

# History of the Development and Evolution of Local Anesthesia Since the Coca Leaf

Jesús Calatayud, M.D., D.D.S., Ph.D.,\* Ángel González, M.D., D.D.S., Ph.D.†

THE development of anesthesia in general and local anesthetics, in particular, required a cultural change. The concept of pain (especially obstetric pain) was linked to the concept of original sin, and the ability to endure pain was regarded as a sign of character and, in men, was even associated with virility.<sup>1</sup>

The change that took place in Western Europe between 1750 and 1850, encompassing the industrialization, progressive humanization, and democratization of society, created an atmosphere favorable to the discovery of anesthetics. Nothing comparable occurred in Asia, Russia, or the Islamic countries, where feudalism persisted in a variety of forms. This general process altered the cultural, political, and religious climate, affecting a significant number of individuals.<sup>1</sup>

Dentists, not doctors, were responsible for the discovery of anesthesia, given their close day-to-day contact with pain and, hence, their motivation to seek the means to alleviate it.<sup>1</sup> Doctors focused more on infections than pain because people were dying of pneumonia, diphtheria, gangrene, tuberculosis, tetanus, puerperal fever, and so on.<sup>1,2</sup> It was two dentists, then, who first introduced anesthesia: Horace Wells (1815-1848), with nitrous oxide in 1844,<sup>3-5</sup> and William Thomas Green Morton (1819-1868), with ether in 1846.<sup>6</sup>

Local anesthesia, the basis of modern local anesthetics for dentistry and medicine, developed later. This article reviews the discovery and evolution of local anesthesia from the Spanish discovery of the coca leaf in America, outlining certain ill-known aspects of this early period.

## The Coca Leaf

Coca leaves are taken from a shrub of the genus *Erythroxylum*, a member of the Erythroxylaceae family, so named by Patricio Browne because of the reddish hue of the wood of the main species.<sup>7</sup> Of the various species in this genus, *Erythroxylum coca* contains the highest concentration of the alkaloid known as cocaine in its leaves,

up to 0.7-1.8% by weight.<sup>8,9</sup> Many species of this genus have been grown in Nicaragua, Venezuela, Bolivia, and Peru since pre-Columbian times.<sup>7</sup>

The earliest cultivation and use of the coca leaf in the Bolivian and Andean region date back to 700 B.C.,<sup>7</sup> though recent discoveries in Ecuador indicate human use more than 5,000 years ago.<sup>9</sup> Alfred Bühler hypothesized that the Arhuaco, a tribe from the Negro River region, were the first to discover the properties of the drug and spread this knowledge to other neighboring peoples.<sup>10</sup>

Further, according to Bühler, the first written record of the coca leaf is a mention by the Spanish Dominican friar Tomas Ortiz in 1499,<sup>11</sup> a reference which is also cited by other authors.<sup>12,13</sup> This is, however, incorrect. A recent review of documents on Friar Tomas Ortiz (1470-1538)<sup>14</sup> show that he was ordained in the Convent of San Esteban in Salamanca, Spain, in 1511, and it was only later that he set out for America, where he eventually became bishop of Santa Marta (Colombia).<sup>14-16</sup>

For some writers, Florentine Amerigo Vespucci (1451-1512) was the first European to document the human use of the coca leaf.<sup>9,14</sup> Thus, in his account of his voyage to America on the second Alonso de Ojeda and Juan de la Cosa expedition in 1499-1500,<sup>17</sup> he reported that the aborigines of the Island of Margarita chewed certain herbs containing a white powder. He included this observation in a letter written in Lisbon, Portugal, in 1504, sent to the Chief Magistrate (*Gonfaloniero Perpetuo*) of the Florentine Republic, Piero Soderini, and possibly published in Florence in 1505 or 1506.<sup>14,17</sup> Nevertheless, Vespucci's documents are partially or largely questionable and open to doubt and investigation,<sup>14,18</sup> and because his book contains no reference to the printer, year, or place, all of these facts are little better than educated guesses<sup>14,17</sup> and are regarded as not wholly reliable by many historians.

Among sixteenth century Spanish chroniclers, the appearance of coca is associated with Francisco Pizarro's (1475-1541) conquest of the Inca or Tawantinsuyo empire in 1532. It is interesting to note that the early chroniclers make no mention of the plant. Thus, the document known as the "anónimo," dated in Seville in 1534 (probably written by Cristóbal Mena, one of Pizarro's captains)<sup>19</sup> or the chronicle of Francisco de Xerez (1497-1565),<sup>20</sup> Francisco Pizarro's secretary during the conquest, contain no reference to coca. Neither of the two editions of the *Historia General de las Indias*, the one dated in 1535 in Seville<sup>21</sup> or the Salamanca edition<sup>22</sup> dated in 1547 by Gonzalo Fernández de Oviedo

\* Professor in Pediatric Dentistry, † Professor in Preventive Dentistry.

Received from the Departamento de Profilaxis, Odontopediatría y Ortodoncia, Facultad de Odontología, Universidad Complutense de Madrid, Madrid, Spain. Submitted for publication January 24, 2002. Accepted for publication November 13, 2002. Supported by the Departamento de Profilaxis, Odontopediatría y Ortodoncia, Facultad de Odontología, Universidad Complutense de Madrid, Madrid, Spain.

