consent:** "Informed consent was obtained from parents of eligible infants based on entry criteria." **IRB approval:** No documentation.

Kass and Holman¹²⁷

Patients: 71 patients, randomized by computer modeling. **Setting:** November 1, 1996, through March 13, 1997, Naval Hospital Bremerton. **Interventions:** 50% dextrose solution, DPNB, placebo. **Outcome measures:** Time spent crying, heart rate, pulse oximetry, modified behavioral pain scale (MBPS) score. **Informed consent:** "After obtaining informed consent for the procedure and participation in the study." **IRB:** "Approval by the Human Subjects Review Committee."

References

- World Medical Association Declaration of Helsinki, "Ethical Principles for Medical Research Involving Human Subjects," available at <<http://www.wma.net/e/policy/b3.htm>> (last visited September 22, 2008).
- Department of Health and Human Services, *Code of Federal Regulations, Title 45 Public Welfare, Department of Health and Human Services, Part 46 Protection of Human Subjects*, 45 C.F.R. §46.
- R. Baker, "A Theory of International Bioethics: Multiculturalism, Postmodernism, and the Bankruptcy of Fundamentalism," *Kennedy Institute of Ethics Journal* 8, no. 3 (1998): 201-231.
- R. Baker, "A Theory of International Bioethics: The Negotiable and the Non-negotiable," *Kennedy Institute of Ethics Journal* 8, no. 3 (1998): 233-273.
- W. L. Hill, D. Borovsky, and C. Rovee-Collier, "Continuities in Infant Memory Development," *Development Psychiatry Biology* 21, no. 1 (1988): 43-62; J. Katz, "The Question of Circumcision," *International Surgery* 62, no. 9 (1977): 490-492; D. M. Levy, "The Infant's Earliest Memory of Inoculation: A Contribution to Public Health Procedures," *Journal of General Psychiatry* 96 (March 1960): 3-46; E. D. Smith, "Another View of Circumcision," *Australian Paediatrics Journal* 6, no. 2 (1970): 67-69.
- K. J. S. Anand and P. R. Hickey, "Pain and Its Effects in the Human Neonate and Fetus," *New England Journal of Medicine* 317, no. 21 (1987): 1321-1329.
- C. Kirya and M. W. Werthmann, Jr., "Neonatal Circumcision and Penile Dorsal Nerve Block: A Painless Procedure," *Journal of Pediatrics* 92, no. 6 (1978): 998-1000.
- P. A. Poma, "Painless Neonatal Circumcision," *International Journal of Gynaecology and Obstetrics* 18, no. 4 (1980): 308-309.
- L. G. Maxwell, M. Yaster, and R. C. Wetzel et al., "Penile Nerve Block for Newborn Circumcision," *Obstetrics and Gynecology* 70, no. 3, pt. 1 (1987): 415-419.
- P. S. Williamson and N. D. Evans, "Neonatal Cortisol Response to Circumcision with Anesthesia," *Clinical Pediatrics* (Philadelphia) 25, no. 8 (1986): 412-415.
- A. L. Masciello, "Anesthesia for Neonatal Circumcision: Local Anesthesia Is Better than Dorsal Penile Nerve Block," *Obstetrics and Gynecology* 75, no. 5 (1990): 834-838.
- R. L. Holve, P. J. Bromberger, and H. D. Groveman et al., "Regional Anesthesia during Newborn Circumcision. Effect on Infant Pain Response," *Clinical Pediatrics* (Philadelphia) 22, no. 12 (1983): 813-818.
- P. S. Williamson and M. L. Williamson, "Physiologic Stress Reduction by a Local Anesthetic during Newborn Circumcision," *Pediatrics* 71, no. 1 (1983): 36-40.
- H. J. Stang, M. R. Gunnar, and L. Snellman et al., "Local Anesthesia for Neonatal Circumcision: Effects on Distress and Cortisol Response," *JAMA* 259, no. 10 (1988): 1507-1511.
- D. Mudge and J. B. Younger, "The Effects of Topical Lidocaine on Infant Response to Circumcision," *Journal of Nurse-Midwifery* 34, no. 6 (1989): 335-340.
- K. B. Weatherstone, L. B. Rasmussen, and A. Erenberg et al., "Safety and Efficacy of a Topical Anesthetic for Neonatal Circumcision," *Pediatrics* 92, no. 5 (1993): 710-714.
