Summary

Background Preliminary studies suggested that pain experienced by infants in the neonatal period may have long-lasting effects on future infant behaviour. The objectives of this study were to find out whether neonatal circumcision altered pain response at 4-month or 6-month vaccination compared with the response in uncircumcised infants, and whether pretreatment of circumcision pain with lidocaine-prilocaine cream (Emla) affects the subsequent vaccination response.

Methods We used a prospective cohort design to study 87 infants. The infants formed three groups—uncircumcised infants, and infants who had been randomly assigned Emla or placebo in a previous clinical trial to assess the efficacy of Emla cream as pretreatment for pain in neonatal circumcision. Infants were videotaped during vaccination done at the primary care physician's clinic. Videotapes were scored without knowledge of circumcision or treatment status by a research assistant who had been trained to measure infant facial action, cry duration, and visual analogue scale pain scores.

Findings Birth characteristics and infant characteristics at the time of vaccination, including age and temperament scores, did not differ significantly among groups. Multivariate ANOVA revealed a significant group effect ($p<0.001$) in difference (vaccination minus baseline) values for percentage facial action, percentage cry time, and visual analogue scale pain scores. Univariate ANOVAs were significant for all outcome measures ($p<0.05$): infants circumcised with placebo had higher difference scores than uncircumcised infants for percentage facial action (136·9 *vs* 77·5%), percentage cry duration (53·8 *vs* 24·7%), and visual analogue scale pain scores (5·1 *vs* 3·1 cm). There was a significant linear trend on all outcome measures, showing increasing pain scores from uncircumcised infants, to those circumcised with Emla, to those circumcised with placebo.

Interpretation Circumcised infants showed a stronger pain response to subsequent routine vaccination than uncircumcised infants. Among the circumcised group, preoperative treatment with Emla attenuated the pain response to vaccination. We recommend treatment to prevent neonatal circumcision pain.

Department of Paediatrics, Hospital for Sick Children (A Taddio MSc, Prof G Koren MD); **Department of Psychology, Toronto Hospital** (J Katz PhD); **and Faculty of Pharmacy** (A Taddio), **Departments of Behavioural Science and Anaesthesia** (J Katz), **and Health Administration** (A L Ilersich MSc), **and Department of Paediatrics and Faculty of Medicine** (G Koren), **University of Toronto, Ontario, Canada**

Correspondence to: Prof Gideon Koren, Division of Clinical Pharmacology and Toxicology, Department of Paediatrics, Hospital for Sick Children, 555 University Avenue, Toronto, Ontario M5G 1X8, Canada

Introduction

Neonatal circumcision is a common surgical procedure in male infants. Despite evidence that circumcision causes intense pain and short-term alterations in infant feeding, sleeping, and crying behaviours,[1-3] analgesia is rarely given.[4-6] There is a common belief that the effects of circumcision pain are short-lived and clinically insignificant, and, therefore, that the benefits of analgesic treatment do not outweigh the risks of adverse effects from currently available therapies.[7,8]

We looked at the foundations for the belief that the effects of circumcision pain are short-lived by examining infant behaviour several months after surgery. We analysed data from a clinical trial that studied the use of topical lidocaine-prilocaine 5% cream (Emla, Astra Pharma, Canada) during routine vaccination at 4 or 6 months.[9] Male infants showed a greater pain response than female infants. This difference may be linked with neonatal circumcision in male infants. Male infants who had been circumcised also exhibited a greater pain response than those who had not been circumcised.[10] This initial analysis raised concerns about the possible long-term effects of untreated pain in infants, especially those who have repeated experience of pain. However, we could not draw definite conclusions because of the post-hoc nature of the analysis and the small sample size. The objectives of our study were, therefore, to investigate prospectively whether neonatal circumcision affects infant pain response to routine vaccination 4–6 months after surgery and whether vaccination response is affected by pretreatment of neonatal circumcision pain with Emla.

Methods

We carried out a prospective cohort study of 87 healthy, full-term, male, newborn infants who had, when aged 5 days or less, participated in a clinical trial that investigated the safety and efficacy of Emla cream for neonatal circumcision.[11] The participants in this study included uncircumcised boys, who served as controls (n=32), and circumcised boys who had been randomly assigned treatment with Emla (n=29) or placebo (n=26) during circumcision. All parents who had allowed their infants to participate in the circumcision trial were asked to enrol their infants in this study and sign a consent form for their participation. We recruited uncircumcised infants from the same study by the same inclusion criteria as for the circumcised infants, the difference being that their parents had chosen not to have their infants circumcised. The protocol received approval from the Research Ethics Boards of the Hospital for Sick Children and Women's College Hospital.