Address reprint requests to Prof. Calatayud: Departamento de Profilaxis, Odontopediatría y Ortodoncia, Facultad de Odontología, Universidad Complutense de Madrid, 28040 Madrid, Spain. Address electronic mail to: ciglesuela@terra.es. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

y Valdés (1478–1557), the official chronicler of the conquest, make any reference to coca leaves, either. Nonetheless, Fernández de Oviedo continued to rework his chronicles until the time of his death, and much later publications of his complete works do contain mentions of the coca leaf.<sup>23</sup>

Still, these early Spaniards must already have known of the plant and its use, because it is clearly described in the later chronicles written by some of the men involved. For instance, an account dated 1571 and authored by Pedro Pizarro (1515–1571), Francisco Pizarro's cousin who played a leading role in the capture of Atahualpa (last king of the Incas), described coca consumption by the nobles and high officials of the Inca empire.<sup>24</sup> Moreover, in the closing lines of his 1571 chronicle, Diego Trujillo, one of Pizarro's soldiers, mentions coca reserves stored in Cuzco, the capital city.<sup>25</sup>

The reason for the belated mention of the coca leaf and its consumption may lie, as the sixteenth century Spanish chroniclers sustain, in the fact that its use was restricted to the ruling class of the Inca empire and to certain religious rites but did not extend to the population as a whole. The notes that have reached our times, taken by Francisco de Toledo (1514–1584), Viceroy of Peru in his report to the "Patronato de Indias" of the Indies in 1571,<sup>26</sup> Pedro Pizarro<sup>24</sup> as mentioned above, and Francisco Falcon, a lawyer established in Lima<sup>27</sup> in 1582, provide support for this assumption. Modern authors have been able to verify that after the fall of the Inca empire in 1532, coca consumption spread to the population at large<sup>7,12</sup> as the entire social system underwent drastic change, particularly after 1540.<sup>7</sup>

The first reliable account we have of coca leaf consumption (if we disregard Amerigo Vespucci's version) is a manuscript letter from the bishop of Cuzco, Friar Vicente de Valverde (15?–1542), to Emperor Charles V in 1539.<sup>28</sup> This letter is important because Friar Vicente de Valverde accompanied Francisco Pizarro throughout the conquest of Peru and was present at all of the relevant events.

... *coca*, which is the leaf of a small tree that resembles the sumac found in our own Castile, is one thing that the Indians are ne'er without in their mouths, that they say sustains them and gives them refreshment, so that, even under the sun they feel not the heat, and it is worth its weight in gold in these parts, accounting for the major portion of the tithes.

The second reliable reference is another manuscript, likewise a letter, from the President of the Peruvian Assembly, member of the clergy and man of letters Pedro de la Gasca (1485–1567), to the Council of the Indies in 1549, in which he described the measures taken by Francisco Pizarro to distribute the coca stores.<sup>29</sup> The third reference, and the first to be published, is attributed to traveler Pedro Cieza de León (1520–1554), whose chronicle of Peru, published in Seville in 1553, refers to the chewing of coca leaves with a chalk-like powder to assuage

hunger and increase strength and stamina.<sup>30</sup> Pedro Cieza traveled through America between 1530 and 1550 and lived in Peru from 1548 to 1550.<sup>31</sup> All of these chroniclers observed that coca consumption was widespread throughout the population.

The most prominent medical studies by contemporary Spanish doctors are the surveys by Nicolas Bautista Monardes Alfaro (1493–1588). Monardes, possibly the most famous Spanish physician of his time, practiced in Seville, where, in 1574, he published a collection of writings previously printed in 1565, 1569, and 1571, to which he added a third part<sup>32</sup> containing his first reference to coca, with a description of its forms, uses, effects, and so on.<sup>33</sup> The other great Spanish physician of the period was Francisco Hernández (1517–1587), Emperor Philip II's court physician. Hernández traveled through in Mexico in 1570–1577 to collect material on flora and fauna. After returning to Spain, he continued to receive material and devoted his time to the minute task of ordering and cataloging his discoveries.<sup>34</sup> Unfortunately, Hernández' immense volume of work was not published in his lifetime, and only fragments appeared in later years. Thus, the first text containing a reference to the coca leaf was published in 1615, after it had been edited by Dominican Francisco Ximenez.<sup>35</sup> Hernández' complete works, published much later (mid-twentieth century) depict the use and consumption of the coca leaf by Native Americans.<sup>36</sup>

All of the sixteenth century Spanish chroniclers' accounts of the use of coca concur that it was mixed with white powder from shell ash or chalk and rolled into small balls which were kept and later chewed to alleviate hunger and thirst and to bolster strength. They were also aware of the drug's euphoric effects. Currently, we know that the white powder, calcium carbonate, enhances the subjective effect of coca<sup>37</sup> and absorption of the alkaloid.<sup>7</sup> Moreover, although in current practice in industrialized countries, cocaine is inhaled, Van Dyke has shown that when taken orally, it passes into the bloodstream and affects the nervous system.<sup>37</sup>

We owe the first reference to the anesthetic effects of coca to Spanish Jesuit Bernabé Cobo (1582–1657),<sup>38</sup> who, in his 1653 manuscript work on the New World, mentions that toothaches can be alleviated by chewing coca leaves.<sup>39</sup>

And this happen'd to me once, that I repaired to a barber to have a tooth pull'd, that had work'd loose and ach'd, and the barber told me he would be sorry to pull it because it was sound and healthy; and a monk friend of mine who happen'd to be there and overhearing, advised me to chew for a few days on *Coca*. As I did, indeed, soon to find my toothache gone.

