

Anesthesiology  
82:779-784, 1995  
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## “In the Present State of Our Knowledge”

### Early Use of Opioids in Obstetrics

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In the present state of our knowledge upon this point, no reflecting practitioner can use opium with decision and satisfaction.

**William Tyler Smith, 1849**

*Principles and Practice of Obstetrics*, p 213

HAD they wished to do so, physicians could have relieved labor pain long before 1847. They had the means: opium had been used for centuries for management of many medical problems. By 1809, Sertürner had isolated two of its active components, morphine and codeine, thereby making available more stable and predictable preparations.<sup>1</sup> They also had the experience: physicians used opium and morphine for treatment of disease problems ranging from smallpox, dementia, and cough, to sciatica, diabetes, and colic.<sup>2-6</sup> In particular, they gave it for pain. As one pharmacologist said, “*Pain always indicates morphia.*”<sup>7</sup> The Scottish obstetrician, James Young Simpson, who first suggested anesthesia for childbirth, even speaks of this.<sup>8</sup> Despite this, neither he nor most other obstetricians mention using opioids for a normal delivery.<sup>9-21</sup> Some even advised *against* it.<sup>22-25</sup>

An explanation for the therapeutic lapse might lie in early perceptions of pain and its significance.<sup>26</sup> Before the 19th century, many people believed that disease and suffering, including labor pain, were normal and unavoidable components of daily life. After 1800, however, this attitude changed. With confidence in their power to improve life, Western Europeans em-

barked upon extensive social, political, and technical reform to eliminate pain and suffering from human experience. For many, the discovery of the anesthetic properties of ether in 1846 signified the beginning of a new era. A famous American physician of this period wrote, “It is, indeed, possible to eliminate all pain.”<sup>27</sup> Thus, for many, 1846 marked a turning point in the history of medicine.

The zeal to eliminate pain and suffering included that associated with childbirth. In 1847, James Young Simpson discovered the anesthetic properties of chloroform and began to popularize its use for labor.<sup>28</sup> Within a few years, pain relief for childbirth became standard and was the subject of many medical publications. For example, of the 104 anesthesia references cited in a medical bibliography published in 1878, 33 mention an obstetric application in their titles.<sup>29</sup> Obstetricians sometimes argued the merits of different anesthetic agents or debated the circumstances in which they should be used, but after 1855, no reputable authority suggested anesthesia should not be used for pain associated with a normal delivery.<sup>28</sup> Some, bold enough to include chloroform, nitrous oxide, methylene chloride, carbon tetrachloride, salicylic acid, cocainization of the cervix, spinal anesthesia, and hypnotism among their recommended methods, advised *against* opioids.<sup>9,30</sup> Given the propensity of Victorians to abolish suffering, to experiment with new medications, to treat labor pain, and to use opioids for a variety of other conditions, their failure to recommend opioids for normal labor becomes even more perplexing. A review of 19th century medical literature suggests that they had many reasons, derived from clinical experience and theory.

### Opioids and Twilight Sleep

#### *Reactions of Physicians*

Opioids only became part of normal labor management after the introduction of twilight sleep in 1902.

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Received from the Departments of Anesthesiology and Obstetrics and Gynecology, University of Florida College of Medicine, Gainesville, Florida. Submitted for publication July 5, 1994. Accepted for publication November 23, 1994. Supported in part by a Research Travel Grant from the Burroughs Wellcome Fund.

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This method consisted of an injection of morphine and scopolamine. Originally used for surgery, von Steinbüchel, of Graz, Austria, adapted twilight sleep for obstetrics.<sup>31</sup> It remained for another obstetrician, Gauss, of Freiburg, Germany, to popularize the method through public lectures and publications.<sup>32</sup> Gauss was very cautious with his opioid dosages, recommending no more than 10 mg morphine for an entire labor. He administered scopolamine as needed, depending on the patient's response to a "memory test." In this way, twilight sleep, which included morphine, became popular for obstetrics, whereas opium or morphine alone had not.

Despite Gauss's enthusiasm for twilight sleep, obstetricians remained skeptical. J. Whitridge Williams, an influential professor of obstetrics at Johns Hopkins, mentioned the method in two early editions of his textbook (1908 and 1912) but warned that it often was associated with problems. Though he admitted he had no personal experience with the technique, he did not hesitate to write that he did not consider it to be a "suitable technique for private practice."<sup>33</sup> Joseph DeLee, no less influential than Williams, mentioned twilight sleep in the 1918 edition of his textbook (he traveled to Gauss's clinic to observe its use), but he noted "unsatisfactory results in 10 of 10 cases."<sup>34</sup> Similar warnings appeared in other clinical texts; all agreed that inhalation agents gave safer and better results.