- F. Benini, C. C. Johnston, and D. Faucher et al., "Topical Anesthesia during Circumcision in Newborn Infants," *Journal of the American Medical Association* 270, no. 7 (1993): 850-853.
- See Masciello, *supra* note 11.
- American Academy of Pediatrics, "Report of the Task Force on Circumcision," *Pediatrics* 84, no. 2 (1989): 388-391.
- F. G. Miller and H. Brody, "What Makes Placebo-Controlled Trials Unethical?" *American Journal of Bioethics* 2, no. 2 (2002): 3-9.
- N. S. Jecker, "Exploiting Subjects in Placebo-controlled Trials," *American Journal of Bioethics* 2, no. 2 (2002): 19-20.
- A. Taddio, B. Stevens, and K. Craig, et al., "Efficacy and Safety of Lidocaine-Prilocaine Cream for Pain during Circumcision," *New England Journal of Medicine* 336, no. 17 (1997): 1197-1201.
- M. Butler-O'Hara, C. LeMoineand, and R. Guillet, "Analgesia for Neonatal Circumcision: A Randomized Controlled Trial of EMLA Cream Versus Dorsal Penile Nerve Block," *Pediatrics* 101, no. 4 (1998): E5; M. Herschel, B. Khoshnood, and C. Ellman et al., "Neonatal Circumcision: Randomized Trial of a Sucrose Pacifier for Pain Control," *Archives of Pediatrics & Adolescent Medicine* 152, no. 3 (1998): 279-284; C. R. Howard, F. M. Howard, and K. Fortune et al., "A Randomized, Controlled Trial of a Eutectic Mixture of Local Anesthetic Cream (lidocaine and Prilocaine) Versus Penile Nerve Block for Pain Relief during Circumcision," *American Journal of Obstetrics and Gynecology* 181, no. 6 (1999): 1506-1511; J. Lander, B. Brady-Fryer, and J. B. Metcalfe et al., "Comparison of Ring Block, Dorsal Penile Nerve Block, and Topical Anesthesia for Neonatal Circumcision: A Randomized Controlled Trial," *Journal of the American Medical Association* 278, no. 24 (1997): 2157-2162.
- Fetus and Newborn Committee, Canadian Paediatric Society, "Neonatal Circumcision Revisited," *Canadian Medical Association Journal* 154, no. 6 (1996): 769-780; J. F. Leditschke, *Guidelines for Circumcision*, Australasian Association of Paediatric Surgeons, Herston, Queensland, April 1996; College of Physicians and Surgeons of British Columbia, *Policy Manual: Infant Male Circumcision*, Vancouver, B.C., 2004; Medical Ethics Committee, *The Law & Ethics of Male Circumcision — Guidance for Doctors*, British Medical Association, London, 2003; S. Beasley, B. Darlow, and J. Craig et al., *Position Statement on Circumcision*, Royal Australasian College of Physicians, Sydney, 2002; D. A. Kendel, *Caution against Routine Circumcision of Newborn Male Infants (Memo to Physicians and Surgeons of Saskatchewan)*, College of Physicians and Surgeons of Saskatchewan, Saskatoon, February 20, 2002; British Medical Association, "The Law and Ethics of Male Circumcision: Guidance for Doctors," *Journal of Medical Ethics* 30, no. 3 (2004): 259-263.
- Committee on Bioethics, "Informed Consent, Parental Permission, and Assent in Pediatric Practice," *Pediatrics* 95, no. 2 (1995): 314-317.
- J. G. Dwyer, "Parents' Religion and Children's Welfare: Debunking the Doctrine of Parents' Rights," *California Law Review* 82, no. 6 (1994): 1371-1447; J. G. Dwyer, "The Children We Abandon: Religious Exemptions to Child Welfare and Education Laws as Denials of Equal Protection to Chil-

- dren of Religious Objectors," *North Carolina Law Review* 74 (1996): 1321-1478.
27. S. Mason, "Obtaining Informed Consent for Neonatal Randomised Controlled Trials — An 'Elaborate Ritual'?" *Archives of Disease in Childhood* 76, no. 3 (1997): F143-F145.
 28. See Butler-O'Hara et al., *supra* note 23.
 29. *Id.*; C. G. Mohan, D. A. Risucci, and M. Casimir et al., "Comparison of Analgesics in Ameliorating the Pain of Circumcision," *Journal of Perinatology* 18, no. 1 (1998): 13-19.