In subsequent centuries, most writers stressed the stimulant effects of coca but paid little or no heed to its dangers. They were mainly apologists for the drug. Thus, physicians such as Peruvian José Hipólito Unanue (1755–1833)<sup>40</sup> recommended the use of coca leaves in

**Table 1. Earliest Descriptions of the Coca Leaf and its Anesthetic and Adverse Effects**

## Earliest writings on the coca leaf

- 1505? Amerigo Vespucci (printed but subject to doubts about authenticity)<sup>17</sup>
- 1539 Fray Vicente de Valverde (letter)<sup>28</sup>
- 1549 Pedro de la Gasca (letter)<sup>29</sup>
- 1553 Pedro Cieza de León (first reference in print)<sup>30</sup>

## First description of anaesthetic effect:

- 1653 Bernabé Cobo (manuscript)<sup>39</sup>

## First references to harmful effects of consumption

- 1582 Francisco Falcon<sup>27</sup>
- 1836 Eduard Friedrich Pöppig<sup>43</sup>

1794,<sup>41</sup> whereas Austrian physician Sigmund Freud (1856–1939) recommended cocaine itself in 1884.<sup>42</sup> Scholar Francisco Falcon was the one to draw attention to the dangers of coca for the first time, in 1582, on the grounds of the mortality it produced among the aboriginal peoples (although this was mainly a result of disease acquired during its cultivation) and the difficulty of ridding oneself of the “custom” of using it. The word *custom*, in sixteenth century usage, is indicative of addiction. Falcon also recommended measures to restrict its consumption.<sup>27</sup> Nevertheless, it was not until the nineteenth century that the voice of alarm was sounded about the negative effects of coca abuse. German doctor Eduard Friedrich Pöppig (1798–1868), who made a minute description of coca leaf addiction after a voyage to the Amazon in 1827–1832, stressed the digestive changes, migraine, weakness, weight loss, and alterations of personality it induced and the low public opinion of coca consumption and consumers, who were more poorly regarded than alcoholics in Europe and unable to give up their habit.<sup>43</sup> The most important landmarks in connection with the coca leaf are outlined in table 1.

### Cocaine

Isolating the active principle of the coca leaf was no simple task. Austrian naturalist Carl Von Scherzer (1821–1903) traveled around the world in the frigate *Novara* in 1857–1958; during his stay in Peru, he collected a sizeable sample of coca leaves, which he sent to German chemist Albert Niemann (1834–1861).<sup>11,44</sup> Niemann, in the Friedrich Wöhler Laboratory in Göttingen, in 1860, managed to isolate the active principle, which he named *cocaine*.<sup>44</sup> Although Niemann unfortunately died the following year, his work was carried on by his disciple Wilhelm Lossen (1838–1906),<sup>11</sup> who determined the correct molecular formula— $C_{17}H_{21}NO_4$ —in 1865. (Niemann had concluded that the formula was  $C_{16}H_{20}NO_4$ .<sup>45</sup>) Discovery of the new alkaloid’s structural formula was difficult, and in fact, it was not fully known until it was developed by chemist Richard Willstätter (1872–1942) in 1898.<sup>46</sup> He and his colleagues in Munich, Bavaria, and the Merck Laboratory in Darmstadt, Hesse (both in Germany), synthesized artificial cocaine in 1923.<sup>47</sup>

From the time cocaine was isolated, steps were taken to apply it as the first local anesthetic. Nothing had changed since the early reference to the anesthetic effect of the coca leaf by Jesuit Bernabé Cobo in 1653.<sup>39</sup> In 1860, Niemann reported and clearly demonstrated numbness of the tongue caused by the new alkaloid,<sup>44</sup> an observation corroborated by Lossen in his 1865 article.<sup>45</sup> The first experimental study on cocaine, however, was conducted by Peruvian Thomas Moreno y Maiz, ex-naval surgeon, as part of his doctoral thesis published in Paris in 1868.<sup>48</sup> He found that injecting cocaine solutions caused insensitivity in rats, guinea pigs, and, above all, frogs; in a footnote on page 77, he even mentioned its local anesthetic effects. Nevertheless, he made no mention of its use in surgery.<sup>48</sup> In 1880, Russian aristocrat and physician Basil Von Anrep of the University of Würzburg published an interesting article on his experiments on animals (rats, dogs, cats, rabbits, and pigeons), animal tissues and organs, and, especially himself.<sup>49</sup> Anrep injected a small quantity of 0.003–0.5 cocaine solution (equivalent to 0.6%) under the skin on his arm, which left the area insensitive to jabs. He did the same with an externally applied 0.005–0.05 solution (equivalent to 1%) to his tongue, which also caused insensitivity to jabs. Finally, in his conclusions, he recommended cocaine as a surgical anesthetic.<sup>49</sup>

The ground was laid, but the final step to the clinical use of cocaine had yet to be taken, until Viennese ophthalmologist Carl Koller (1857–1944)<sup>50</sup> rose to that challenge. Koller was working in the Wiener Allgemeines Krankenhaus (Viennese General Hospital, Vienna, Austria) where he got to know and become friends with Sigmund Freud. Freud was interested in the stimulant effects of cocaine for use in overcoming morphine addiction and encouraged Koller to take part in a series of experiments with cocaine during the spring and summer of 1884.<sup>50,51</sup> Koller noted the deadening effect on his tongue when he swallowed the cocaine.<sup>52</sup> In July 1884, Freud published an interesting review on cocaine and his experiments, again noting but without lending any particular attention to the alkaloid’s anesthetic effect on mucous membranes.<sup>42</sup> It was Koller who grasped its importance. Thus, he experimented with dog and guinea pig corneas with 2–5% cocaine solutions,<sup>53</sup> although it appears that the first animals he experimented on were frogs.<sup>54</sup> He also used it on himself and on patients from Professor Von Reuss’ clinic.<sup>53</sup> On September 11, 1884, he performed the first operation using local anesthetic on a patient with glaucoma.<sup>55</sup> The German Ophthalmologist Society Congress was to meet in Heidelberg on September 15 and 16, 1884, but Koller was unable to attend for a lack of wherewithal. However, he asked Dr. Josef Brettauer, an ophthalmologist from Trieste passing through Vienna on his way to Heidelberg, to read his paper at the congress.<sup>55</sup> The impact was instantaneous. Koller himself read his paper on