The setting for this study was the clinic of the infant's primary care physician, where vaccination was done. Each infant's physician was contacted before the study commenced and informed about its purpose and procedures. One of the investigators telephoned all the parents 2–4 weeks before the anticipated date of the 4-month or 6-month vaccination to obtain details of the appointment date and time. We chose to study pain response during routine vaccination at 4 or 6 months to reduce the effects of fear and anticipation on infant pain response seen in older infants and children, and because vaccination pain responses do not vary greatly within this age range.[9]

Parents were sent copies of the revised infant temperament questionnaire for infants aged 4–8 months,[12] to complete within

	Uncircumcised	Circumcised with Emla	Circumcised with placebo
Eligible infants	45	37	31
Excluded			
Refused to participate	2 (4%)	6 (16%)	3 (10%)
Lost to follow-up	4 (9%)	1 (3%)	3 (10%)
Logistic difficulties	4 (9%)	1 (3%)	2 (6%)
Circumcised after initial contact	3 (7%)	..	..
Included in study	32 (71%)	29 (78%)	26 (84%)*

*Includes 3 infants from uncircumcised group who were circumcised after initial contact.

Table 1: **Flow of participating infants through trial**

the 2 weeks before the vaccination appointment. An investigator met one or both parents and their infant at the primary care physician's clinic on the day of vaccination, and the parents returned the completed questionnaire to the investigator at that time.

The vaccination procedure was standardised across settings. The infant was physically examined before the vaccination. If the infant was unsettled by this examination, the parents were asked to settle him. Immediately before the vaccination the infant was placed supine on the examination table. A physician or nurse then gave the infant an intramuscular injection of the vaccine (0·5 mL DPT-Polio & Act-HIB, Connaught Laboratories, Ontario, Canada) in the left or right thigh. An investigator recorded the infant's face for a minimum of 20 s with a video camera (Panasonic, Ontario, Canada, model #PV-S770A-K), before, during, and for up to 1 min after vaccination. Parents were instructed not to hold the infant for the first 30 s after the injection but were not discouraged from touching or speaking to him during the procedure.

Pain assessment

Infant pain response was scored from the videotape by a research assistant who was unaware of both the purpose of the study and the treatment-group status of the infants. The research assistant was trained to score reliably infant pain reactions using the neonatal facial coding system[13] and cry duration (test-retest κ=0·76, p<0·001).

Three behavioural pain measures were used to assess pain: infant facial action, cry duration, and visual analogue scale scores. Infant facial action was a composite score from three specific facial actions (brow bulge, nasolabial furrow, and eyes squeezed shut) taken from the neonatal facial coding system.[13] This system is a sensitive and specific way of rating infant pain,[14,15] and is the most extensively used behavioural pain measure in infant pain research.[16] The neonatal facial system was chosen as the primary outcome measure for this study because it is considered to be the gold standard for infant pain assessment.

	Uncircumcised (n=32)	Circumcised with Emla (n=29)	Circumcised with placebo (n=26)	p
Infants' characteristics: mean (SD)				
Postnatal age (days)	133 (12·9)	140 (23·7)	143 (29·4)	0·22
Weight (g)	7278 (792·5)	7608 (768·4)	7496 (762·9)	0·25
Time from last feed (min)	111 (82·7)	107 (71·8)	101 (67·7)	0·90
Time from last nap (min)*	117 (73·1)	125 (66·4)	111 (72·4)	0·79
Vaccination procedure: number of infants				
Treated with paracetamol	4 (13%)	3 (10%)	3 (12%)	0·97
Vaccinated by physician	24 (75%)	21 (72%)	20 (77%)	0·93
Maternal characteristics				
Mean (SD) age (years)	31 (3·5)	31 (4·2)	33 (3·7)	0·07
Number of primiparas	15 (47%)	16 (55%)	10 (39%)	0·46
Mean (SD) Blishen score[18]†	54 (17·8)	53 (12·3)	56 (13·4)	0·74

*Not known for 2 infants circumcised with Emla and 1 circumcised with placebo.
†Not known for 2 infants circumcised with Emla and 2 circumcised with placebo.