Twilight sleep fared no better in pharmacologic circles. As late as 1923, Whitla omitted childbirth from his list of therapeutic indications for opioids.<sup>35</sup> Cushny mentioned twilight sleep in the 1915 edition of his text,<sup>36</sup> but not until 1928 did he specifically mention childbirth as an indication.<sup>37</sup> Textbooks published as late as 1947 continued to warn that it be used with "great caution."<sup>38,39</sup>

Eventually, physicians accepted twilight sleep<sup>40,41</sup> but only on the insistence of their patients. In 1923, Williams also finally mentions trying twilight sleep, but then adds, somewhat acerbically, "Following a magazine and newspaper campaign in 1914 a great interest in the procedure was aroused among the laity, and obstetricians all over the country were constrained to experiment with the method, and a large number of publications of varying value have been made concerning it."<sup>42</sup>

#### Reactions of Patients

The "great interest . . . among the laity" that Williams disparaged was, in fact, a well organized public campaign.<sup>43-46</sup> Women harbored none of the doubts

expressed by physicians. They embraced twilight sleep with the same eagerness that they had accepted inhalation anesthesia half a century earlier.<sup>28</sup> Many traveled to Freiburg just to deliver their child in Gauss's clinic. Several Americans, who were especially pleased, returned with the conviction that all women should have access to twilight sleep. Advocates formed the "National Twilight Sleep Association," and, with the backing of popular magazines, such as *McClure's*, helped promote the technique by staging rallies in department stores, distributing pamphlets, and writing articles for the press. Proponents criticized physicians for their reluctance to use the method, their timidity, and their insensitivity to the plight of laboring women. Such sentiments even appeared in editorials in *The New York Times*.<sup>46</sup> The campaign lost some momentum after 1914, when Mrs. Frances X. Carmody, an ardent and prominent supporter, died in childbirth, even though her physicians assured the public that her death was unrelated to the morphine and scopolamine that she had received for her delivery.

Historians, particularly those interested in social issues, cite twilight sleep as an early example of a struggle between patients and physicians for the "power" to shape medical practice.<sup>44,45</sup> In this they identify an important medical and social issue, but their treatment of the problem sometimes overstates the issue. Those physicians who wrote about the use of opium, morphine, and twilight sleep for obstetrics address problems of safety and efficacy, not issues of "power" or "control." With this in mind, let us consider the experience that led physicians to oppose twilight sleep for labor.

#### Nature of Medical Objections

Williams believed that twilight sleep would cause three problems: stop contractions, unduly affect the child, and fail to provide satisfactory pain relief.<sup>35</sup> Ironically, the first two reasons resemble objections that physicians raised half a century earlier when Simpson suggested using ether for labor pain.<sup>28</sup> In one important respect, however, the situation differed. Simpson suggested diethyl ether and chloroform at a time when no one had experience with the obstetric use of these drugs. In contrast, when Gauss suggested twilight sleep, physicians had several centuries of experience with opioids. Consider what they knew.

#### Concerning Opioids and Labor

Williams' statement that opioids adversely affect labor agreed with long-standing clinical theory and practice.

For centuries, physicians had used opium for a variety of conditions associated with smooth muscle spasm and abdominal pain, for example, cholera, typhus, and renal stones.<sup>2-7</sup> They knew that it abolished the pain and diminished bowel function. From this, they reasoned that opium and morphine stopped the pain because it had stopped the smooth muscle contractions. In other words, they appear to have confused the management of pain with treatment of the condition that caused it.

Physicians sometimes used opioids for obstetrics, but they reserved them for special problems. For example, some recommended opioids for primiparous patients with an especially long and difficult labor, for women with a contracted pelvis, or for patients with "hyperexcitable nervous system" (puerperal convulsions).<sup>47-51</sup> In particular, physicians used opioids when they wanted to stop uterine contractions. Accordingly, among the indications they included<sup>18,21,22,49,51</sup>:

1. abortion or preterm labor;
2. *rigid os*: hard contractions without cervical dilatation, *i.e.*, in modern terms, failure to progress or dysfunctional labor;
3. ruptured uterus: after delivery of the child with the idea that an "inactive uterus," during this time, gave the woman the best chance for recovery (remember this treatment preceded anesthesia and surgical repair);
4. severe afterbirth pains; and
5. to "turn the child": an internal version.

It is important to note that several of the aforementioned indications conform to current practice. For instance, we recognize that an opioid, or any other sedative, given early in labor, may stop it and that there are times when it is advantageous to do so. On the other hand, we now know that an opioid, given during the active phase does *not* stop labor. This marks a significant change from early practice. In fairness, we must note that early obstetricians did not distinguish "active" and "latent" phases of labor as we do now.