 30. J. S. Svoboda, R. S. Van Howe, and J. G. Dwyer, "Informed Consent for Neonatal Circumcision: An Ethical and Legal Conundrum," *Journal of Contemporary Health Law and Policy* 17, no. 1 (2000): 61-133.
 31. See Svoboda et al., *supra* note 30.
 32. C. J. Cold, "Neonatal Circumcision," *The Lancet* 349, no. 9060 (1997): 1257-1258.
 33. M. Angell, "The Ethics of Clinical Research in the Third World," *New England Journal of Medicine* 337, no. 12 (1997): 847-849.
 34. R. J. Levine, "The 'Best Proven Therapeutic Method' Standard in Clinical Trials in Technologically Developing Countries," *AIDS & Public Policy Journal* 31, no. 1 (1998): 30-35.
 35. See Taddio et al., *supra* note 22.
 36. R. L. Poland, R. J. Roberts, and J. F. Guitierrez-Mazorra et al., Committee on Fetus and Newborn, Committee on Drugs, Section on Anesthesiology, Section on Surgery, "Neonatal Anesthesia," *Pediatrics* 80, no. 3 (1987): 446.
 37. K. J. Ferguson, R. M. Caplan, and P. S. Williamson, "Factors Associated with Behavior Change in Family Physicians after CME Presentation," *Journal of Medical Education* 59, no. 8 (1984): 662-666; H. J. Stang and L. W. Snellman, "Circumcision Practice Patterns in the United States," *Pediatrics* 101, no. 6 (1998): E5; W. L. Toffler, A. E. Sinclair, and K. A. White, "Dorsal Penile Nerve Block during Newborn Circumcision: Underutilization of a Proven Technique?" *Journal of the American Board of Family Practice* 3, no. 3 (1990): 171-174; N. Wellington and M. J. Rieder, "Attitudes and Practices Regarding Analgesia for Newborn Circumcision," *Pediatrics* 92, no. 4 (1993): 541-543.
 38. See Poland et al., *supra* note 36.
 39. P. Carlsson and J. Svensson, "The Duration of Pain Relief after Penile Block to Boys Undergoing Circumcision," *Acta Anaesthesiologica Scandinavica* 28 (1984): 432-434; S. Franci Ventosa and W. Espinosa Soldevila, "Utilidad del Bloqueo Peneano en la Analgesia Postoperatoria de Intervenciones de Circuncion," [Usefulness of penile blockade in postoperative analgesia of circumcision procedures] *Revista Española de Anestesiología y Reanimación* 37, no. 4 (1990): 238-240; P. R. McGowan, H. May, Z. Molnar, and M. Cunniffe, "A Comparison of Three Methods of Analgesia in Children Having Day Case Circumcision," *Paediatric Anaesthesia* 8, no. 5 (1998): 403-407; A. Martinez Telleria, M. E. Cano Serrano, and M. J. Martinez Telleria et al., "Análisis de la Eficacia Analgesica de la Anestesia Locoregional en Cirugía Infantil," [Analysis of regional anesthetic efficacy on pediatric postoperative pain] *Cirugía Pediátrica* 10, no. 1 (1997): 18-20; D. F. Murphy and E. M. Gallagher, "Dorsal Nerve Blockade for Pain Relief after Circumcision," *Irish Journal of Medical Science* 153, no. 8 (1984): 282-283; P. A. Nielsen, L. Jorgensen, and L. Fonsmark et al., "Penisblok til Phimosisoperation. Peroperativt Anlagt Som Postoperativ Analgesi Hos Born," [Penile block in circumcision. Peroperative use as postoperative analgesia in children] *Ugeskrift for Læger* 150, no. 22 (1988): 1348-1350; R. Ramboatiana, C. Gassner, and J. P. Schoch et al., "Analgesie Post-operative pour la Circoncision Chez L'enfant," [Postoperative analgesia for circumcision in children] *Agressologie* 31, no. 1 (1990): 39-42; M. R. Rodrigo, L. L. Ong, and A. A. Waheed, "Dorsal Nerve Block of Penis in Chinese Children," *British Journal of Anaesthesia* 56, no. 8 (1984): 934-935; A. Van Zundert, "Penile Dorsal Nerve Block for Penile Surgery," *Acta Anaesthesiologica Belgium* 36, no. 1 (1985): 41-46; K. M. Wong, "[Penile Block for Postoperative Pain Relief in Children]" *Ma Tsui Hsueh Tsa Chi* 24, no. 3 (1986): 193-195.
