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Children—Not Simply “Little Adults”

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Before IASP was founded, our knowledge of children’s pain was severely limited. Clinical decisions about whether children were experiencing pain and, if so, about the particular pain therapies required, were based primarily on physicians’ personal beliefs rather than on scientific evidence. Regrettably, common misbeliefs that children did not feel pain in the same manner as adults and consequently did not require similar analgesics, along with pervasive fears that children were at heightened risk for opioid addiction and should receive minimal analgesic doses, caused many children to suffer needlessly.

Two studies highlight how children’s pain problems were undertreated during this period. In 1968, Swafford and Allan surveyed analgesic use for all children treated in an intensive care unit during a 4-month period. Only 14% of children (26 of 180) had received any opioids for pain relief. Moreover, only 3% of children received analgesics after general surgery, presumably because “pediatric patients seldom need relief of pain after general surgery. They tolerate discomfort well” (Swafford and Allan 1968).

Subsequently, Eland (1974) compared medication use for 18 adults and 25 children with similar medical conditions during their hospitalization. While 372 opioid doses and 299 non-opioid doses were administered to adults, only 24 analgesic doses were administered to children. In fact, more than half of the children did not receive any analgesics, despite undergoing major trauma including amputation of the foot, excision of neck mass, and heminephrectomy.

Since Eland’s thesis, extensive research has refuted the erroneous beliefs that once guided pediatric practice. Through innumerable personal and

professional efforts, children's pain has emerged as an important research and clinical specialty. The last 30 years comprise an unparalleled period of critical advances in this enormous field, encompassing a "bench to bedside to community health research" perspective, covering a population "from in utero through adolescence," and including all types of acute and persistent pain. This chapter provides a historical review of our field, highlighting pivotal discoveries and the challenges encountered to make children's pain control a higher priority throughout the world.

AN EMERGING FIELD

Clinicians and scientists who were interested in children's pain had worked in relative isolation from one another in many different centers around the world until the founding of IASP. The journal *Pain* and the triennial world congresses created a unique opportunity for these interdisciplinary "children's pain people" to connect with one another in a dynamic manner. By 1985, IASP had become a home base for many pediatric specialists. The next few years were an exceptional period, marked by an exhilarating whirlwind of sharing ideas, forming friendships, and laying the foundation for an interdisciplinary and international scientific network devoted to children's pain. Significant historical moments include the first International Conference on Pediatric Pain, convened by Dr. Donald Tyler (July 1988; Seattle, Washington); the first Consensus Conference on the Management of Pain in Childhood Cancer, convened by Dr. Neil Schechter (October 1988; Chester, Connecticut); and the first European Conference on Pediatric Pain, convened by Dr. Huda Abu Saad (June 1989; Maastricht, the Netherlands). These three meetings linked experienced clinicians and scientists to obtain the first "evidence base by consensus" for understanding and treating children's pain.

At that time, the first books to cover all aspects of childhood pain were written: three were authored (McGrath and Unruh 1987; Ross and Ross 1988; McGrath 1990) and three were edited texts (Pichard-Léandri and Gauvain-Piquard 1989; Bush and Harkins 1991; Tyler and Krane 1990). These books, heralding the beginning of the field, continue to provide valuable insights about a child's perception, versatile assessment techniques, and the management of common pain problems from a practical hands-on perspective. Today, thousands of articles and almost a hundred books on children's pain have been published. During the period 2001–2003, 14 books and 1728 articles were published, averaging 575 articles per year in a broad spectrum of pain, medical, dental, nursing, psychology, and health journals.

Yet, in striking contrast, in the 3-year period near the founding of IASP (1973–1975), only one book, *The Child with Abdominal Pains* (Apley 1975) and only 61 articles, an average of 20 articles per year, were published.

Thirty years ago, medical texts contained almost no information about the general topic of children's pain, nor any reference to specific pain conditions. Only 26 pages referred to pain across five major pediatric texts (Forfar 1973; Hutchison 1975; Nelson 1975; Silver et al. 1975; Ziai et al. 1975), whereas 270 pages refer to children's pain in recent texts (Behrman et al. 2002, 2004; Rudolph et al. 2002; Robinson and Robertson 2003; Rudolph and Rudolph 2003). The 1973–1975 medical texts devoted less than 1% of their pages to children's pain, while recent textbooks devoted 4% of pages to the topic.