Table 2: **Demographic characteristics of infants at time of vaccination**

	Mean (SD) score		
	Uncircumcised (n=32)	Circumcised with Emla (n=29)	Circumcised with placebo (n=25)
Category			
Activity	4·1 (0·5)	4·2 (0·5)	3·9 (0·6)
Adaptability	2·3 (0·7)	2·0 (0·6)	2·1 (0·6)
Approachability	2·3 (0·7)	2·1 (0·7)	2·1 (0·8)
Distractability	2·4 (0·7)	2·1 (0·6)	2·4 (0·6)
Intensity	3·4 (0·8)	3·3 (0·7)	3·1 (0·7)
Mood	2·9 (0·8)	2·5 (0·6)	2·8 (0·6)
Persistence	3·3 (0·7)	3·2 (0·9)	3·5 (0·8)
Rhythm	2·7 (0·6)	2·8 (0·9)	3·2 (0·9)
Threshold	3·7 (0·8)	3·8 (0·8)	3·5 (0·9)
Overall temperament	2·1 (0·8)	2·3 (1·2)	2·3 (1·1)

Table 3: **Revised infant temperament questionnaire scores**

We used these three facial actions because they are particularly sensitive for indicating pain.[17]

The three facial actions and cry duration were coded as present or absent for each 1 s period of the 20 s before the vaccination (baseline), and the first 20 s during and after the vaccination. These data were then converted into percentages of time that the infants exhibited the actions or cried (ie, % time=number of times action observed/20×100, where 20 was the number of assessments made during the 20 s period).

An overall facial action pain score for the procedure was calculated by adding together the facial action scores for the three specific facial actions. The overall facial action pain score ranged from 0–300%. Percentage cry duration ranged from 0–100%. Visual analogue scale pain scores were rated with a 10 cm pain ruler.

The revised infant temperament questionnaire records the relative frequency with which infants exhibit particular responses to specified situations, such as feeding or bathing. Nine temperament characteristics were derived from the questionnaire. The revised infant temperament questionnaire has favourable psychometric properties; internal consistency and test-retest reliability coefficients are reported to be 0·83 and 0·86, respectively.[12] As well as being scored for the nine different categories, infants were assigned an overall temperament rating of easy (1), intermediate-low (2), slow to warm up (3), intermediate-high (4), or difficult (5). The numerical scores were used for ease of analysis.

On the day of vaccination, parents were asked questions about their infant's last feeding and nap times, ingestion of paracetamol for vaccination-fever prophylaxis, and previous painful experiences. Information on birth characteristics and previous vaccinations was obtained from the infant's medical records. Socioeconomic status was scored by the Blishen scale[18] based on maternal occupation.

We based the calculation of necessary sample size on the difference in pain scores between circumcised and uncircumcised infants observed in our initial study of vaccination pain responses,[10] in which the mean visual analogue scale pain score (unpublished) was 4·6 cm in the circumcised group and 2·7 cm in the uncircumcised group, and the SD was about 2·5 cm. Setting an α of 0·05 and β of 0·2, and to account for possible drop-outs such as parents who refused to let their children participate, those lost to follow-up, or those who could not be included for reasons arising after initial contact, we estimated that about 30 infants per group were needed.[19]

Statistical analysis

The main analysis compared difference scores (vaccination score minus baseline value) for percentage facial action, percentage cry duration, and visual analogue scale pain scores among the groups, by multivariate ANOVA. Univariate, one-way ANOVAs were carried out only if the multivariate ANOVA was significant (p<0·05). The pattern of significant differences between pairs of means was examined by post-hoc comparisons by Duncan's method. Trend analysis was used to establish the significance of the rank order among the groups, with the expectation that the

	Uncircumcised (n=32)	Circumcised with Emla (n=29)	Circumcised with placebo (n=26)	p
Mean (SD)				
Gestational age (days)	278 (8·4)	279 (9·6)	277 (9·3)	0·65
Birthweight (g)	3645 (428·8)	3636 (426·1)	3530 (443·5)	0·55
5 min Apgar score	9 (0·3)	9 (0·3)	9 (0·4)	0·24
Number of infants				
Caucasian	29 (91%)	26 (90%)	23 (89%)	0·96
Vaginal delivery	22 (69%)	22 (76%)	18 (69%)	0·80

Table 4: **Birth characteristics**

Emla-treated group would have a pain response intermediate to those of the other groups. Demographic characteristics were compared among groups by ANOVA or χ^2 test, as appropriate. Temperament scores were analysed by multivariate ANOVA. The strength of linear relations between pain measures and infant variables was assessed by the Pearson or Spearman correlation coefficient as appropriate; correction for multiple correlations was made with the Bonferroni method.