 40. See Anand and Hickey, *supra* note 6.
 41. See Leditschke, *supra* note 24.
 42. See Miller and Brody, *supra* note 20.
 43. See Cold, *supra* note 32.
 44. S. Hardwick-Smith, J. M. Mastrobattista, and P. A. Wallace et al., "Ring Block for Neonatal Circumcision," *Obstetrics and Gynecology* 91, no. 6 (1998): 930-934.
 45. See Mohan et al., *supra* note 29.
 46. P. S. Kurtis, H. N. DeSilva, and B. A. Bernstein et al., "A Comparison of the Mogen and Gomco Clamps in Combination with Dorsal Penile Nerve Block in Minimizing the Pain of Neonatal Circumcision," *Pediatrics* 103, no. 2 (1999): E23.
 47. F. C. Kass and J. R. Holman, "Oral Glucose Solution for Analgesia in Infant Circumcision," *Journal of Family Practice* 50, no. 9 (2001): 785-788.
 48. See Herschel et al., *supra* note 23; M. Herschel, Letter to the Editor, "Circumcision — the Debates Goes On," *Pediatrics* 105, no. 3, Part 1 (2000): 681.
 49. See Lander et al., *supra* note 23.
 50. B. Freedman, "Equipose and the Ethics of Clinical Research," *New England Journal of Medicine* 317, no. 3 (1987): 141-145.
 51. See Benini et al., *supra* note 17.
 52. See Taddio et al., *supra* note 22.
 53. See Butler-O'Hara et al., *supra* note 23.
 54. G. Hill, Letter to the Editor, "Pain Indication in Circumcision," *Archives of Pediatrics & Adolescent Medicine* 154, no. 12 (2000): 1275.
 55. A. Taddio and G. Koren, Response to Letter to the Editor, "Pain Indication in Circumcision," *Archives of Pediatrics & Adolescent Medicine* 154, no. 12 (2000): 1275.
 56. See Taddio et al., *supra* note 22; A. Taddio, J. Katz, A. L. Ilersich, and G. Koren, "Effect of Neonatal Circumcision on Pain Response during Subsequent Routine Vaccination," *The Lancet* 349, no. 9052 (1997): 599-603.
 57. See Miller, *supra* note 20.
 58. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *Research Involving Children: Report and Recommendations*, DHEW Publication No. (OS) 77-0004, Washington, D.C., at Appendix; DHEW Publication No. (OS) 77-0005, 1977, both cited in R. J. Levine, *Ethics and Regulation of Clinical Research*, 2nd ed. (New Haven: Yale University Press, 1986).
 59. T. G. Ganiats, J. B. Humphrey, and H. L. Taras et al., "Routine Neonatal Circumcision: A Cost-Utility Analysis," *Medical Decision Making* 11, no. 4 (1991): 282-293; R. S. Van Howe, "A Cost-Utility Analysis of Neonatal Circumcision," *Medical Decision Making* 24, no. 6 (2004): 584-601.
 60. A. Taddio, M. Goldbach, and M. Ipp et al., "Effect of Neonatal Circumcision on Pain Responses during Vaccination in Boys," *The Lancet* 345, no. 8945 (1995): 291-292; see Taddio et al., *supra* note 56.
 61. See Taddio et al., *supra* note 22.
 62. C. J. Kowalski, "Placebo Controls: Scientific and Ethical Issues," *American Journal of Bioethics* 2, no. 2 (2002): 33-34.
 63. *Id.*
 64. F. L. Porter, S. W. Porges, and R. E. Marshall, "Newborn Pain Cries and Vagal Tone: Parallel Changes in Response to Circumcision," *Child Development* 59, no. 2 (1988): 495-505.
 65. M. R. Gunnar, F. L. Porter, and C. M. Wolf et al., "Neonatal Stress Reactivity: Predictions to Later Emotional Temperament," *Child Development* 66, no. 1 (1995): 1-13.
