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History of Local Anesthesia in Dentistry

The development of anesthesia in general and local anesthetics in particular required a cultural change. The concept of pain (especially obstetrical 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 (Greene 1971).

The changes taking place in Western Europe between 1750 and 1850, with the enlightenment, industrialization, progressive democratization, and humanization 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 (Greene 1971).

Dentists, not medical 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 (Greene 1971). Doctors focused more on infections than on pain, for people were dying of pneumonia, diphtheria, gangrene, tuberculosis, tetanus, puerperal fever, and appendicitis (Greene 1971; Vandam 1973). Two dentists were the first to introduce anesthesia: Horace Wells (1815–1848), with nitrous oxide in 1844 (Wells 1847; Menczer and Jacobsohn 1992; Jacobsohn 1994), and William Thomas Green Morton (1819–1868), with ether in 1846 (Greene 1979).

Local anesthesia, the basis of modern local anesthetics for dentistry, developed later. This chapter reviews the discovery and evolution of local anesthesia from the Spanish discovery of the coca leaf in America to recently established forms of local anesthesia in dentistry.

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 (Loza-Balsa 1992). 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 (Caldwell and Sever 1974; Van Dyke and Byck 1982). Many species of this genus have been grown in Nicaragua, Venezuela, Bolivia, and Peru since pre-Columbian times (Loza-Balsa 1992).

The earliest cultivation and use of the coca leaf in the Bolivian and Andean region date back to 700 BCE (Loza-Balsa 1992), although recent discoveries in Ecuador indicate human usage more than 5000 years ago (Van Dyke and Byck 1982). Alfred Bühler premised 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 neighboring peoples (Bülher 1944a,b).

Sixteenth century Spanish chroniclers associated the appearance of coca with Francisco Pizarro's (1475–1541) conquest of the Inca or Tahuantinsuyo empire in 1532. The earliest chroniclers made no mention of the plant. The reason for the belated mention of the coca leaf and its consumption may lie, as the sixteenth century Spanish chroniclers aver, 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 (Calatayud and González 2003). Modern authors have verified those assumptions; noting that after the fall of the empire in 1532 coca consumption became popular among the population at large (Gutierrez-Noriega and Zapata 1947; Loza-Balsa 1992) as the entire social system underwent drastic change, particularly after 1540 (Loza-Balsa 1992).

The first reliable account of coca leaf consumption is a manuscript letter from the Bishop of Cuzco, Friar Vicente de Valverde (15..–1542), to Emperor Charles V in 1539 (*Carta* 1864). His letter is important because Valverde accompanied Francisco Pizarro throughout the conquest of Peru and was present at all the significant events. The second reliable reference is another manuscript, also a letter, from the President of the Peruvian Assembly, member

Local Anesthesia in Dentistry: A Locoregional Approach, First Edition. Jesús Calatayud and Mana Saraghi.

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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 coca (Carta 1954). The third reference, and the first to be published in print, 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 (Cieza de Leon 1553). Pedro Cieza traveled through America between 1530 and 1550, and lived in Peru from 1548 to 1550 (Cieza de Leon 1984). All these chroniclers observed that coca consumption was widespread throughout the population (Table 1.1).

The first reference to the anesthetic effects of coca is attributed to Spanish Jesuit Bernabé Cobo (1582–1657) (Torres 1943), who, in his 1653 manuscript work on the new world, mentioned that toothaches could be alleviated by chewing coca leaves (Cobo 1890).

In subsequent centuries, most writers tended to be apologists, stressing the stimulant effects of coca but paying little or no heed to its dangers. Physicians such as Peruvian José Hipólito Unanúe (1755–1833) (Vicuña-Mackenna 1914) recommended the use of coca leaves in 1794 (Unanúe 1914) while Austrian physician Sigmund Freud (1856–1939) recommended cocaine itself in 1884. Scholar Francisco Falcon 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 due to disease acquired during its cultivation) and the difficulty of ridding oneself of the "custom" of using it. The choice of that word in sixteenth century usage is indicative of certain characteristics of addiction. Falcon also recommended measures to restrict its consumption (*Representación* 1946), but 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 drew a detailed picture 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 its consumers, who were more poorly regarded than alcoholics in Europe, and unable to give up their habit (Poeppig 1836). The most important landmarks in connection with the coca leaf are outlined in Table 1.1.

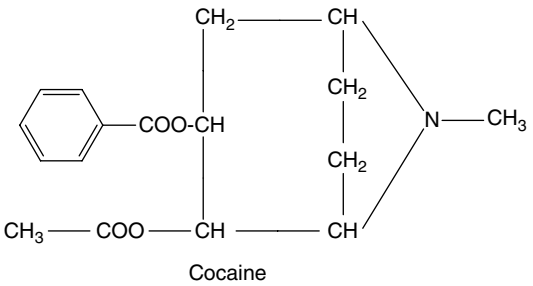
Table 1.1 Earliest descriptions of the coca leaf, its anesthetic effect, and harmful side effects.