Early physicians appear to have confused the issue by being imprecise with their use of the words "pain" and "contraction." Ramsbotham, for example, described uterine pain as "the external manifestation of the force of the contraction."<sup>51</sup> He said, quite specifically, that he freely substitutes one word for the other and he believes that others do, too. It is easy to see how this may have led them to believe that any drug that diminishes pain has a corresponding effect on contractions. The interdependency offered no problem to

physicians treating cholera; they sought to diminish both peristalsis and pain. Moreover, they knew that constipation was a frequent problem associated with opioid therapy. On the other hand, the putative effects of opioids on uterine smooth muscle did constitute a significant problem; they knew that labor stopped without contractions, and they assumed that contractions stopped when the pain stopped.

Clinical teaching agreed with prevailing pharmacology and physiology theory. Pharmacologists believed that opioids worked primarily on the nervous system, depressing all of its components: the brain and brain stem, spinal cord, sensory nerves, and, if given in very large doses, even motor nerves. Some authors speculated about direct effects of opioids on end organs, but most authorities discounted this idea.<sup>2-6,52</sup> Depression of neurologic function, whether by morphine or any other drug, was a point of some concern because scientists and clinicians believed the central nervous system to be the dominant, if not the sole, regulatory mechanism of body function. This line of investigation ran throughout the 1800s and reached an apogee in 1906 with the publication of Sir Charles Sherrington's book, *The Integrative Action of the Nervous System*, which describes the work that won him a Nobel Prize.<sup>53</sup> To many, the regulation of respiration, well studied by 1900, represented a model for the regulation of other physiologic processes, including parturition. W. H. Howell, professor of physiology at Johns Hopkins, believed this,<sup>54</sup> and so did Michael Foster, of Cambridge University, founder of one of the most influential schools of physiology in the 1800s. Foster wrote, "The whole process of parturition may be broadly considered as a reflex act."<sup>55</sup>

Obstetricians, like physiologists, also believed parturition to be a "reflex act." As early as 1849, one popular textbook<sup>25</sup> includes a long discussion of neurologic mechanisms that initiate and sustain labor. Early editions of Williams' textbook contain similar material, even to the point of including an extensive description of supportive experimental data.<sup>30,33</sup> Williams, influenced perhaps by his Johns Hopkins colleague, Howell, placed the primary control of parturition in the brain stem, which he believed might be activated by a variety of stimuli including anemia and stress. Cognizant of clinical and experimental observations of spontaneous labor after spinal cord transection,<sup>56</sup> he postulated a second center in the lumbar cord and speculated that nerves "intrinsic to the uterus" might have a regulatory function. In support of these data, he pointed to clinical observations of reflex uterine contractions that occur

with suckling or with dilatation of the vagina. Given its pivotal role in the initiation and regulation of parturition, clinicians argued that any drugs that depress the central nervous system also will stop labor. Hence their reluctance to use opioids.

It should be noted that not everyone agreed with Williams' theory. In 1869, P. C. Barker, a New Jersey obstetrician, published a paper based on his experience with several patients. He suggested that opioids might be used as "parturient agents," *i.e.*, uterine stimulants.<sup>57</sup> Possibly his interest reflects an earlier debate in pharmacology about the mechanism of action of opioids, whether they acted primarily as central nervous stimulants or depressants.<sup>2,25</sup> Although the issue had not been resolved conclusively, opinion favored the latter.<sup>3-6</sup> A few years later, a German obstetrician measured the intrauterine pressure of laboring women with a balloon apparatus and a recording on a kymograph drum. He observed no effect on labor when he gave morphine. His paper, however, had no discernible effect on clinical opinion.<sup>58</sup>

In retrospect, it is interesting to see how tenaciously obstetricians clung to the idea that the nervous system initiates and sustains labor. Remember, however, that they formulated their ideas before anyone knew about hormones (Starling only coined the term in 1905) and before anyone had isolated estrogens, progesterone, oxytocin, or prostaglandins, much less demonstrated their role in parturition. Only during the past few decades have physiologists started to understand the complex interactions between neural and endocrine regulation of the events of pregnancy. Given the level of understanding of physiologic mechanisms in 1920, it is easy to understand the reluctance of physicians to use opioids.