Results

87 (77%) of the 113 eligible infants participated in the study (table 1). Three infants in the uncircumcised group were circumcised after initial contact with the investigator. Two of the three infants were circumcised within 5 days of birth and the other at age 20 days. None of these infants received analgesia for circumcision pain and, therefore, their results were added to the group circumcised with placebo for data analysis.

There were no significant differences among the three groups in any demographic characteristics at the time of vaccination (table 2). Infant temperament was simlar in all groups (multivariate ANOVA main group effect; p=0·20); (table 3), as were birth characteristics (table 4). 64 clinics took part in the study. Five (6%) infants were held by a parent during vaccination, and 76 (87%) were vaccinated with a 25-gauge needle. Eight infants were pretreated with Emla for circumcision pain openly in the clinical trial from which they were recruited.

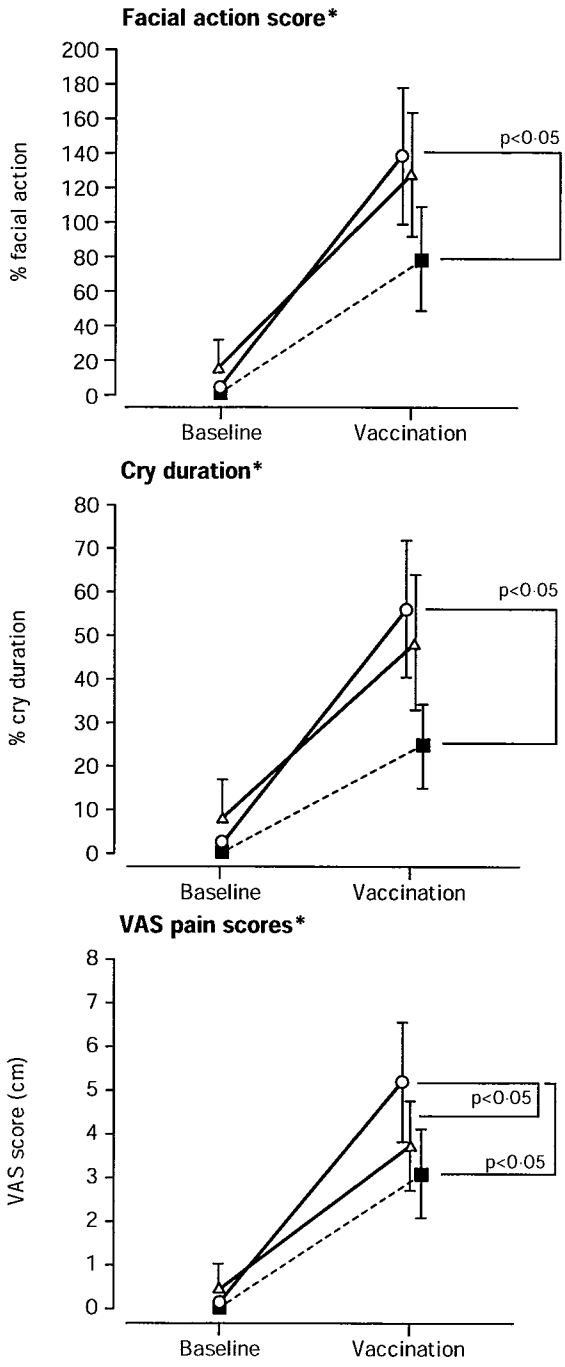
Multivariate ANOVA revealed a significant group effect for difference in pain scores (p<0·001). Univariate ANOVAs (figure) showed significant group effects for percentage facial action (p=0·04), percentage cry duration (p=0·01), and visual analogue scale pain scores (p=0·02). Post-hoc analysis showed that the group circumcised with placebo had higher difference scores (p<0·05) than the uncircumcised group for percentage facial action (136·9 *vs* 77·5%), percentage cry duration (53·8 *vs* 24·7%), and visual analogue scale pain scores (5·1 *vs* 3·1 cm). In addition, visual analogue scale pain scores were significantly higher in infants circumcised with placebo than in those circumcised with Emla (5·1 *vs* 3·3 cm; p<0·05). There was a significant linear trend (p<0·05) in all three outcome measures, with scores increasing from the uncircumcised to the circumcised with placebo group.

