More than 25 years have passed since the first reports were published of the inadequate treatment of children’s pain.\textsuperscript{1,2} Since then, even the youngest and most immature infant has been shown to be potentially in need of analgesia, improvements in the quality of pain treatment have been documented, and pain treatment services for children have been established.\textsuperscript{3-5} Researchers in many countries have also discovered much about the causes, mechanisms, and treatment of pain; much more is now known about the safe and effective management of pain in infants and children. However, bridging the gap between this knowledge and everyday clinical practice remains a major difficulty.\textsuperscript{6-8} Implementation of pain measurement for all children who are potentially in pain, application of effective up-to-date treatments, and improved research and education on the causes, prevention, and short-term and long-term effects of pain and analgesia remain important priorities.

Early research and teaching in pediatric pain management were largely directed toward identifying and allaying the undertreatment of acute pain in hospital settings. Particular emphasis was placed on pain in infancy, postoperative pain, and the pain of diagnostic and therapeutic procedures, often in ill patients in intensive care and in children with cancer. In recent years, there has been increasing awareness that children who are otherwise healthy at home may needlessly experience pain during minor illness or after surgery.\textsuperscript{9,10}

Pain and its treatment may have consequences beyond the normal period of recovery, and there is a substantial population of children who endure long-term pain and would benefit from access to better pain management.\textsuperscript{11}

This article describes the elements of contemporary pain-management practice in children, with particular emphasis on some of the areas in which there have been recent improvements in understanding or that remain particularly problematic. Future research studies and areas of practice in need of further development are suggested. Certain related fields, such as pediatric palliative care and symptom management, have not been specifically considered here.

Many changes have taken place in pediatric pain management since the undertreatment of children’s pain was first reported. Notable advances include an increase in understanding pain during development and improvements in the management of acute pain. Although much more about the safe and effective management of pain in children is now known, this knowledge has not been widely or effectively translated into routine clinical practice. Lack of suitable research on which to firmly establish evidence-based care is likely to have contributed to this situation. A subject of considerable interest recently is the discovery that the experience of pain in early life may lead to long-term consequences. New research findings from laboratory and clinical studies have clearly identified possible mechanisms and provided evidence that long-term behavioral changes can extend far beyond what would be considered the normal period of postinjury recovery. Timing, degree of injury, and administered analgesia and its nature may be important determinants of the long-term outcome of infant pain. Chronic pain, including neuropathic pain, is far more common in children than was thought. The assessment and treatment of this pain and its functional consequences present a considerable unmet challenge. There is a pressing need for further research and clinical development in the management of pain in children.
The Study of Pain in Children

If clinical practice is not guided by sound evidence, it is likely to become entrenched and empirical and is unlikely to progress and improve. The study of pain in children requires considerable ingenuity and innovation. The diversity and developmental range of the pediatric population have enormous implications for the design and conduct of clinical research and the interpretation of research findings.

There is a lack of comparable randomized controlled trials of children’s pain management, and consequently there are relatively few published meta-analyses or systematic reviews. Because of this low availability of data, recommendations are frequently not based on the highest possible levels of evidence.12-14 There are many reasons: difficulties in the measurement of pain, developmental differences that can confound comparisons between ages, important ethical and methodologic considerations in the conduct of clinical trials, and economic factors. There have been calls to improve this situation, and initiatives by the US Food and Drug Administration and other agencies have been helpful in encouraging the pharmaceutical industry to invest in the proper determination of efficacy, safety testing, and licensing of analgesics and other drugs for children.15,16 This is good news for newer treatments, but despite these efforts many analgesics that are most commonly used for infants and children remain unlikely to undergo this process and still need investigation.

Pain Measurement

Commonly used definitions of pain emphasize its personal sensory, emotional, and contextual nature, placing much reliance on an individual’s ability to express what he or she feels when in pain.17 Children, particularly those who are preverbal or with limited cognitive capability, are clearly disadvantaged by this approach. In a sustained effort to overcome this problem, an extensive body of literature about the measurement of pain in children has arisen. Quantification is central to the investigation of pain and analgesia, and pain measurement is essential in clinical practice.

