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.1

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.1

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.1 Doctors focused more on infections than pain because people were dying of pneumonia, diphtheria, gangrene, tuberculosis, tetanus, puerperal fever, and so on.1,2 It was two dentists, then, who first introduced anesthesia: Horace Wells (1815–1848), with nitrous oxide in 1844;3–5 and William Thomas Green Morton (1819–1868), with ether in 1846.6

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.7 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.8,9 Many species of this genus have been grown in Nicaragua, Venezuela, Bolivia, and Peru since pre-Columbian times.7

The earliest cultivation and use of the coca leaf in the Bolivian and Andean region date back to 700 B.C.,7 though recent discoveries in Ecuador indicate human use more than 5,000 years ago.9 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.10

Further, according to Bühler, the first written record of the coca leaf is a mention by the Spanish Dominican friar Tomas Ortiz in 1499,11 a reference which is also cited by other authors.12,13 This is, however, incorrect. A recent review of documents on Friar Tomas Ortiz (1470–1538)14 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).14–16

For some writers, Florentine Amerigo Vespucci (1451–1512) was the first European to document the human use of the coca leaf.9,14 Thus, in his account of his voyage to America on the second Alonso de Ojeda and Juan de la Cosa expedition in 1499–1500,17 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 1506.14,17 Nevertheless, Vespucci’s documents are partially or largely questionable and open to doubt and investigation.14,18 and because his book contains no reference to the printer, year, or place, all of these facts are little better than educated guesses14,17 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 “ánónimo,” dated in Seville in 1534 (probably written by Cristóbal Mena, one of Pizarro’s captains)19 or the chronicle of Francisco de Xerez (1497–1565),20 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 Seville21 or the Salamanca edition22 dated in 1547 by Gonzalo Fernández de Oviedo

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y Valdés (1478–1557), the official chronicler of the con-
quest, make any reference to coca leaves, either. None-
theless, 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.25

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.24 More-
over, in the closing lines of his 1571 chronicle, Diego
Trujillo, one of Pizarro’s soldiers, mentions coca reserves
stored in Cusco, the capital city.25

The reason for the belated mention of the coca leaf and
its consumption may lie, as the sixteenth century Span-
ish chroniclers sustain, in the fact that its use was re-
stricted to the ruling class of the Inca empire and to
certain religious rites but did not extend to the popula-
tion 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 1571,26 Pedro Pizarro24 as mentioned above,
and Francisco Falcon, a lawyer established in Lima27 in
1582, provide support for this assumption. Modern au-
thors have been able to verify that after the fall of the
Inca empire in 1532, coca consumption spread to the
population at large7,12 as the entire social system under-
gwent drastic change, particularly after 1540.7

The first reliable account we have of coca leaf con-
sumption (if we disregard Amerigo Vespucci’s version)
is a manuscript letter from the bishop of Cusco, Friar
Vicente de Valverde (15?–1542), to Emperor Charles V in
1539.28 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.29 The
third reference, and the first to be published, is attributed
to traveler Pedro Giez 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.30 Pedro Giez
traveled through America between 1530 and 1550 and
lived in Peru from 1548 to 1550.31 All of these chroniclers
observed that coca consumption was widespread through-
out the population.

The most prominent medical studies by contemporary
Spanish doctors are the surveys by Nicolas Bautista Mo-
nardes 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 part52 containing his first refer-
cence to coca, with a description of its forms, uses,
effects, and so on.35 The other great Spanish physician of
the period was Francisco Hernández (1517–1587), Em-
peror 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.34 Unfortu-
nately, 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 Ximenes.35 Hernández’
complete works, published much later (mid-twentieth
century) depict the use and consumption of the coca leaf
by Native Americans.36

All of the sixteenth century Spanish chroniclers’ ac-
counts 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, en-
hances the subjective effect of coca37 and absorption of
the alkaloid.7 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.37

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

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 ache’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 Unanúe
(1755–1833)40 recommended the use of coca leaves in
Table 1. Earliest Descriptions of the Coca Leaf and its Anesthetic and Adverse Effects

<table>
<thead>
<tr>
<th>Earliest writings on the coca leaf</th>
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</thead>
<tbody>
<tr>
<td>1508? Amerigo Vespucci (printed but subject to doubts about authenticity)</td>
</tr>
<tr>
<td>1539 Fray Vicente de Valverde (letter)</td>
</tr>
<tr>
<td>1549 Pedro de la Gasca (letter)</td>
</tr>
<tr>
<td>1553 Pedro Cieza de León (first reference in print)</td>
</tr>
<tr>
<td>First description of anaesthetic effect:</td>
</tr>
<tr>
<td>1653 Bernabé Cobo (manuscript)</td>
</tr>
<tr>
<td>First references to harmful effects of consumption</td>
</tr>
<tr>
<td>1582 Francisco Falcon</td>
</tr>
<tr>
<td>1836 Eduard Friedrich Pöppig</td>
</tr>
</tbody>
</table>

1794, whereas Austrian physician Sigmund Freud (1856–1939) recommended cocaine itself in 1884. Scholar Francisco Falcon was the one to draw attention to the dangers of coca for the first time, in 1852, 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 rid-
ing 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. 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, mi-
gaine, 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.