The main results were similar when the analysis was repeated by univariate ANCOVAs with vaccination pain score as the outcome and baseline value as the covariate.

	Correlation coefficient*		
	% facial action	% cry duration	VAS pain score
Postnatal age (days)	−0·03	−0·11	−0·09
Weight (g)	−0·12	−0·19	−0·17
Time from last feed (min)	−0·10	−0·15	−0·06
Time from last nap (min)	0·09	0·16	0·04
Treated with paracetamol	−0·10	−0·05	−0·05
Temperament score			
Overall	−0·07	−0·14	−0·05
Activity	−0·04	−0·09	0·04
Adaptability	0·01	−0·07	−0·003
Approachability	0·03	−0·03	0·03
Distractability	−0·15	−0·09	−0·11
Intensity	0·02	−0·04	−0·05
Mood	−0·20	−0·19	−0·13
Persistence	0·02	0·03	−0·02
Rhythm	−0·01	−0·07	−0·003
Threshold	−0·08	0·02	−0·03

VAS=visual analogue scale.
*Pearson's or Spearman's; p>0·05 on all variables.

Table 5: **Relation between infant characteristics and pain response**



Infant pain response to vaccination for infants in all groups
VAS=visual analogue scale.
*Values shown as mean (95% CI).

Characteristics of the infants, such as age, weight, temperament, ingestion of paracetamol, time of last feeding, and time of last sleep before vaccination, did not correlate significantly with pain response (table 5).

Discussion

This study showed that neonatal circumcision in male infants is associated with increased pain response in vaccination 4–6 months after surgery. The results support our previous finding of a higher pain response in circumcised than uncircumcised male infants during routine vaccination.[10]

We postulate that circumcision may induce long-lasting changes in infant pain behaviour because of alterations in the infant's central neural processing of painful stimuli. Transmission of noxious afferent input from the periphery (eg, brought about by skin incision) to the spinal cord induces a sustained state of central neural sensitisation or hyperexcitability that amplifies subsequent input from the wound and leads to increased postoperative pain. The specific mechanisms by which noxious peripheral stimulation induces long-lasting central neuronal changes are not yet fully established, but the N-methyl-D-aspartic acid (NMDA) receptor ion-channel complex, excitatory aminoacids (eg, glutamate), and C-fibre neuropeptides (eg, substance P) have been implicated. Peripheral noxious stimulation leads to the release of excitatory aminoacids and neuropeptides in the dorsal horn of the spinal cord. Activation of the NMDA receptor in dorsal horn neurons produces an increase in intracellular calcium and other secondary messengers, which stimulate protein kinases and new gene expression.[20,21]

This study was designed to investigate whether premedication with a topical local anaesthetic for circumcision pain would attenuate the pain response to vaccination several months later in circumcised infants. We postulated that Emla would at least partially block nociceptive afferent input originating from the surgical site at the time of circumcision and, therefore, any long-lasting consequences of this input on the central nervous system. The results of the study do not entirely support this hypothesis. Differences in vaccination pain response between infants pretreated with Emla and those given no anaesthesia for circumcision pain were seen for visual analogue scale pain scores, but not for facial action and cry duration. However, there was a significant trend for Emla-treated infants to have an intermediate pain response across all three measures of pain (figure). Although primary afferent injury discharge and subsequent noxious perioperative events contribute to enhanced postoperative pain,[22] other factors, such as postoperative inflammatory inputs, may also induce a state of central sensitisation.[23] Insufficient afferent blockade during circumcision and in the days that follow surgery may have contributed to central sensitisation in both treated and untreated circumcision groups. Study of the vaccination pain response of infants who had received more effective circumcision pain management (ie, dorsal penile nerve block and adequate postoperative pain management) would be interesting.