**Table 2. Stages in Discovery of Local Anesthetic Effect of Cocaine in Late 1884**

Date	Landmark
July	Sigmund Freud publishes his paper on cocaine <sup>42</sup>
September 11	Carl Koller performs the first operation, on a glaucoma patient, using cocaine as a local anesthetic <sup>55</sup>
September 15–16	German Society of Ophthalmology Congress in Heidelberg <sup>50</sup>
October 11	Henry D. Noyes publishes a review of the Heidelberg Congress in the <i>New York Medical Record</i> <sup>56</sup>
October 17	Carl Koller reads his paper to the Medical Society of Vienna <sup>50,52,54</sup>
October 25	Carl Koller publishes his paper in the <i>Wiener Medizinische Wochenschrift</i> <sup>53</sup>
December 6	J. N. Bloom translates Koller's paper and publishes it in <i>The Lancet</i> <sup>57</sup> Richard John Hall reports the first application of local anesthesia in dentistry, and William Stewart Halsted conducts the first truncular block of the mandibular nerve <sup>60</sup>

October 17 in the Wiener Medizinische Gesellschaft (the Viennese Medical Society),<sup>50,52,54</sup> and it was published on October 25.<sup>53</sup> Dr. Henry D. Noyes of New York, who attended the Heidelberg Congress, sent a summary highlighting Koller's work, published on October 11 in the *New York Medical Record*.<sup>56</sup> Dr. Bloom translated Koller's article into English and had it published in *The Lancet* on December 6.<sup>57</sup> The news of Koller's findings appeared in other publications of the time and sparked the development of regional and local anesthesia. Between September 1884 and late 1885, 60 publications concerning local anesthesia using cocaine appeared in the United States and Canada.<sup>58</sup>

Dr. William Stewart Halsted (1852–1922) and his co-worker Richard John Hall (18?–1897) read Noyes' report and immediately became interested in local anesthesia.<sup>59</sup> On December 6, 1884, Hall published a report on the first successful nerve block, which happened to be achieved in the context of dentistry: Dr. Nash of New York was able to block the infraorbital plexus with 8 minims (approximately 0.5 ml) of 4% cocaine hydrochloride ("hydrochlorate of cocaine" in Hall's report) to obturate an upper incisor, whereas Dr. Halsted blocked the inferior dental nerve in a medical student using 9 minims of the same solution.<sup>60</sup> Halsted and his colleague Hall went on to develop nerve and regional blocking techniques, although it was François Franck who coined the term in 1892.<sup>61</sup> Table 2 lists the main landmarks in the discovery of local anesthesia using cocaine in late 1884.

### *Development of the Syringe*

The development of local anesthesia was contingent on the invention of the hypodermic syringe for subcutaneous injections. Subcutaneous administration of medication had already begun by way of incisions in the skin. Von Neuner introduced an early syringe in 1827 to introduce fluids into animals.<sup>62</sup> According to Charles Pfender's studies of the origin of hypodermic medication,<sup>63</sup> the first to use it was Irish surgeon Francis Rynd of Meath Hospital. In 1845, he described two cases in which he injected morphine acetate (which he called "acetate of morphia").<sup>64</sup> One of the cases was an injection in the vicinity of the supraorbital nerve to treat neuralgia. Nevertheless, Rynd did not publish the design

of his syringe until 1861.<sup>65</sup> In 1853, veterinary surgeon Charles Gabriel Pravaz (1791–1855) of Lyon developed a syringe to treat aneurysm in animals with iron perchloride.<sup>66</sup> Finally, and almost at the same time, in 1855, the Scotch physician Alexander Wood (1817–1844) published a report of nine cases treated with a syringe with which he had injected morphine muriate ("muriate of morphia").<sup>67</sup> From then on, the hypodermic syringe was readily available to the medical community. Wood was instrumental in the extension of its use, although it is to Charles Hunter that we owe the term "hypodermic," which he coined to refer to these subcutaneous methods in 1859.<sup>58,63</sup>

### *Dangers of Cocaine*

After Koller's discovery of cocaine's local anesthetic powers, its use spread rapidly, but because it was administered in high concentrations (on the order of 10–30%),<sup>62,68</sup> practitioners soon began to report its alarming side effects. Between 1884 and 1891, 200 cases of systemic intoxication and 13 deaths attributed to the drug were recorded,<sup>69</sup> quenching enthusiasm for it and prompting physicians to turn to gases such as nitrous oxide and ether, particularly for minor surgery such as involved in dentistry.<sup>70</sup> Furthermore, about this time, the addictive effects of cocaine began to emerge as several early users, Freud and Halsted among them, fell victim to it.<sup>50,59</sup>

The credit for making the infiltration of cocaine safer is shared by a number of researchers. In Germany, Maximilian Oberst of Halle (1849–1925)<sup>51</sup> applied low concentrations of cocaine to the fingers, compressing them for slower release of the drug into the bloodstream, a technique that proved to be effective, as reported on April 3, 1890, by another scientist from Halle, Ludwig Pernice, who had worked with Oberst.<sup>68</sup> On June 11, 1892, Carl Ludwig Schleich (1859–1922), a surgeon from Berlin, published the results of a study using a solution of 0.1–0.2% cocaine hydrochloride, infiltrating it under several layers of skin and chilling the area with an ether aerosol (to fix the drug and enhance its effects).<sup>71</sup> In turn, Parisian surgeon Paul Reclus (1847–1914) published an article in 1895 in which he described the use of low concentrations of cocaine (from 2% down to 0.5%) to achieve a good local anesthetic that, although

slower in taking hold, caused no side effects.<sup>72</sup> Coincidentally, the operations described in Reclus' work included tooth extractions and pulpotomies.