Earliest writings on the coca leaf
• 1539 Friar Vicente de Valverde. Manuscript letter
• 1549 Pedro de la Gasca. Manuscript letter
• 1553 Pedro Cieza de León. First book in print
First description of the anesthetic effect
• 1653 Bernabé Cobo. Manuscript
First references to harmful effects
• 1582 Francisco Falcon
• 1836 Eduard Friedrich Pöppig

Cocaine

The active principle of the coca leaf was first isolated in 1860 at Friedrich's laboratory in Göttingen by German chemist Albert Niemann (1834–1861) (Niemann 1860; Bühler 1944b), who called it "cocaine." Although Niemann unfortunately died the following year, his work was carried on by his disciple Wilhelm Lossen (1838–1906) (Bühler 1944b), who determined the correct molecular formula, $C_{17}H_{21}NO_4$, in 1865 (Lossen 1865). The structural formula of the new alkaloid was far from obvious and in fact was not fully known until chemist Richard Willstätter (1872–1942) analyzed it successfully in 1898 (Figure 1.1). He and his colleagues in Munich, and the Merck Laboratory in Darmstadt, synthesized artificial cocaine in 1923 (Willstätter 1898; Willstätter et al. 1923).

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 (Cobo 1890). In 1860, Niemann reported and clearly demonstrated numbness of the tongue caused by the new alkaloid, an observation corroborated by Lossen in his 1865 paper (Lossen 1865). The first experimental study on cocaine, however, was conducted by Peruvian Thomas Moreno y Maïz, ex-naval surgeon, as part of his doctoral thesis published in Paris in 1868. While observing that injecting a cocaine solution in animals induced insensitivity to pain, he made no mention of its use in surgery (Moréno y Maïz 1868). In 1880, Russian aristocrat and physician Vassily von Anrep of the University of Würzburg published a paper on his experiments on animals, animal tissues and organs, and, especially, himself and recommended the use of cocaine as a surgical anesthetic (Anrep 1880).



Cocaine

Figure 1.1 Structural formula for cocaine.

The ground was laid but the final step had yet to be taken when Viennese ophthalmologist Carl Koller (1857–1944) rose to the challenge (Liljestrand 1967). Koller was working in the Wiener Allgemeines Krankenhaus (Viennese General Hospital) where he got to know and become friends with Sigmund Freud. Freud, interested in the stimulant effects of cocaine to overcome morphine addiction, encouraged Koller to participate in a series of experiments with cocaine during the spring and summer of 1884 (Buess 1944; Liljestrand 1967). Koller noted the numbing effect on his tongue when he swallowed the cocaine (Koller 1928). In July 1884, Freud published a review on cocaine and his experiments, again noting but without lending any particular attention to the alkaloid's anesthetic effect on mucous membranes (Freud 1884). It was Koller who grasped its importance, experimenting with animal corneas (Leonard 1998) as well as on himself and on patients (Koller 1884a). On 11 September 1884, he performed the first operation using local anesthetic on a patient suffering from glaucoma (Fink 1985). The German Ophthalmologyt Society Congress met in Heidelberg on 15–16 September 1884, but Koller was unable to attend. 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 (Fink 1985). The impact was instantaneous. Koller himself read his paper on 17 October in the Wiener Medizinische Gesellschaft (Vienna's medical society) (Koller 1884a, 1928; Liljestrand 1967) and it was published on 25 October (Leonard 1998). Dr. Henry D. Noyes of New York, who attended the Heidelberg Congress, sent a summary highlighting Koller's work to the *New York Medical Record*, who published it on 11 October (Noyes 1884). Dr. Bloom translated Koller's article into English and had it published in *The Lancet* on 6 December (Koller 1884b). 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 (Matas 1934a).

Vassily von Anrep (1852–1927) published the first report of a truncal block in an intercostal nerve on 15 November (Yentis and Vlassakov 1999) and Dr. William Stewart Halsted (1852–1922) and his co-worker Richard John Hall (1856–1897) read Noyes's report and immediately became interested in local anesthesia (Olch and William 1975). On 6 December 1884, Hall published a report on the first mandibular block. Dr. Nash of New York was able to block the infraorbital plexus with 8 minims (about 0.5 ml) of 4% cocaine hydrochloride to obturate an upper incisor, while Dr. Halsted performed a mandibular block of the inferior alveolar nerve in a medical student using 9 minims of the same solution (Hall 1884). In 1892, François Franck coined the term "block" to describe this type of local anesthesia (Matas 1934b). The most significant milestones in the discovery of local anesthesia based on cocaine in late 1884 are listed in Table 1.2.

Table 1.2 Stages in the discovery of the local anesthetic effect of cocaine in late 1884.