Today, most texts on pain include at least one chapter devoted to children's issues. Moreover, the pediatric field is enriched by recent comprehensive texts (Olsson and Jylli 2001; Schechter et al. 2003) and by specialized texts on neonates (Anand et al. 2000), children's headache (McGrath and Hillier 2001), procedure-related pain (Finley and McGrath 2001; Lioffi 2002), and biological-social factors (McGrath and Finley 2003). The IASP's *Core Curriculum on Pain* has recently been revised with expanded sections to encompass new findings in the fields of developmental neurobiology, pain assessment, and evidence-based pain management (www.iasp-pain.org).

Dynamic growth is noted for almost all scientific and clinical activities related to pediatric pain—the number of scientific presentations on pediatric pain at international and national pain meetings; the formation of special interest groups on pain in children to address common scientific, clinical, and advocacy issues; the establishment of interdisciplinary pain clinics for children; and the organization of interdisciplinary meetings focused exclusively on children's pain.

THE DEVELOPING NOCICEPTIVE SYSTEM: INCREASED SENSITIVITY AND PLASTICITY

Ethical concerns and increasing publicity about the lack of analgesia for infants led to a dramatic upsurge in clinical research to document objectively how infants respond to surgical trauma and how analgesic administration affects postsurgical outcome. At the same time, basic scientific research focused on the development of the nociceptive system in animals. Fitzgerald and colleagues initiated a series of elegant anatomical and physiological investigations to detail the development of the nociceptive system (for review, see Andrews 2003; Fitzgerald and Howard 2003). The basic nociceptive

connections are formed before birth, but systems at birth are immature and exhibit increased responsivity in comparison to the adult animal.

Considerable neuronal plasticity is evident throughout the developing system from the periphery to the brain. For example, the conduction velocity of afferent fibers, action potential shape, receptor transduction, firing frequencies, and receptive field properties change substantially over the post-natal period (Fitzgerald 1987; Koltzenburg and Lewin 1997; Fitzgerald and Jennings 1999; Woodbury and Koerber 2003). Both high-threshold A δ and low-threshold A β mechanoreceptors respond with lower firing frequencies at birth compared to those in the adult animal. A β afferents extend dorsally into laminae II and I along with C fibers, rather than into only laminae III and IV as in the adult animal. Activation of these A β afferents evokes excitatory responses more typical of those evoked by A δ and C fibers in the adult animal. In addition, the receptive fields of dorsal horn cells and somatosensory cortical cells are larger in the newborn. With these larger receptive fields and the dominant A-fiber input, there is an increased likelihood that central cells will be excited by peripheral sensory stimulation, thereby increasing the sensitivity of infant sensory reflexes to stimulation. Moreover, descending inhibitory mechanisms are not functional at birth (Boucher et al. 1998), so that an important endogenous analgesic system is lacking, which means that noxious input may affect neonates more than adults.

Nerve injury, which can evoke persistent neuropathic pain, has dramatically different effects in neonates and adults. During a critical neonatal period, peripheral nerve injury causes rapid and extensive death of axotomized dorsal root ganglion cells, producing major changes within the spinal cord. The central terminals of damaged axons withdraw while adjacent, intact axon collaterals sprout into the denervated region, disrupting the somatotopic organization of central terminals within the dorsal horn and also at higher levels of the nervous system including the cortex (Kaas et al. 1983). Although this process may be a potentially useful compensatory device to restore sensory input from an area of the body surface in which it has been lost, its effects may be detrimental and may trigger chronic pain (Fitzgerald and Howard 2003).

Most studies in developmental neurobiology have been conducted on rat pups because they have comparable developmental timetables with respect to the anatomy, chemistry, and physiology of maturing human pain pathways. To study neural function in human infants, investigators have monitored behavioral and neurophysiological responses, revealing extensive plasticity and increased excitability in the developing nervous system (for review, see Andrews 2003; Johnston et al. 2003). In comparison to adults, young infants have exaggerated reflex responses (i.e., lower thresholds and longer-

lasting muscle contractions) in response to certain types of trauma, such as needle insertion (Andrews and Fitzgerald 1999). Repeated mechanical stimulation at strong (but not pain-inducing) intensities can cause sensitization in very young infants, while repeated painful procedures such as those required during intensive care can profoundly affect sensory processing in infants. Infants after surgery can develop a striking hypersensitivity to touch, as well as to pain.

While we do not know specifically how such injuries may affect the mature human pain system or influence adult pain perception, increasing attention is focused on the possible consequences of untreated pain, particularly in infants (Grunau 2000). For example, circumcised newborn infants display a stronger pain response to subsequent routine immunizations at 4 and 6 months compared to uncircumcised infants, but application of lidocaine-prilocaine anesthetic cream at circumcision attenuates the pain response to subsequent immunizations (Taddio et al. 1997). The results of behavioral studies in humans, like those from neurobiological studies in animals, indicate increased responsiveness to pain. Clinicians should appreciate that if an injury or medical procedure is noxious to adults, it will be noxious to infants (Porter et al. 1999).