Currently, we know that, at around the same time, Halsted was working with solutions containing low cocaine concentrations to be applied by compression; unfortunately, he became addicted to cocaine and morphine and was unable to publish his results.<sup>55,59,61</sup> The maximum cocaine dosage for infiltration was eventually established at 50 mg.<sup>73,74</sup>

### After Cocaine

As the undesirable effects of cocaine (toxicity, addiction, and others) gradually became known, new anesthetic drugs were sought to replace it. None of these attempts were successful, however, until November 27, 1904, when German chemist Alfred Einhorn (1856–1917)<sup>75</sup> patented 18 para-aminobenzoic derivatives that had been developed in the Meister Lucius and Brünig plants at Höchst, in Hesse, Germany. His compound number two was to bring about a radical change in the existing scenario.<sup>76</sup>

Its name, novocaine, appeared for the first time in 1905 in an article published by Professor Heinrich Braun, in which he compared it to other promising local anesthetics such as stovaine and alypine. Braun reported excellent results in a comparison of compounds with different concentrations of novocaine and adrenaline.<sup>77</sup> Novocaine was found to be safe and quickly became the standard local anesthesia. Nonetheless, the anesthetic effects of the drug, rechristened *procaine* in the United States during the First World War,<sup>75,78</sup> were weak, and it required high concentrations of adrenaline, particularly when infiltration techniques were used. Moreover, some patients and health professionals proved to be highly allergic to it.<sup>79,80</sup>

These drawbacks prompted the search for an alternative drug, but none of the anesthetics developed in the first half of the twentieth century proved to be clearly more effective. In 1943–1946, Nils Löfgren and Bengt Lundquist developed a xylydine derivative they called lidocaine, whose chemical composition is very different from novocaine but which is nonetheless safe and has a stronger effect and scant allergenic action.<sup>81</sup> Soon thereafter, amide-type anesthetic drugs began to be developed. In 1957, Bo af Ekenstam *et al.*<sup>82</sup> synthesized mepivacaine and bupivacaine; in 1969, prilocaine was synthesized by Nils Löfgren and Cläes Tegner<sup>83</sup>; and in 1972, Adams *et al.*<sup>84</sup> developed etidocaine. The first article published on articaine<sup>85</sup> also appeared in 1972.

Currently, the pharmaceutical industry continues to explore the development of safer and more effective local anesthetics in a pursuit that has come a long way since the earliest experiments with cocaine.

The authors thank the entire staff of the Library of the Faculty of Dentistry, Complutense University of Madrid, Madrid, Spain, and, especially, Rosa María

Rodríguez-Durántez (Head Librarian, Library of the School of Dentistry, Complutense University of Madrid) for their kind cooperation. They also thank the Spanish National Library, Madrid Spain, and Antonia Colomar (Archivist, General Archive of the Indies, Seville, Spain) for their cooperation. Finally, the authors thank Francisco Guerra, M.D., D.Sc., Ph.D. (Emeritus Professor, University of Alcalá de Henares, Madrid, Spain), for his counsel and information on the early Spanish chroniclers.