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 size-
able sample of coca leaves, which he sent to German chemist Albert Niemann (1834–1861). Niemann, in the Friedrich Wöhler Laboratory in Göttingen, in 1860, managed to isolate the active principle, which he named cocaine. Although Niemann unfortunately died the following year, his work was carried on by his disciple Wilhelm Lossen (1838–1906), who determined the correct molecular formula—C17H21NO4—of cocaine. Lossen was unable to attend for a lack of wherewithal. How-
ever, he asked Dr. Josef Brettauer, an ophthalmologist 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. Anrep injected a small quantity of 0.003–0.5 cocaine solu-
tion (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 (equiva-
lent to 1%) to his tongue, which also caused insensitivity to jabs. Finally, in his conclusions, he recommended cocaine as a surgical anesthetic.

The ground was laid, but the final step to the clinical use of cocaine had yet to be taken, until Viennese oph-
thalmologist Carl Koller (1857–1944) rose to that challenge. Koller was working in the Wiener Allgemein-
es Krankenhaus (Viennese General Hospital, Vienna, Aus-
tia) 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 ad-
diction and encouraged Koller to take part in a series of experiments with cocaine during the spring and summer of 1884. Koller noted the deadening effect on his tongue when he swallowed the cocaine. 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. It was Koller who grasped its importance. Thus, he experimented with dog and guinea pig corneas with 2–5% cocaine solutions, although it appears that the first animals he experimented on were frogs. He also used it on himself and on patients from Professor Von Reuss’ clinic. On September 11, 1884, he performed the first operation using local anesthetic on a patient with glaucoma. 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. How-
ever, he asked Dr. Josef Brettauer, an ophthalmologist from Trieste passing through Vienna on his way to Hei-
delberg, to read his paper at the congress. The impact was instantaneous. Koller himself read his paper on
Table 2. Stages in Discovery of Local Anesthetic Effect of Cocaine in Late 1884

<table>
<thead>
<tr>
<th>Date</th>
<th>Landmark</th>
</tr>
</thead>
<tbody>
<tr>
<td>July</td>
<td>Sigmund Freud publishes his paper on cocaine</td>
</tr>
<tr>
<td>September 11</td>
<td>Carl Koller performs the first operation, on a glaucoma patient, using cocaine as a local anesthetic</td>
</tr>
<tr>
<td>September 15–16</td>
<td>German Society of Ophthalmology Congress in Heidelberg</td>
</tr>
<tr>
<td>October 11</td>
<td>Henry D. Noyes publishes a review of the Heidelberg Congress in the New York Medical Record</td>
</tr>
<tr>
<td>October 17</td>
<td>Carl Koller reads his paper to the Medical Society of Vienna</td>
</tr>
<tr>
<td>October 25</td>
<td>Carl Koller publishes his paper in the Wiener Medizinische Wochenschrift</td>
</tr>
<tr>
<td>December 6</td>
<td>J. N. Bloom translates Koller’s paper and publishes it in The Lancet</td>
</tr>
</tbody>
</table>

October 17 in the Wiener Medizinische Gesellschaft (the Viennese Medical Society),\textsuperscript{50,52,54} and it was published on October 25,\textsuperscript{53} 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.\textsuperscript{56} Dr. Bloom translated Koller’s article into English and had it published in The Lancet on December 6.\textsuperscript{57} 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.\textsuperscript{58}

Dr. William Stewart Halsted (1852–1922) and his co-worker Richard John Hall (1878–1897) read Noyes’ report and immediately became interested in local anesthesia.\textsuperscript{59} 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.\textsuperscript{60} 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.\textsuperscript{61} 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.\textsuperscript{62} According to Charles Pfender’s studies of the origin of hypodermic medication,\textsuperscript{63} 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”).\textsuperscript{54} 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.\textsuperscript{65} In 1853, veterinary surgeon Charles Gabriel Pravaz (1791–1855) of Lyon developed a syringe to treat aneurysm in animals with iron perchoride.\textsuperscript{66} 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”).\textsuperscript{67} 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.\textsuperscript{58,63}

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%),\textsuperscript{62,68} 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,\textsuperscript{69} 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.\textsuperscript{70} 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.\textsuperscript{50,59}

The credit for making the infiltration of cocaine safer is shared by a number of researchers. In Germany, Maximilian Oberst of Halle (1849–1925) 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.\textsuperscript{68} 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).\textsuperscript{71} 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.72 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.35,59,61 The maximum cocaine dosage for infiltration was eventually established at 50 mg.73,74

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 (1856–1946, Nils L. Ståhl, in Hesse, Germany. His compound number two was to bring about a radical change in the existing scenario.76

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.77 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,77,78 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.79,80

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 xylidine derivative they called lidocaine, whose chemical composition is very different from novocaine but which is nonetheless safe and has a stronger effect and scant allergic action.81 Soon thereafter, amide-type anesthetic drugs began to be developed. In 1957, Bo af Ekenstam et al.82 synthesized meptizaine and bupivacaine; in 1969, prilocaine was synthesized by Nils Löfgren and Claes Tegner;83 and in 1972, Adams et al.84 developed etidocaine. The first article published on articaine85 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.

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