Self-report, usually by using a linear visual analog scale, is regarded as the most reliable estimate of pain, but only children who have attained a certain degree of cognitive ability are able to provide information this way.18 Many self-report scales specifically designed to be easy for young children to understand and use have been developed; facial expression (either drawings or photographs representing increasing degrees of pain), color analog scales (a variant of the visual analog scale), and ordinal rating scales, eg, the Poker Chip Tool, are popular and have been used by children as young as 4 years.19-22 These scales are useful, but there are concerns about the sensitivity and specificity of such tools, particularly for younger children who may not report accurately or reproducibly and who may be influenced by how a scale is presented.23,24

When a self-report cannot be obtained or its validity is questionable, other more indirect measures must be used. Infants, preverbal children, and individuals with communication difficulties may be among the most vulnerable to unrecognized pain, and yet they are unable to describe or rate it. Behavioral observations, changes in physiologic characteristics, or combinations of these indirect measures are used, depending on the child, context of pain, and setting. A number of pain-related behaviors have been identified, facial expression being one of the most reproducible; however, this behavior is age related.25 Some physiologic measures, such as heart rate, are convenient and respond rapidly to brief nociceptive stimuli, but they are nonspecific. Generally, the utility of physiologic measures is diminished by homeostatic mechanisms, which tend to oppose such changes and reduce their value over time.

Scales may incorporate any of these types of measures, and many have been described, each with its own advantages and limitations; there are more than 20 validated for use in infancy alone, and to date, no individual tool has emerged as superior.26 The lack of a gold standard or universally reliable indicator by which to assess the accuracy of indirect pain measurement is an important limitation. Novel approaches may be required to obtain more specific information about the effects of injury and analgesia on the central nervous system (CNS). Quantitative sensory testing has been used in children able to cooperate and may be able to provide much-needed information.27 Sensory reflexes, such as the flexion withdrawal reflex or the abdominal skin reflex, have properties reflecting the sensory modulation of external stimuli in different pain states. The withdrawal reflex is sensitized (eg, the threshold for response is reduced) in neonates with local inflammation caused by repeated heel lance.28 The abdominal skin reflex has been shown to reflect CNS hypersensitivity after surgery and that caused by the visceral distention of chronic hydronephrosis in infants.29,30

Children with neurodevelopmental delay are a particularly important group at risk of experiencing undiagnosed or untreated acute and chronic pain.31,32 Many of these children have extreme impairment of communication and present enormous diagnostic and therapeutic problems.33 Pain assessment tools specifically designed for use in this group have recently been developed and are under investigation.34-35

Mechanisms of Pain in Development

The extent to which a newborn is able to detect and respond to a painful stimulus was once a critical question in pediatric medicine and the subject of considerable debate. The study of developmental neurobiology has clarified how sensory information is processed in early life and has begun to fully elucidate the mechanisms of the short-, medium-, and long-term effects of pain. Clear, measurable responses to noxious stimulation, which are suppressed by local anesthetics, opioids, and other drugs with known an-
algesic activity, can be observed from the earliest age. The stress response to pain is considerable at all ages, and the effects of pain on the immune system may also be important.36,37

The nervous system at birth displays a remarkable hypersensitivity to sensory stimuli in comparison with that of the adult. Thresholds of response to mechanical and thermal stimulation are reduced, and further sensitization can occur with sustained or repetitive inputs in the noxious and nonnoxious range, which is a manifestation of profound differences in pain processing between the immature and mature nervous system.38 Primary sensory neuron function, modulation of inputs by spinal and descending mechanisms, and the processes of central and peripheral sensitization undergo extensive postnatal reorganization and change to reach maturity. Such structural and functional changes in the peripheral nervous system and CNS involve alterations in expression, distribution, and function of receptors, ion channels, and neurotransmitters, of regulatory factors such as neurotrophins, and of intracellular regulatory proteins, all of which profoundly affect the character of nociceptive responses at different stages of development.39