### References

1. Greene NM: A consideration of factors in the discovery of anesthesia and their effects on its development. *ANESTHESIOLOGY* 1971; 35:515–22
2. Vandam LD: Early American anesthetists: The origins of professionalism in anesthesia. *ANESTHESIOLOGY* 1973; 38:264–74
3. Wells H: A History of the Discovery of the Application of Nitrous Oxide Gas, Ether and Other Vapors to Surgical Operations. Hartford, J Gaylord Wells, 1847, pp 5–14
4. Menczer LF, Jacobsohn PH: Dr Horace Wells: The discoverer of general anesthesia. *J Oral Maxillofac Surg* 1992; 50:506–9
5. Jacobsohn PH: Dentistry's answer to "the humiliating spectacle": Dr. Wells and his discovery. *J Am Dent Assoc* 1994; 125:1576–81
6. Greene NM: Anesthesia and the development of surgery (1846–1896). *Anesth Analg* 1979; 58:5–12
7. Loza-Balsa G: Monografía sobre la coca. La Paz, Bolivia, Edita Sociedad Geográfica de la Paz, 1992, pp ix:x, xiv, xv, 3
8. Cadwell J, Sever PJ: The biochemical pharmacology of abused drugs: I. Amphetamines, cocaine, and LSD. *Clin Pharm Ther* 1974; 16:625–38
9. Van Dyke C, Byck R: Cocaine. *Sci Am* 1982; 246:128–41
10. Bühler A: Die Koka bei den Indianern südamerikas. *Ciba Z* 1944; 8:3338–51
11. Bühler A: Zur erforschung des Kokagenusses. *Ciba Z* 1944; 8:3353–9
12. Gutierrez-Noriega C, Zapata V: Estudios sobre la coca y la cocaína en el Perú. Lima, Perú, Ediciones de la Dirección de Educación Artística y Extensión Cultural del Ministerio de Educación Pública, 1947, pp 21
13. Killian H: Die Geschichte von die Lokalanästhesie. Edited by Killian H. Lokalanästhesie und Lokalanästhetika, 2nd edition. Stuttgart, George Thieme Verlag, 1973, pp 5–12
14. Guerra F: The Pre-Columbian Mind. London, Seminar Press, 1971, pp 47, 52, 126, 191
15. Beristain JM: Catálogo y noticias de los literatos, que o nacidos, o educados, o florecientes en la America septentrional Española, han dado a luz algún escrito o lo han dejado preparado para la prensa. Mexico. Biblioteca Hispano Americana Septentrional. Oficina de Don Alejandro Valdés, 1819, Vol II, pp 368–9
16. Hurtado P: Indianos cacereños. Notas biográficas de los hijos de la Alta Extremadura que sirvieron en América durante el primer siglo de su conquista. Barcelona, Tipografía Luis Tasso, 1892, pp 38–9
17. Vespucci A: Lettera di Amerigo Vespucci delle isole nuovamente trovate in quattro suoi viaggi. 237 Firenze. Gian Stefano, 1505, L 21 253. Modern edition: Amerigo Vespucci. Cartas de viaje. Introducción y notas de Luciano Formisano. Madrid. Alianza Editorial SA, 1986, pp 11:13, 48, 102–137
18. Sierra VD: Epistolario de Amerigo Vespucci y sus supuestos descubrimientos. Santa Fe. Universidad Nacional del Litoral-Ministerio de Educación de la Nación. Publicación de Extensión Universitaria n°79, 1954
19. Anonymous (Cristobal de Mena): La conquista del Peru llamada Nueva Castilla. Sevilla. Impresa en Casa de Bartolome Perez, 1534. (Facsimile edition with annotations by Joseph H. Sinclair. New York Public Library Ed. New York, 1929). Modern edition: Raul Porras Barrenechea. Las relaciones primitivas de la conquista del Perú. Paris. Imprimeries les Presses Modernes, 1937, pp 45–56, 79–101
20. Xerez F de: Verdadera relacion de la conquista del Peru. Sevilla. Impreso en casa de Bartolome Perez, 1534. (Facsimile edition by Marcelo Grota. Francisco de Jerez, la conquista del Perú. Madrid. El Crotalon. Crónicas del Espejo, serie folio I. Pedro M. Cátedra and Victor Infantes, eds., 1983)
21. Fernandez de Oviedo G: La historia general de las Indias. Sevilla, Impreso por Juan de Cromberger, 1535
22. Fernandez de Oviedo G: Cronica de las Indias. Historia general de las Indias agora nuevamente impresa corregida y enmendada y la conquista del Peru. Salamanca, Impresa por Juan de Junta, 1547
23. Fernandez de Oviedo G: Historia general y natural de las Indias, islas y tierra-firme del mar océano. Primera parte. Madrid. Modern edition by José Amador de los Rios. Real Academia de la Historia, 1851, Vol I. Book VI, Chapter XX, pp 206–7
24. Pizarro P: Relación del descubrimiento y conquista de los reinos del Peru, y del gobierno y orden que los naturales tenían, y tesoros que en ella se hallaron: y de las demas cosas que en el han subcedido hasta el día de la fecha. Hecha por Pedro Pizarro conquistador y poblador destos reinos y vecino de la ciudad de Arequipa. Año 1571. Modern edition: Descubrimiento y conquista del Perú por Pedro Pizarro conquistador y poblador de este reino (1571). Lima, Perú. Notas biográficas y concordancias con las crónicas de las Indias por Horacio H. Urteaga. Biografía de Pedro Pizarro por Carlos A. Romero. Imprenta y librería Sanmartí y Cía. Colección de libros y documentos referentes a la historia del Perú, 1917, Vol VI, pp 1–187
25. Relacion del descubrimiento del reyno del Peru que hizo Diego de Trujillo

en compañía del gobernador Don Francisco Pizarro y otros capitanes desde que llegaron a Panamá el año 1530, en que refieren todas las derrotas y sucesos hasta el día 15 de abril de 1571. Modern edition: Diego Trujillo. *Relación del descubrimiento del reyno del Perú*. Sevilla. Edición, prólogo y notas de Raul Porras Barrenechea. Publicación de la Escuela de Estudios Hispano-Americanos de Sevilla, 1948, Vol XLVIII (Series 7, No 4), pp 18, 24, 63

26. Información de las idolatrias de los Incas e indios y de como se enterraban, etc. 1571. Patronato de Indias. Colección de documentos inéditos relativos al descubrimiento, conquista y organización de las antiguas posesiones españolas de América y Oceanía, sacados de los archivos del reino y muy especialmente del de indias. Madrid, Imprenta Manuel G. Hernández, 1874, Vol XXI, pp 131-220

27. Representación hecha por el licenciado Falcón en concilio provincial sobre los daños y molestias que se hacen a los indios. Lima, Perú, 1582. Publicado en: Los pequeños grandes libros de la historia Americana. Lima, Perú. Arreglos, introducción, notas y comentarios de Francisco A. Loayza, 1946, Series I, Vol X, pp 123-164

28. Carta del Obispo del Cuzco al Emperador sobre asuntos de su iglesia y otros de la gobernación general de aquel país. Cuzco, Perú, 20 de marzo de 1539. Modern edition: Colección de documentos inéditos relativos al descubrimiento, conquista y colonización de las posesiones españolas de América y Oceanía, sacados en su mayor parte del Real Archivo de Indias. Madrid. Bajo la dirección de Joaquín F. Pacheco, Francisco de Cardenas y Luis Torres de Mendoza. Imprenta de Manuel B. de Quiros, 1864, Vol III, pp 92-137