Although vaccination pain response displayed by the infants circumcised without analgesia was higher than the uncircumcised infants, this response may not be specific only to pain. The site of injury during vaccination differed from that during circumcision. In addition, vaccination pain measured by facial action and cry duration did not differ significantly between infants circumcised with or without Emla. Although postsurgical central sensitisation (allodynia and hyperalgesia) can extend to sites of the body distal from the wound,[24] suggesting a supraspinal effect, the long-term consequences of surgery done without anaesthesia are likely to include post-traumatic stress as well as pain.[25] It is, therefore, possible that the greater vaccination response in the infants circumcised without anaesthesia may represent an infant analogue of a post-traumatic stress disorder triggered by a traumatic and painful event and re-experienced under similar circumstances of pain during vaccination.

Factors other than circumcision may account for the observed differences in pain response. For example, there may be differences in genetic attributes, socioeconomic status, and parent-infant interactions between people who have their sons circumcised and those who do not. However, race and socioeconomic status did not differ between groups in this study and there were no observable qualitative differences in the way parents interacted with their infants during the vaccination.

Another possible explanation is that parents of infants who have undergone painful surgical procedures such as circumcision begin to interact differently with their infants compared with parents whose infants have not undergone such procedures. Parents' patterns of behavioural reinforcement may develop so that by the age of 4 or 6 months, circumcised infants may display a heightened pain response to vaccination. Infant temperament was measured to discern differences among groups due to effects of the infants' personalities. However, the revised infant temperament questionnaire did not show any differences in infant behaviour among the groups.

To keep potential bias during data collection to a minimum, we standardised the infants' position before vaccination. Second, we waited for infants to calm down if they were unsettled by the physical examination. Third, each infant was videotaped in his own primary physician's clinic. Finally, videotapes were coded by a research assistant who was not aware of the status of infants in each treatment group or the purpose of the study.

Several other investigators have studied the long-term effects of untreated pain in newborn infants. Fitzgerald and colleagues[26] showed that repeated heel lancing may induce a state of hypersensitivity in pain response, and that this atypical response can be prevented by pretreament with Emla. Grunau and colleagues[27,28] found that children born prematurely have a tendency to somatise and interpret pictures of pain-producing situations differently from other children. Finally, long stays in hospital and repeated medical procedures in the perinatal period have been proposed as factors affecting long-term cognitive and motor deficits seen in low-birthweight infants.[29,30]

The results of this study are consistent with studies of pain response in animals and behavioural studies in humans showing that injury and tissue damage sustained in infancy can cause sustained changes in central neural function, which persist after the wound has healed and influence behavioural responses to painful events months later. Pretreatment and postoperative management of neonatal circumcision pain is recommended based on these results. Investigation of the neurological basis of these effects is warranted.

This study was supported by the Hospital for Sick Children Trainee Start-up Fund, a Postgraduate Connaught Scholarship awarded to AT, and a Medical Research Council of Canada Scholar Award to JK.

We thank the parents who gave permission for their infants to participate in the study, and the physicians, nurses, receptionists, and Lucia Taddio for their assistance.

References

1 Anders TF, Chalemian RJ. The effects of circumcision on sleep-wake states in human neonates. *Psychosom Med* 1974; **36:** 174–79.

2 Emde RN, Harmon RJ, Metcalf D, Koenig KL, Wagonfeld S. Stress and neonatal sleep. *Psychosom Med* 1971; **33:** 491–97.

3 Marshall RE, Porter FL, Rogers AG, Moore J, Anderson B, Boxerman SB. Circumcision II: effects upon mother-infant interaction. *Early Hum Dev* 1982; **7:** 367–74.

4 Wellington N, Rieder MJ. Attitudes and practices regarding analgesia for newborn circumcision. *Pediatrics* 1993; **92:** 541–43.

5 Howard CR, Howard FM, Garfunkel L, deBlieck EA, Weitzman M. Neonatal circumcision and pain relief: current training practices. *Arch Pediatr Adolesc Med* 1996; **150:** 42 (abstr 120).

6 Toffler WL, Sinclair AE, White KA, Dorsal penile nerve block during newborn circumcision: underutilization of a proven technique? *J Am Board Fam Pract* 1990; **3:** 171–74.

7 Schoen EJ. The status of circumcision of newborns. *N Engl J Med* 1990; **322:** 1308–12.

8 American Academy of Paediatrics Task Force on Circumcision. Report of the task force on circumcision. *Pediatrics* 1989; **84:** 388–91.