The postnatal appearance of allodynia and hyperalgesia associated with tissue injury is superficially similar to that of the adult but differs in onset, pattern, and sensitivity to treatment; eg, inflammatory hypersensitivity in the early postnatal period is more sensitive to epidurally administered local anesthetic than later in development, and differences in opioid receptor distribution and function lead to altered, age-dependent, opioid analgesic effects.40,41

Central nervous system plasticity, including novel gene induction and altered synaptic excitability, is now well recognized as an important component of physiologic and pathologic pain states at all ages, and the effects of this plasticity on a developing nervous system that is already undergoing reorganization is considerable.42 Study of the underlying mechanisms and consequences of pain and analgesia in development is currently a particularly exciting and important field of neurobiology. An understanding of these events is essential for effective analgesic intervention and the discovery of new targets for therapies.

Prolonged Effects of Early Pain Experience

Pain and its management, especially in infancy, may have consequences for later pain-related behavior and perception.43-45 Studies in infants having repeated heel lance have shown behavioral and other effects that outlast the painful stimulus by hours or days.46-50 Local anesthesia modified the development of sensitivity in 1 study.51 More long-term differences (months) in subsequent pain behavior between infants who had circumcision as neonates with and without analgesia have also been reported.51 A recent study found that major surgery in the neonatal period, in this case with effective postoperative analgesia, had little effect on subsequent pain response in infancy.52

Laboratory studies in animal models have shown that it is quite possible to induce long-term behavioral and CNS effects from early injury, which persist into adulthood. In the rat, wounding of the skin at birth leads to a number of changes in the skin and CNS that do not occur with similar wounds in adults, including local hyperinnervation and prolonged mechanical sensitivity for some time after healing.53 In humans, repeated needle prick in the neonatal period causes complex and persistent behavioral effects later, including reduced pain thresholds. More severe injury in the form of inflammation is capable of permanent alterations in sensory processing; some, but not all, of these effects appear to be modified by analgesia.54-56 The clinical significance of such findings remains unclear, so further study is required.

Acute Pain

Multimodal therapy is the mainstay of acute pain treatment. It may involve pharmacologic and nonpharmacologic methods and should take place in a child-friendly environment. Severe pain should never go untreated. Safe protocols have been devised for the use of potent opioid analgesia, and experience with analgesic use in children is now extensive.57 Pharmacotherapy for pediatric pain has been well reviewed recently.58,59 Techniques such as patient-controlled analgesia can be used for children older than 3 years, and nurse-controlled morphine infusions that allow more flexibility in administering analgesia are common for those too young to use patient-controlled analgesia.56

Local anesthesia in many forms has also become routine; topical preparations (lidocaine-prilocaine or amethocaine) are the mainstay of procedural pain management, and local nerve blocks and epidural analgesia are used extensively for perioperative pain.57,58 Early studies of epidural analgesia have confirmed the cardiovascular safety and efficacy of the technique for postoperative pain and reduction of the stress response to surgery, but its place in the practice of pediatric pain management is still not clearly established.59,60

Although newer local anesthetic drugs are now available, bupivacaine remains frequently used; however, either L-bupivacaine or ropivacaine may be a more sensible choice when toxicity is a particular concern.61 Agents new to acute pain treatment and with novel mechanisms of action, such as ketamine and clonidine, are being used systemically and epidurally.62-64 The appropriate use of many, more established agents such as acetaminophen and codeine is being updated and refined.65,66 The management of acute procedural pain often includes the use of cognitive-behavioral strategies: distraction, guided imagery, and hypnosis by trained practitioners. Intuitively, these approaches are helpful and are generally liked by children, many of whom respond positively.67 For infants and younger children, comfort measures such as cuddling, swaddling, auditory and tactile stimulation, and sucking may reduce behavioral and physiologic responses to acute pain.68-70 They
are not regarded as a substitute for analgesia but are generally easy to implement and can be particularly effective at reducing the unpleasantness and distress of painful events.