A CHILD'S PAIN PERCEPTION: PLASTICITY AND COMPLEXITY

A child's pain perception can be regarded as plastic from a psychological, as well as biological, perspective. Tissue damage initiates a sequence of neural events that may lead to pain, but many developmental, social, and psychological factors can intervene to alter the sequence of nociceptive transmission and thereby modify a child's pain. Child characteristics, such as cognitive level, sex, gender, temperament, previous pain experience, family, and cultural background generally shape how children interpret and cope with pain (Katz et al. 1980; Blount et al. 1991; Bennett-Branson and Craig 1993; Schanberg et al. 1998; Peterson et al. 1999; Chen et al. 2000; Chambers et al. 2002).

Other factors vary dynamically, depending on the specific circumstances in which a child experiences pain. These situation-specific factors can be shortened to "what children and parents understand, what they (and health care staff) do, and how children and parents feel." Certain situational factors can intensify pain and distress, while others can eventually trigger pain episodes, prolong pain-related disability, or maintain the cycle of repeated pain episodes in recurrent pain syndrome (McGrath and Hillier 2001). Parents and health care providers can dramatically improve children's pain

experience and minimize their disability by modifying children's understanding of a situation, their focus of attention, their perceived control over the pain, their expectations for obtaining eventual recovery and pain relief, and the meaning or relevance of the pain (McGrath and Dade 2004).

Situational factors may affect children even more than adults. Adults typically have experienced a wide variety of pains of diverse etiology, intensity, and quality, providing them with a broad base of knowledge and coping behaviors. When adults encounter new pains, they evaluate them primarily from the context of their cumulative life experience. In contrast, children with more limited pain experience must evaluate new pains primarily from the context of the immediate circumstances.

Children's understanding of pain, pain-coping strategies, and the impact of pain increase with age (Gaffney and Dunne 1987), but many questions remain about the interplay of maturation, cognitive development, and experience in mediating a child's pain. Children's procedural pain generally decreases with age (Jay et al. 1983; Lander and Fowler-Kerry 1991; Goodenough et al. 1999), but the effect of age probably varies depending on the type of pain and the nature of the child's previous pain experiences—that is, positive experiences with similar painful situations (Dahlquist et al. 1986; Bijttebier and Vertommen 1998). For example, some studies show increasing postoperative pain with age (Bennett-Branson and Craig 1993), while others show decreasing pain or no age differences (Palermo and Drotar 1996).

Age, sex, and psychosocial factors are now recognized as important factors in the development of persistent pain and pain-related disability. Although the overall prevalence of pain increases with age, girls may be at greater risk than boys for developing certain types of persistent pain (Unruh and Campbell 1999). We do not yet know the specific prevalence of most types of chronic pain in children, but recent research is focusing on the epidemiology of childhood persistent pain to obtain age- and sex-related prevalence estimates, identify vulnerability and prognostic factors, and determine the long-term impact for children and their families.

PAIN ASSESSMENT: A MULTITUDE OF PAIN MEASURES FOR INFANTS AND CHILDREN

Pain assessment is an intrinsic component of pain management in infants and children. Clinicians need an objective measure of pain intensity and an understanding of the factors that cause or exacerbate pain for an individual child. Thus, extensive research has focused on designing pain

measures that are convenient to administer and whose resulting scores provide meaningful information about children's pain experiences. More than 60 pain measures are now available for infants, children, and adolescents (for review, see Champion et al. 1998; McGrath 1998; McGrath and Gillespie 2001; Stevens and Franck 2001). While no single pain measure is appropriate for all children and for all situations in which they experience pain, we should be able to evaluate pain for almost every child.

Physiological parameters including heart rate, respiration rate, blood pressure, palmar sweating, cortisol and cortisone levels, oxygen levels, vagal tone, and endorphin concentrations have been studied as potential pain measures. However, they reflect a complex and generalized stress response, rather than correlating with a particular pain level. As such, they may have more relevance as distress indices within a broader behavioral pain scale. Behavioral scales record the type and amount of pain-related behaviors children exhibit. Since a child's specific pain behaviors depend on the type of pain experienced, different scales are usually required for acute and persistent pain. Clinicians monitor children for a specified time period and then complete a checklist noting distress behaviors such as crying, grimacing, and guarding. Behavioral scales must be used for infants and children who are unable to communicate verbally. Recently, investigators are validating pain scales for children who are developmentally disabled (Breau et al. 2002; Terstegen et al. 2003). However, the resulting pain scores are indirect estimates of pain and do not always correlate with children's own pain ratings (Beyer et al. 1990). Even though clinicians may use diaries rather than formal scales, prospective evaluation of a child's behavior is an essential component of pain management, providing information about medication use, compliance with treatment recommendations, and the extent of pain-related disability (missed school attendance, physical activities, and social activities with peers).