9 Taddio A, Nulman I, Goldbach M, Ipp M, Koren G. The use of lidocaine-prilocaine cream for vaccination pain in infants. *J Pediatr* 1994; **124:** 643–48.

10 Taddio A, Goldbach M, Ipp M, Stevens B, Koren G. Effect of neonatal circumcision on pain responses during vaccination in boys. *Lancet* 1995; **345:** 291–92.

11 Taddio A, Stevens B, Craig K, et al. Efficacy and safety of lidocaine-prilocaine cream for pain during circumcision. *N Engl J Med* (in press).

12 Carey WB, McDevitt SC. Revision of the infant temperament questionnaire. *Pediatrics* 1978; **61:** 735–39.

13 Grunau RVE, Craig KD. Pain expression in neonates: facial action and cry. *Pain* 1987; **28:** 395–410.

14 Grunau RVE, Johnston CC, Craig KD. Neonatal facial and cry responses to invasive and non-invasive procedures. *Pain* 1990; **42:** 295–305.

15 Craig KD, Grunau RVE, Aquan-Assee J. Judgment of pain in newborns: facial activity and cry as determinants. *Can J Behav Sci/Rev Can Sci Comp* 1988; **20:** 442–51.

16 Johnston CC, Stevens B, Craig KD, Grunau RVE. Developmental changes in pain expression in premature, full-term, two- and four-month-old infants. *Pain* 1993; **52:** 201–08.

17 Stevens B, Johnston C, Petryshen P, Taddio A. The premature infant pain profile: development and validation. *Clin J Pain* 1996; **12:** 13–22.

18 Blishen BR, Carroll WK, Moore C. The 1981 index for occupations in Canada. *Rev Can Soc Anth/Can Rev Soc Anth* 1987; **24** (4): 465–85.

19 Altman DG. Practical statistics for medical research. New York: Chapman and Hall, 1991.

20 Coderre TJ, Katz J, Vaccarino AL, Melzack R. Contribution of central neuroplasticity to pathological pain: review of clinical evidence. *Pain* 1993; **52:** 259–85.

21 Woolf CJ, Thompson SWN. The induction and maintenance of central sensitization is dependent on N-methyl-D-aspartic acid receptor activation: implications for the treatment of postinjury pain hypersensitivity states. *Pain* 1991; **44:** 293–99.

22 Katz J, Clairoux M, Kavanagh BP, et al. Pre-emptive lumbar epidural anaesthesia reduces postoperative pain and patient-controlled morphine consumtpion after lower abdominal surgery. *Pain* 1994; **59:** 395–403.

23 Woolf CJ, Chong MS. Preemptive analgesia—treating postoperative pain by preventing the establishment of central sensitization. *Anesth Analg* 1993; **77:** 362–79.

24 Dahl JB, Erichsen CJ, Fuglsang-Frederiksen A, Kehlet H. Pain sensation and nociceptive reflex excitability in surgical patients and human volunteers. *Br J Anaesth* 1992; **69:** 117–21.

25 Katz J. The reality of phantom limbs. *Motivation Emotion* 1993; **17:** 147–79.

26 Fitzgerald M, Millard C, McIntosh N. Cutaneous hypersensitivity following peripheral tissue damage in newborn infants and its reversal with topical anaesthesia. *Pain* 1989; **39:** 31–36.

27 Grunau RVE, Whitfield MF, Petrie JH, Fryer EL. Early pain experience, child and family factors, as precursors of somatization: a prospective study of extremely premature and full term children. *Pain* 1994; **56:** 353–59.

28 Grunau RVE, Whitfield MF, Petrie J, Fryer L. Children's interpretations of pain-producing situations at 8½ years: are they affected by prior nociceptive experiences in the newborn period? *Pediatr Res* 1996; **39:** 266 (abstr).

29 Als H, Lawhon G, Duffy FH, McAnulty GB, Gibes-Grossman R, Blickman JG. Individualized developmental care for the very low-birth-weight preterm infant: medical and neurofunctional effects. *JAMA* 1994; **272:** 853–58.

30 Pharoah POD, Stevenson CJ, Cooke RWI, Stevenson RC. Clinical and subclinical deficits at 8 years in a geographically defined cohort of low birthweight infants. *Arch Dis Child* 1994; **70:** 264–70.