Parents are increasingly recognized as important participants in pain management in hospital settings and as primary caregivers at home.\textsuperscript{71} Parents may underestimate and undertreat pain, a particular concern because outpatient surgery is prevalent.\textsuperscript{10,72,73} Pain assessment tools for use by parents have been designed to help parents recognize pain and guide pain management. Better communication with parents can improve subsequent pain management.\textsuperscript{74,75}

**Chronic Pain**

Chronic or recurrent pain affects a large number of children, girls more often than boys. Epidemiologic studies suggest that many children do not receive appropriate help or treatment.\textsuperscript{51,76-78} The underlying causes of childhood chronic pain and the emotional, social, health, and economic impact on an individual and on society have been insufficiently studied.\textsuperscript{79} Recurrent abdominal pain, for example, can lead to physical and emotional disability in later life. Little is known of its mechanisms or the effects of treatments on long-term outcomes.\textsuperscript{80-83} Recurrent headache is common among adolescents; chronic musculoskeletal pain is also increasingly diagnosed, as are other so-called idiopathic pain syndromes. Some patients respond to reassurance and treatment with simple analgesics, but a significant proportion go on to develop various degrees of chronicity and disability that are difficult to treat.\textsuperscript{84,85}

Neuropathic pain, ie, pain caused by abnormal functioning of the nervous system, may also have been underrecognized; reflex sympathetic dystrophy or chronic regional pain syndrome was thought to be rare in children until reports started to appear in the 1980s, and it is now much more frequently diagnosed.\textsuperscript{86,87} Unintentional injuries, surgery including amputation, tumor, metabolic disorders, toxic neuropathies, and neurodegenerative disorders leading to nerve damage or disordered function are some of the recognized sources of neuropathic pain in children.\textsuperscript{88} Treatment of neuropathic pain is often unsatisfactory, and in common with other childhood chronic pain syndromes, there is evidence that the best results are obtained by combining psychologic, physical, and pharmacologic treatments.\textsuperscript{89-91}

Chronic pain management services, some with inpatient treatment and rehabilitation programs, have been developed in several pediatric centers around the world. Such programs typically involve clinicians who have pain management skills and are from a number of disciplines; they provide direct patient treatment and serve as practical and educational resources to others. Examples of patients with underlying disease who may also benefit from this multispecialist approach to pain management include some cancer patients and those with juvenile rheumatoid arthritis, sickle cell disease, or epidermolysis bullosa.\textsuperscript{78,92-94} The assessment and treatment of such patients should place particular emphasis on restoration of function and improvements in the quality of life, in addition to control of pain intensity.\textsuperscript{95}

**Future Research and Developments**

Clearly, there is enormous potential for future research and a pressing need for further clinical development in the field of pediatric pain. The neurophysiology of infant pain has been little studied in the human, and many important questions about basic functions remain unanswered. The mechanisms of nociceptive and neuropathic pain in development are far less well understood than in the adult, and considerable research effort will be required to redress this imbalance. The circumstances in which injury can lead to long-term consequences, which is likely to be different from those of the adult and to depend on the stage of development at which it occurs, the nature of those consequences, and whether they can be prevented or modified by treatment are important clinical issues yet to be resolved.

Treatment itself may also have positive or negative long-term effects on the developing nervous system; again, further study is needed. Only close collaborations between clinicians and scientists are likely to be able to provide the means to answer these questions.

The design of clinical trials in infants and children needs more careful consideration. Many studies have not paid sufficient attention to developmental influences, eg, infants and teenagers are often included in the same study group. Strategies for the assessment of efficacy in research studies should be more standardized, and the adoption of a common scale of values for pain assessment tools would be helpful.\textsuperscript{96} More attention should also be paid to assessment of the sensitivity of an individual tool to detect the desired outcome within each trial. More easily comparable and appropriate outcome measures, such as restoration of function, are needed to assess the clinical efficacy and value of many treatments currently in use and with which to make comparisons with new treatments. Novel approaches to pain management and assessment, particularly for children with long-term pain, should be carefully evaluated, and the use of more established but less conventional pain management techniques, such as massage or acupuncture, also needs further exploration.