29. Carta del licenciado Gasca al Consejo de Indias avisando las disposiciones que se habían adoptado respecto al repartimiento de la coca que tuvo Francisco Pizarro. Lima, Perú. 16 de septiembre de 1549. Modern edition: María del Carmen Pescador del Hoyo. Documentos de Indias. Siglos XV-XIX. Catálogo de la serie existente en la sección diversos. Madrid. Dirección General de Archivos y Bibliotecas. Servicio de Publicaciones, 1954, pp 40 (microfilm No 97)

30. Cieza de Leon P: Parte primera de la crónica del Peru. Que trata de la demarcacion de sus provincias: La descripción de ellas. Las fundaciones de las nuevas ciudades. Los ritos y costumbres de los indios. Y otras cosas extrañas dignas de ser sabidas. Sevilla. Imprensa en casa de Martín de Montesdoca, 1553, Chapter XCVI, ff 111-2

31. Cieza de Leon P: La crónica del Perú. Madrid, Edición de Manuel Ballesteros. Crónicas de América 4. Edita Historia 16, 1984, pp 10, 17, 19, 21 and 346-7

32. Guerra F. Nicolas Bautista Monardes: Su vida y su obra (1493-1588). Mexico DF, Compañía Fundidora de Fierro y Acero de Monterrey SA, 1961, pp 5:15, 133

33. Monardes N: Primera y segunda y tercera partes de la historia medicinal de las cosas que se traen de las indias Occidentales que sirven en medicina. Tratado de la piedra Bezaar y de la yerva Escuerconera. Dialogo de las grandezas del hierro y de sus virtudes medicinales. Tratado de la nieve y del beuer frio. Sevilla, Impreso en casa de Alonso Escrivano, 1574, ff 114-5

34. Francisco Hernandez obras completas. Tomo I. Vida y obra de Francisco Hernández. Mexico, Por German Somolinos D'Ardois. Universidad Nacional de Mexico, 1960, pp 100-1:154, 284-5, 405-6

35. Hernandez F: Quatro libros de la naturaleza, y virtudes de las plantas, y animales que estan recevidos en el uso de Medicina en Nueva España, y la Methodo, y correccion, y preparacion, que para administrallas se requiere con lo que el Doctor Francisco Hernandez escrivio en lengua latina. Mexico, Impreso en casa de la viuda de Diego Lopez Davalos, 1615, segunda parte del libro tercero, Chapter LVIII, ff 171-2

36. Francisco Hernandez obras completas. Tomo III. Historia natural de Nueva España. Volumen II. Mexico, Universidad Nacional de Mexico, 1959, libro vigesimo primero. Chapter LXXII, pp 238

37. Van Dyke C, Jatlow P, Ungerer J, Barash PG, Byck R: Oral cocaine: Plasma concentrations and central effects. *Science* 1978; 200:211-3

38. Torres E: Prólogo. En: P. Bernabe Cobo. Historia del Nuevo Mundo. Madrid, Colección Cisneros, Editorial Atlas, 1943, pp 5-6

39. Cobo B: Historia del Nuevo Mundo. Manuscrito en Lima, Perú, 1653, libro 5º, capítulo XXIX. Modern edition: Bernabe Cobo. Historia del Nuevo Mundo. Sevilla. Publicado por la Sociedad de Bibliófilos Andaluces. Con notas de Marcos Jiménez de la Espada. Impreso por E. Rasco, 1890, Vol I, Book 5th, Chapter XXIX, pp 473-7

40. Vicuña-Mackenna B. Hipólito Unanue. En: Obras científicas y literarias del Doctor J. Hipólito Unanue. Barcelona, Tipografía la Academia de Serra Hermanos y Russell 1914, Vol I, pp ix-xxiv

41. Unanue JH: Disertación sobre el cultivo, comercio y las virtudes de la famosa planta del Perú nombrada "coca". Al Excelentísimo Señor Don Luis Fermín Carbajal y Vargas, Conde de la Unión. Lima, Perú, 1794. En: Obras científicas y literarias del Doctor J. Hipólito Unanue. Barcelona, Tipografía la Academia de Serra Hermanos y Russell, 1914, Vol II, pp 90-125

42. Freud S: Ueber coca. *Centralbl Gesamte Ther* 1884; 2:289-314

43. Pöppig E: Reise in Chile, Peru und auf dem Amazonenstrom während der Jahre 1827-1832. Leipzig, Friedrich Fleischer, JC Hinrichssche Buchhandlung, 1836, vol II, pp 209-17

44. Niemann A: Ueber eine neue organische Base in den Cocablättern. *Arch Pharm* 1860; 153:129-55, 291-308

45. Lossen W: Ueber das Cocain. *Ann Chem Pharm* 1865; 133:351-71

46. Willstätter R: Ueber die constitution der Spaltungsproducte von Atropin und Cocain. *Ber Dtsch Chem Ges* 1898; 31:1534-53

47. Willstätter R, Wolfes D, Mäder H: Synthese des natürlichen Cocains. *Justus Liebig's Ann Chem* 1923; 434:111-39

48. Moréno y Maiz T: Recherches chimiques et physiologiques sur l'erythroxylum coca du Perou et la cocaine. Paris, Louis Leclerc Libraire-Editeur, 1868, pp 76-9