 66. M. R. Gunnar, R. O. Fisch, and S. Korsvik et al., "The Effects of Circumcision on Serum Cortisol and Behavior," *Psychoneuroendocrinology* 6, no. 3 (1981): 269-275; M. R. Gunnar, R. O. Fisch, and S. Malone, "The Effects of a Pacifying Stimulus on Behavioral and Adrenocortical Responses to Circumcision in the Newborn," *Journal of the American Academy of Child Psychiatry* 23, no. 1 (1984): 34-38; M. R. Gunnar, S. Malone, and G. Vance et al., "Coping with Aversive Stimulation in the

- Neonatal Period: Quiet Sleep and Plasma Cortisol Levels during Recovery from Circumcision," *Child Development* 56, no. 4 (1985): 824-834; M. R. Gunnar, J. Connors, and J. Isensee et al., "Adrenocortical Activity and Behavioral Distress in Human Newborns," *Developmental Psychobiology* 21, no. 4 (1988): 297-310; L. M. Talbert, E. N. Kraybill, and H. D. Potter, "Adrenal Cortical Response to Circumcision in the Neonate," *Obstetrics and Gynecology* 48, no. 2 (1976): 208-210.
67. See Lander et al., *supra* note 23; see Mohan et al., *supra* note 29.
 68. See Gunnar (1995), *supra* note 65.
 69. M. E. Holton, "Comparison of Newborn Circumcision Pain to Calcaneal Heel Puncture Pain: Is Newborn Circumcision Pain Control Clinically Warranted?" *Journal of the American Osteopathic Association* 96 (1996): 31-33.
 70. M. L. Williamson, "Circumcision Anesthesia: A Study of Nursing Implications for Dorsal Penile Nerve Block," *Pediatric Nursing* 23, no. 1 (1997): 59-63.
 71. See Butler-O'Hara et al., *supra* note 23.
 72. See Mohan et al., *supra* note 29.
 73. See Taddio et al., *supra* note 22.
 74. *Id.*
 75. B. Brady-Fryer, "A Dilemma in Infant Research: Can It Be Ethical to Have a Treatment Group in Which Pain Is Not Treated?" *Bioethics Bulletin* 7, no. 1 (1995).
 76. See Butler-O'Hara et al., *supra* note 23.
 77. Citation in Angell et al., *supra* note 33; M. Angell, "Ethical Imperialism? Ethics in International Collaborative Clinical Research," *New England Journal of Medicine* 319, no. 16 (1988): 1081-1083.
 78. See Angell, *supra* note 33.
 79. T. E. Wiswell, "Circumcision Circumspection," *New England Journal of Medicine* 336, no. 17 (1997): 1244-1245.
 80. X. Castellsagué, F. X. Bosch, and N. Muñoz et al., "Male Circumcision, Penile Human Papillomavirus Infection, and Cervical Cancer in Female Partners," *New England Journal of Medicine* 346, no. 15 (2002): 1105-1112.
 81. L. G. Maxwell and M. Yaster, "Analgesia for Neonatal Circumcision: No More Studies, Just Do It," *Archives of Pediatrics & Adolescent Medicine* 153, no. 5 (1999): 444-445.
 82. R. Temple and S. S. Ellenberg, "Placebo-Controlled Trials and Active-Control Trials in the Evaluation of New Treatments. Part 1: Ethical and Scientific Issues," *Annals of Internal Medicine* 133, no. 6 (2000): 455-463.
 83. R. M. Veatch, "Subject Indifference and the Justification of Placebo-Controlled Trials," *American Journal of Bioethics* 2, no. 2 (2002): 12-13.
 84. See Committee on Bioethics, *supra* note 25.
 85. See Lander et al., *supra* note 23.
 86. See Brady-Fryer, *supra* note 75.
 87. J. M. Mastrobattista and S. Hardwick-Smith, Response to a Letter to the Editor, "Ring Block for Neonatal Circumcision," *Obstetrics and Gynecology* 92, no. 5 (1998): 892.
 88. See Hardwick-Smith et al., *supra* note 44.
 89. See Brady-Fryer, *supra* note 75; see Mastrobattista and Hardwick-Smith, *supra* note 87; A. Taddio and G. Koren, "Lidocaine-Prilocaine Cream for Pain during Circumcision [reply]," *New England Journal of Medicine* 337, no. 8 (1997): 569-570; A. Taddio and G. Koren, Response to a Letter to the Editor, "The Pediatric Forum: Is Research on Newborn Circumcision Ethical?" *Archives of Pediatrics & Adolescent Medicine* 155, no. 5 (2001): 618.
 90. M. A. Somerville and D. M. Alwin, "Lidocaine-Prilocaine Cream for Pain during Circumcision," *New England Journal of Medicine* 337, no. 8 (1997): 568.
 91. See Hill, *supra* note 54.
 92. See Taddio and Koren, *supra* note 55.
 93. *Id.*
 94. *Id.*
 95. See Gunnar et al. (1981), Gunnar et al. (1984), Gunnar et al. (1985), Gunnar et al. (1988), and Talbert et al., *supra* note 66.