Psychological or self-report measures include a broad spectrum of projective techniques, interviews, questionnaires, qualitative descriptive scales, and quantitative rating scales designed to capture the subjective experience of a child's pain. Since children's understanding and language depends on their cognitive level and previous pain experience, clinicians should communicate with children about pain using their own simple words. Most toddlers (approximately 2 years of age) can communicate the presence of pain, using concrete analogies and words learned from their parents to describe the sensations they feel when they hurt themselves. Gradually children learn to differentiate three basic levels of pain intensity—"a little," "some or medium," and "a lot."

By the age of five, most children can differentiate a wide range of pain intensities, and many can use simple ratio and interval pain scales (e.g., visual analogue scales, numerical scales, faces scales, and verbal descriptor scales) to rate their pain intensity. Many scales have excellent psychometric properties, are convenient to administer, are easy for children to understand, are adaptable to many clinical situations, and help parents to monitor their children's pain at home. Interviews, usually conducted independently with a child and his or her parents, are the cornerstone of assessment for children with persistent pain, enabling clinicians to identify relevant child, family, and situational factors that contribute to children's pain and disability problems (Varni et al. 1987; Savedra et al. 1993; McGrath and Hillier 2001).

CHILD-CENTERED CLINICAL MANAGEMENT: INTEGRATING DRUG AND NONDRUG THERAPIES

Anand and colleagues (1987) dramatically highlighted the adverse impact of untreated postoperative pain in 1987, when they revealed that premature infants undergoing surgery without adequate analgesic medication had significantly increased postsurgical morbidity and mortality in comparison to a group that had received fentanyl. The ensuing publicity as people learned that minimal anesthesia and analgesia represented "the norm in pediatric postoperative management," rather than the exception, sparked a revolution (for review, see Schechter et al. 2003). Amidst increased pressure from health care providers, public advocates, and distressed parents, clinical practice started to change so that children began to receive more appropriate analgesics in adequate doses and at regular dosing intervals. New interest was directed toward the pharmacokinetics and pharmacodynamics of conventional analgesics in infants and children, the development of pain-free transdermal and transmucosal drug delivery methods, the design of improved sedation regimens for children undergoing painful or aversive therapies, the feasibility of "child- and parent-controlled" analgesia, the use of adjunct analgesics for neuropathic pain, and a broader use of regional anesthetic techniques in pediatric medicine.

At the same time, increasing attention was focusing on the problem of undertreated procedural pain for children with cancer. Many children were incredibly anxious and distressed about scheduled lumbar punctures and bone marrow aspirations; despite receiving sedatives and local infiltrations, they experienced intense pain during these procedures. Clinicians designed versatile cognitive-behavioral programs, incorporating hypnosis, attention and distraction, and relaxation training, to help these children (Zeltzer and

LeBaron 1982; Hilgard and LeBaron 1984). Such child-centered programs incorporated proven psychological methods to target the specific child, family, and situational factors that were intensifying children's pain, anxiety, and distress, specifically helping children to understand the procedure and its significance and increasing their ability to control what would happen (McGrath 1990). Generally, as children received age-appropriate accurate information, gained realistic expectations, had more choices and control, and used independent pain control strategies, they had decreased pain and distress.

Today, counseling, distraction, guided imagery, hypnosis, relaxation training, biofeedback, and behavioral management are used routinely to treat a child's pain. Children seem more adept than adults at using psychological therapies, presumably because they are generally less biased than adults about their potential efficacy. Health care providers should teach children a few basic attention and distraction methods to reduce pain and guide families to recognize the particular circumstances that exacerbate pain and distress.

Pain control is not merely "drug versus nondrug therapy," but rather an integrated approach to reduce or block nociceptive activity by attenuating responses in peripheral afferents and central pathways, activating endogenous pain inhibitory systems, and modifying situational factors that exacerbate pain. As reviewed in other chapters, analgesics include acetaminophen, non-steroidal anti-inflammatory drugs, opioids, and adjuvant analgesics such as various anticonvulsants and tricyclic antidepressants. Adjuvant analgesics are the cornerstone of pain control for children with chronic pain, especially when the pain has a neuropathic component. Children with severe pain may require progressively higher and more frequent opioid doses due to drug tolerance and should receive the doses they need to relieve their pain (Collins and Weisman 2003). The fear of opioid addiction in children has been greatly exaggerated. Neonates and infants require the same three categories of analgesic drugs as older children. However, premature and full-term newborns show reduced clearance of most opioids. The differences in pharmacokinetics and pharmacodynamics among neonates, preterm infants, and full-term infants warrant special dosing considerations for infants and close monitoring when they receive opioids.