In the clinical arena, regulatory changes by authorities such as the Joint Commission on Accreditation of Healthcare Organizations, by leading to the widespread adoption of minimum care standards, are likely also to lead to evidence of positive changes in routine practice.\textsuperscript{97} Such initiatives may also encourage more exploration of the best methods to achieve the basic but often elusive objective of more effective pain control. The implementation of good pain management practices would also be improved by further and better demonstration of the value of frequent pain assessments and of the benefit of better and more appropriate prescribing in reducing pain. The role and structure of pain treatment services should be...
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more carefully examined and modified to help provide the highest possible standard of pain care for all patients. Many children have benefited from the recent substantial improvements in the understanding and treatment of pain; however, there may be many more children whose pain goes unnoticed or is poorly understood and therefore inadequately treated. All such children must have access to appropriate and contemporary pain management based on the best possible evidence.

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REFERENCES

40. Gauvreau E, Dalens B, Gombert A. Epidemiology and morbidity of regional anesthesia in children: a one-

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tivity. On the other hand, glucocorticoids have a direct inhibitory effect on adiponectin secretion and expression. Similarly, resistin concentration is known to increase in response to glucocorticoids and to decrease in response to TNF-α. The complex nature of these various mechanisms could be clarified by studying patients with RA who had not been treated with glucocorticoids.

The authors also reported that adiponectin levels in synovial fluid were positively, although not quite significantly, related to body mass index (BMI). If synovial concentrations of adiponectins reflect plasma concentrations, then this is a surprising finding, as there appears to be a strong negative correlation between plasma adiponectin concentrations and measures of obesity. Moreover, plasma adiponectin concentrations are substantially lower in men than in women, necessitating further adjustment for sex. The lower degree of adiposity among patients with RA may therefore represent an alternative explanation for the higher synovial adiponectin concentrations in these individuals.

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In Reply: Dr Stefan and colleagues suggest that corticosteroids might influence the levels of adipocytokines. Although this is a possibility, none of our patients with OA were receiving corticosteroids or other immunosuppressive therapy. Furthermore, in the subgroup of patients with RA, partial correlation analysis did not show any correlation between adipocytokines and concomitant medication. In addition, none of the patients with RA were receiving TNF-α inhibitors.

We disagree with the suggestion of Stefan et al that our study found a nonnegative association between BMI and either adiponectin or resistin. As expected, patients with OA had significantly higher BMI than patients with RA. However, as mentioned in our article, partial correlation analysis revealed nonsignificant correlations between BMI and concentrations of adiponectin (r=0.246, P = .08) and resistin (r = 0.245, P = .07).

We also doubt their speculation that serum levels reflect synovial fluid levels of inflammatory arthritides such as RA. There is no evidence in the literature for an “overspill” phenomenon between serum and synovial adipocytokines. In contrast, among patients with RA, synovial concentrations of numerous cytokines are clearly elevated compared with serum. Our ongoing studies have found that both adiponectin mRNA and protein are strongly expressed not only in synovial adipocytes but also in activated synovial fibroblasts. Therefore, the absence of any correlation between synovial fluid adipocytokines and BMI is not unexpected, as synovial adipocytokines are probably produced locally, perhaps from activated synovial cells, rather than systemically from body fat stores. Our data suggest that the increased levels of adipocytokines in synovial fluid in patients with active RA are largely derived from activated resident synovial cells.

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CORRECTION

Incorrect Insertion: In the Special Communication entitled “Current Status of Pain Management in Children” published in the November 12, 2003, issue of The Journal of the American Medical Association (JAMA), page 2466 in the second paragraph under “Prolonged Effects of Early Pain Experience,” the third sentence should not begin with the words “In humans” because the paragraph is discussing laboratory studies in animal models.