#### *Concerning the Neonate*

Because physicians seldom gave opioids for normal labor, they had relatively little experience to help them predict effects of morphine or of twilight sleep on the neonate. They did have several reasons for concern, however. Physicians already knew that drugs given to the mother might affect the child. They first argued this point when Simpson suggested using ether for parturients.<sup>28</sup> In fact, John Snow, the physician who anesthetized Queen Victoria for her last two deliveries, said that drugs must cross the placenta because the newborns look lethargic after delivery.<sup>59</sup> Many questioned the significance of this observation until Paul Zweifel, a Swiss obstetrician, demonstrated chloroform in the urine and blood of newborn infants, even after a short

exposure. From then on, physicians acknowledged the rapidity of placental transfer of drugs, although many continued to doubt the clinical significance of the phenomenon.<sup>60</sup>

During the last decades of the 1800s, a social problem surfaced, which redirected attention to the issue of placental transport. In Great Britain and the United States, health officials noted an increasing incidence of drug addiction.<sup>61,62</sup> Coincidentally, obstetricians reported sporadic but disturbing problems: fetal death after the mother had ingested a large dose of opioids, lethargic children delivered by addicted women, hyperactive fetuses after the mother tried to reduce her daily intake of opioid, and infants exhibiting signs of opioid withdrawal within hours of delivery.<sup>63-66</sup> Within a short time, obstetricians began to suspect a causal relationship between maternal addiction and these fetal and neonatal problems.

The introduction of injectable drugs after 1862 aroused more concern.<sup>67</sup> The ease, novelty, and efficacy of injectable morphine for labor stimulated physicians to try it in a wide variety of situations. By 1877, enough obstetricians had tried it for patients in labor to warrant public discussion. One debate extended over several meetings of the New York Obstetrical Society.<sup>65,66</sup> Some participants claimed that morphine injection had no ill effects on the child. Others, however, reported neonatal asphyxia, apnea, lethargy, somnolence, and inability to nurse, which in some cases persisted for several days postpartum. Coincidentally, pharmacology textbooks warned about the greater sensitivity of neonates and children to opioids.<sup>38,39,52</sup> One book states, "In nursing mothers, morphine is apt to be excreted in the milk and will narcotize the child . . . children in utero are also influenced. In all these instances care is necessary."<sup>68</sup>

The initial experience with twilight sleep after 1910 did not allay fears. Despite the small dose of morphine recommended by Gauss, no more than a total of 10 mg for labor,<sup>32</sup> obstetricians expressed concern. DeLee, for example, cited neonatal "narcosis and asphyxia" among the problems that he observed in Gauss's clinic.<sup>34</sup> Cook-Hirst reported a similar experience.<sup>16</sup> Pharmacology textbooks repeat the theme. To be sure, after 1910, more physicians described a satisfactory outcome.<sup>69</sup> The preponderance of early evidence, however, spoke to the contrary.

#### *Concerning the Efficacy of Treatment*

The third issue that Williams raised was the efficacy of twilight sleep. He said that the results were "incon-

sistent," a reasonable observation considering both the small amounts of morphine used initially and the nature of twilight sleep. Opioid doses were inadequate to prevent patients screaming from pain, and scopolamine simply made them amnesic for the experience. Because family members were not present to observe the labor, there was no one to observe the real response. Moreover, physicians knew that *safe* doses of opioids would not give the same relief from pain that they could obtain so easily with ether or with chloroform. Twilight sleep must have seemed a poor substitute. Perhaps they became more tolerant when they realized that the "consumers" were satisfied.<sup>43</sup> It is noteworthy that, after 1920, physicians gradually increased the amounts of morphine that they gave during labor, greatly exceeding limits originally proposed by Gauss. In addition, they began to combine twilight sleep with other forms of anesthesia.<sup>70</sup>

## Summary

In retrospect, physicians responded to the use of twilight sleep in a predictable and appropriate way. Clinical experience and theory led them to expect deleterious effects on labor and the neonate. Moreover, they could see readily that opioids could not provide patients the analgesia that they had come to expect from ether or chloroform. In this context, it seems predictable that physicians would reject the method.

It is more intriguing to ask why, even as physicians continued to reject the use of opioids, they persisted in using inhalation anesthesia. The two most favored inhalation agents, ether and chloroform, caused the problems that physicians feared from opioids. Was it inexperience, naivete, or the novelty of having inhalation anesthesia? Regardless, it is quite clear that, in 1847, as in 1910, patients eventually forced physicians to adopt each new method into practice. Herein may lie an important lesson.

Throughout the last half of the 19th century, women said they did not want to experience pain associated with labor. Certainly this reflects a general attitude toward pain and suffering prevalent throughout Western Europe and the United States during this time. Physicians knew that they could abolish the pain but said this involved medical risks, which they did not feel were warranted. They based this opinion both on theory and experience. In effect, the issue became a confrontation between patients' expectations of physicians and the physicians' attempt to adhere to principles of clinical science. The confrontation occurred as physicians

struggled to establish a scientific basis for their practice. Patients prevailed, and physicians found ways to accommodate them. The compromise, however, had long-reaching effects. Physicians modified the conservative limits on opioid medication for laboring women. More than a generation passed before patients and physicians recognized this change and the problems that it caused.

The author thanks C. Lawrence and S. Bragg, of the Wellcome Institute for the History of Medicine, London, for their assistance.

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