 96. R. S. Van Howe, "Pain Relief for Neonatal Circumcision: Serious Design Flaws?" *Pediatrics* 103, no. 1 (1999): 196.
 97. M. Bulter-O'Hara, C. LeMoine, and R. Guillet, Response to a Letter to the Editor, "Pain Relief for Neonatal Circumcision: Serious Design Flaws?" *Pediatrics* 103, no. 1 (1999): 197.
 98. See Baker, *supra* notes 3 and Baker, *supra* note 4.
 99. P. Alderson, *Children's Consent to Surgery* (Buckingham, England: Open University Press, 1993).
 100. See Poland et al., *supra* note 36.
 101. See Cold, *supra* note 32.
 102. Advisory Committee on Human Radiation Experiments (ACHRE), "Final Report of the Advisory Committee on Human Radiation Experiments," 1996, at 121-122, cited in R. Baker, "A Theory of International Bioethics: Multiculturalism, Postmodernism, and the Bankruptcy of Fundamentalism," *Kennedy Institute of Ethics Journal* 8, no. 3 (1998): 201-231.
 103. R. Goldman, *Questioning Circumcision: A Jewish Perspective* (Boston: Vanguard Publications, 1998).
 104. See *supra* note 24.
 105. A. W. Ham and D. H. Cormack, *Histology*, 8th ed. (Baltimore: Williams & Wilkins, 1979): at 898.
 106. J. R. Taylor, A. P. Lockwood, and A. J. Taylor, "The Prepuce: Specialized Mucosa of the Penis and Its Loss to Circumcision," *British Journal of Urology* 77, no. 2 (1996): 291-295; C. J. Cold and J. Taylor, "The Prepuce," *BJU International* 83, Supplement 1 (1999): 34-44.
 107. See Svoboda et al., *supra* note 30.
 108. S. E. Waldeck, "Using Male Circumcision to Understand Social Norms as Multipliers," *University of Cincinnati Law Review* 72, no. 3 (2003): 455-526.
 109. J. G. Lenhart, N. M. Lenhart, A. Reid, and B. K. Chong, "Local Anesthesia for Circumcision: Which Technique Is Most Effective?" *Journal of the American Board of Family Practice* 10, no. 1 (1997): 13-19.
 110. A. Taddio, N. Pollock, and C. Gilbert-MacLeod et al., "Combined Analgesia and Local Anesthesia to Minimize Pain during Circumcision," *Archives of Pediatrics & Adolescent Medicine* 154, no. 6 (2000): 620-623.
 111. See Howard et al., *supra* note 23.
 112. H. J. Stang, L. W. Snellman, and L. M. Condon et al., "Beyond Dorsal Penile Nerve Block: A More Humane Circumcision," *Pediatrics* 100, no. 2 (1997): e3.
 113. H. W. Tausch, A. M. Martinez, and J. C. Partridge et al., "Pain during Mogen or PlastiBell Circumcision," *Journal of Perinatology* 22, no. 3 (2002): 214-218.
 114. See Anand and Hickey, *supra* note 6.
 115. S. Moses, R. C. Bailey, and A. R. Ronald, "Male Circumcision: Assessment of Health Benefits and Risks," *Sexually Transmitted Infections* 74, no. 5 (1998): 368-373.
 116. See Herschel et al., *supra* note 23.
 117. M. A. Holliday, T. L. Pinckert, and S. C. Kiernan et al., "Dorsal Penile Nerve Block vs Topical Placebo for Circumcision in Low-Birth-Weight Neonates," *Archives of Pediatrics & Adolescent Medicine* 153, no. 5 (1999): 476-480.
 118. See Lander et al., *supra* note 23.
 119. See Holton, *supra* note 69.
 120. See Williamson, *supra* note 70.
 121. See Butler-O'Hara et al., *supra* note 23.
 122. P. J. Woodman, "Topical Lidocaine-prilocaine Versus Lidocaine for Neonatal Circumcision: A Randomized Controlled Trial," *Obstetrics and Gynecology* 93, no. 5, Part 1 (1999): 775-779.
 123. See Taddio et al., *supra* note 22.
 124. See Hardwick-Smith et al., *supra* note 44.
 125. See Mohan et al., *supra* note 29.
 126. See Kurtis et al., *supra* note 46.
 127. See Kass and Holman, *supra* note 47.