Pre-emptive analgesia is the key for managing acute pain from invasive medical procedures. Depending on the procedure, health care providers may choose psychological methods, anesthetic techniques, sedation, and analgesics (Kazak et al. 1998). Children's postoperative pain should be managed from a similar comprehensive perspective aimed to attenuate nociceptive responses from the surgical trauma (when possible) and to prevent pain throughout the recovery period. Children should receive adequate analgesic

prescriptions based on the severity of pain, and drugs should be administered at regular dosing intervals based on their duration of action so as to provide consistent pain relief and prevent breakthrough pain.

As in adults, children's chronic pain often has nociceptive and neuropathic components and requires a multimodal therapeutic regimen comprising pharmacological, physical, and psychological therapies. Most of the pharmacological management of neuropathic pain in children and adolescents is based on extrapolation from adult studies. While tricyclic antidepressants and gabapentin are well-established analgesics for neuropathic conditions in adults, evidence for their efficacy in children is very limited (Rusy et al. 2001). A child's chronic pain is influenced by environmental, family, and psychological factors, necessitating the integration of cognitive-behavioral therapies to mitigate some of the factors that intensify pain, distress, and disability. Strong and consistent evidence supports the efficacy of cognitive-behavioral interventions for relieving children's headache. However, the evidence base supporting use of such interventions for relieving other types of chronic pain is weak, as assessed by the number of controlled trials that have been conducted in children and by the few types of chronic pain that have been formally studied. Pediatric research is just beginning on many of the therapies regarded as complementary to traditional medical approaches, such as acupuncture (Zeltzer et al. 2002).

FUTURE CHALLENGES

As a result of extensive research during the past 30 years, we have gained better insights about how the developing nociceptive system responds to tissue injury, how children perceive pain, how we should assess pain in infants and children, and which drug and nondrug therapies will alleviate their pain. The emphasis has shifted gradually from an almost exclusively disease-centered focus—detecting and treating the putative source of tissue damage—to a more child-centered perspective, assessing the child with pain, identifying contributing psychological and contextual factors, and then targeting interventions accordingly. However, serious challenges remain.

We have discovered much about the plasticity of the developing nociceptive system, but we still have much to learn about how signals from painful stimuli are processed, especially at higher levels. Although we need further developmental research in neurobiology, neurophysiology, and pharmacology, we now know that infants seem particularly vulnerable because of their heightened responsivity to tissue injury and that we must devote particular attention to their pain management.

We need to apply the existing knowledge about pain assessment and pain management more consistently within our clinical practice. Regrettably, many hospitals still do not require consistent documentation of children's pain, preventing us from ensuring that children's pain is adequately controlled. Hospital administrators or accreditation organizations should establish children's pain control as a priority, as recently mandated by the Joint Commission on Accreditation of Healthcare Organizations for the United States. In spite of established analgesic dosing guidelines for infants and children, the undertreatment of postoperative and chronic pain is a continuing problem in many centers.

Moreover, increasing responsibility for evidence-based practice dictates that health care providers adopt clear guidelines for determining when treatments are effective and for identifying children for whom they are most effective. We lack data from well-designed cohort studies and randomized controlled trials to support the efficacy of many interventions (both drug and nondrug therapies) used extensively in clinical practice. Although cognitive-behavioral interventions are critical components of pain management programs for chronic pain, most of the data supporting their efficacy is derived from studies of childhood headache. As Eccleston and colleagues (2002) concluded, we urgently need well-designed studies of non-headache chronic pain in children and adolescents.

We critically need data on child-centered treatment efficacy—that is, when interventions are selected for individual children with pain, based on an assessment of the specific cognitive, behavioral, and emotional factors contributing to their pain and disability. We need longitudinal studies to identify key risk factors that influence a child's vulnerability to chronic pain, in particular the apparent increased vulnerability in females. Future studies should use brain-imaging technology and psychophysical measurement to evaluate the neural mechanisms underlying chronic pain and cognitive function in children. Our ultimate and continuing challenges are to better understand the experience of children's pain and to improve clinical practice, so that health care providers use the existing state-of-the-art pain scales, interpret children's pain scores to guide therapeutic decisions, and document treatment effectiveness.

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