49. Anrep B von: Ueber die physiologische Wirkung des Cocain. *E Pflüger Arch Ges Physiol* 1880; 21:38-77

50. Liljestrand G: Carl Koller and the development of local anesthesia. *Acta Physiol Scand Suppl* 1967; 299:3-30

51. Buess H: Über die Anwendung der Koka und des Kokains in der Medizin. *Ciba Z* 1944; 8:3362-5

52. Koller C: Historical notes on the beginning of local anesthesia. *J Am Med Assoc* 1928; 90:1742-3

53. Koller K: Ueber die Verwendung des Cocain zur Anästhesirung am Auge. *Wien Med Wochenschr* 1884; 34:1276-8, 1884; 34:1309-11

54. Leonard M. Carl Koller: Mankind's greatest benefactor? The story of local anesthesia. *J Dent Res* 1998; 77:535-8

55. Fink BR: Leaves and needles: The introduction of surgical local anesthesia. *ANESTHESIOLOGY* 1985; 63:77-83

56. Noyes HD: The ophthalmological congress in Heidelberg. *Med Rec* 1884; 26:417-8

57. Koller C: On the use of cocaine for producing anaesthesia on the eye. *Lancet* 1884; 2:990-2

58. Matas R: Local and regional anesthesia: A retrospect and prospect: I. *Am J Surg* 1934; 25:189-96

59. Olch PD, William S: Halsted and local anesthesia: Contributions and complications. *ANESTHESIOLOGY* 1975; 42:479-86

60. Hall RJ: Hydrochlorate of cocaine. *N Y Med J* 1884; 40:643-4

61. Matas R: Local and regional anesthesia: A retrospect and prospect: II. *Am J Surg* 1934; 25:362-79

62. McAuley JE: The early development of local anaesthesia. *Br Dent J* 1966; 121:139-42

63. Pfender CA: Historical synopsis of the development of hypodermic medication. *Washington Med Ann* 1911; 10:346-59

64. Rynd: Neuralgia: Introduction of fluid to the nerve. *Dublin Med Press* 1845; 13:167-8

65. Rynd F: Description of an instrument for the subcutaneous introduction of fluids in affections of the nerves. *Dublin Q J Med Sci* 1861; 32:13 (and plate III)

66. Pravaz: Sur un nouveau moyen d'opérer la coagulation du sang dans les artères, applicable à la guérison des anéurismes. *Comp Rend Acad Sci (Paris)* 1853; 36:88-91

67. Wood A: New method of treating neuralgia by the direct application of opiates to the painful points. *Edinburg Med Surg J* 1855; 82:265-81

68. Pernice L: Ueber Cocainanästhesie: *Dtsch Med Wochenschr* 1890; 16: 287-9

69. Anonymus: Cocaine. *Br Med J* 1979; 1:971-2

70. Sauvez: L'anesthésie locale pour l'extraction des dents. Paris, Vigot Frères Editeurs, 1905, pp 1-34, 178

71. Schleich CL: Infiltrationsanästhesie (locale anästhesie) und ihr Verhältnis zur allgemeinen Narcose (inhalationsanästhesie). *Verh Dtsch Ges Chir* 1892; 21:121-7

72. Reclus P: La cocaine en chirurgie. Paris, G Masson Editeurs et Gauthier-Villars et Fils Imprimeurs-Editeurs, 1895, pp 69-91, 172-5

73. Fischer G: Local anesthesia in dentistry, with special reference to the mucous and conductive methods: A Concise Guide for Dentists, Surgeons and Students. Philadelphia, Lea and Febiger, 1912, pp 37

74. Bieter RN: Applied pharmacology of local anesthetics. *Am J Surg* 1936; 34:500-10

75. Link WJ: Alfred Einhorn, Sc. D: Inventor of novocaine. *Dent Radiog Photog* 1959; 32:1, 20

76. Farbwerke vorm: Meister Lucius und Brüning in Höchst A.M. Verfahren zur Darstellung von p-Aminobenzoësäurealkalaminestern. Patentschrift n° 179 627 (klasse 12q. Gruppe 6). November 27, 1904

77. Braun H: Ueber einige neue örtliche anaesthetica (Stovain, Alypin, Novocain). *Dtsch Med Wochenschr* 1905; 31:1667-71

78. Benedict HC, Clark SW, Freeman CW: Studies in local anesthesia. *J Am Dent Assoc* 1932; 19:2087-105

79. Guptill AE: Novocain as a skin irritant. *Dent Cosmos* 1920; 62:1460-1

80. Klauder JV: Novocain dermatitis. *Dent Cosmos* 1922; 64:305-9

81. Löfgren N, Lundquist B: Studies on local anaesthetics: II. *Svensk Kem Tidskr* 1946; 85:206-17

82. Ekenstam B, Egnér B, Pettersson G: Local anaesthetics: I. N-alkyl pyrrolidine and N-alkyl piperidine carboxylic acid amides. *Acta Chem Scand* 1957; 11:1183-90

83. Löfgren N, Tegner C: Studies on local anesthetics: XX. Synthesis of some  $\alpha$ -monoalkylamino-2-methylpropionanilides: A new useful local anesthetic. *Acta Chem Scand* 1960; 14:486-90

84. Adams HJ, Kronberg GH, Takman BH: Local anesthetic activity and acute toxicity of ( $\pm$ ) 2-(N-Ethylpropylamino)-2', 6'-butyroxylidide, a new long-acting agent. *J Pharm Sci* 1972; 61:1829-31

85. Winther JE, Nathalang B: Effectivity of a new local analgesic Hoe 40 045. *Scand J Dent Res* 1972; 80:272-8