Month and day in 1884	Landmark
July	• Sigmund Freud publishes his paper on cocaine (Freud 1884)
11 September	• First operation using cocaine as a local anesthetic, performed by Carl Koller on a glaucoma patient (Fink 1985)
15–16 September	• German Ophthalmological Society congress at Heidelberg (Liljestrand 1967)
11 October	• Henry D. Noyes publishes a summary of the Heidelberg proceedings in the *New York Medical Record* (Noyes 1884)
17 October	• Carl Koller reads his paper at the Vienna Medical Society (Koller 1928; Liljestrand 1967)
25 October	• Carl Koller publishes his paper in the *Wiener Medizinische Wochenschrift* (Koller 1884a)
15 November	• von Anrep reports implementing the first intercostal block (Yentis and Vlassakov 1999)
6 December	• J.N. Bloom translates Koller's paper and publishes it in *The Lancet* (Koller 1884b) • Richard John Hall describes the first application of local anesthesia in dentistry and the first mandibular block, effected by William Stewart Halsted (Hall 1884)

The 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 developed an early syringe in 1827 to introduce fluids into animals (McAuley 1966), and in 1841 the American firm Zophar Jayne, working out of Illinois, began to market its syringe, but to be used it required a prior incision in the skin (McAuley 1966). According to Charles Pfender's studies of the origin of hypodermic medication (Pfender 1911) the first to use injection by syringe was Irish surgeon Francis

Rynd (1801–1861) of Meath Hospital. In 1845, he reported two cases of morphine acetate injection (Rynd. 1845). One of the cases was an injection in the vicinity of the supraorbital nerve to treat neuralgia. Rynd failed to publish the design of his syringe until 1861 (Rynd 1861). In 1853, veterinary surgeon Charles Gabriel Pravaz (1791–1855) of Lyon developed a syringe to inject iron perchloride into animals to treat aneurysm (Pravaz 1853). At almost at the same time, in 1855, the Scottish physician Alexander Wood (1817–1884) (Pfender 1911) published a report of nine cases treated with muriate of morphia, which he had injected via a syringe (Wood 1855). From then on, the hypodermic syringe was readily available to the medical community. Wood was instrumental in the extension of its use, although it was Charles Hunter who first used the term "hypodermic" to refer to these subcutaneous methods of injection in 1859 (Pfender 1911; Matas 1934a).

The Dangers of Cocaine

After Koller's discovery of its local anesthetic powers, the use of cocaine spread rapidly, but since it was administered in high concentrations, on the order of 10–30% (Pernice 1890; Mayer 1924; McAuley 1966), practitioners soon began to report its alarming side-effects. Between 1884 and 1891, 200 cases of systemic intoxication and 13 deaths attributable to the drug were recorded (Anonymus 1979), quenching enthusiasm for it and prompting physicians to turn to gases such as nitrous oxide and ether, particularly for minor surgical procedures, including dentistry (Sauvez 1905). Around this time, the dependence liability of cocaine also began to emerge as several early users, Freud and Halsted among them, fell victims to it (Liljestrand 1967; Olch and William 1975).

The credit for making the infiltration of cocaine safer is shared by a number of researchers. In Germany, Maximilian Oberst of Halle (1849–1925) (Buess 1944) 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 3 April 1890 by another scientist from Halle, Ludwig Pernice, who had worked with Oberst (Pernice 1890). On 11 June 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) (Schleich 1892). Parisian surgeon Paul Reclus (1847–1914), in turn, published a paper in 1895 in which he described the use of low concentrations of cocaine (from 2% to 0.5%) to achieve a good local anesthetic which, though slower in taking hold, caused no side effects (Reclus 1895). The operations described in Reclus's work included dental extractions and pulpotomies.

Today we know that around the same time Halsted was working with solutions containing low cocaine concentrations, to be applied by compression, but he unfortunately became addicted to cocaine and morphine, and was unable to publish his results (Matas 1934b; Olch and William 1975; Fink 1985). The maximum cocaine dosage for infiltration was eventually established at 50 mg (Fischer 1912; Bieter 1936).

Adrenaline and the Vasoconstrictive Effect

From the outset, as discussed above, the development of local anesthesia went hand in hand with studies to improve its effectiveness and safety. The clinical experiments reported by Leonard Corning on 19 September 1885 are a case in point. Corning showed that using compression and a tourniquet on the limbs prevented cocaine from diffusing from the injection site, thereby increasing and deepening its anesthetic effect, in turn making it possible to reduce the dose administered (Corning 1885).

Toward the end of the nineteenth century, the Polish researcher Napoleon Cybulski (1854–1919) (Grybowski and Pietrzak 2013) unsuccessfully attempted to isolate the active principle of the suprarenal medulla, which increased arterial pressure (Cybulski 1895). A similar attempt was made by Dr. John Jacob Abel (1857–1938), a researcher from the Johns Hopkins hospital, who while coming very close, always isolated contaminated forms (Abel and Crawford 1897; Abel 1898, 1899). Abel named his substance "epinephrine" (from the Greek *epi* and *nephros* "on top of the kidneys") (Abel 1899). In that same time frame, Austrian physician Otto Ritter von Fürth (1867–1938) also unsuccessfully attempted to isolate the substance, which he called "suprarenin" (von Fürth 1900). In 1901 two researchers, Jokichi Takamine (1854–1922) (Takamine 1901a,b) and Thomas Bell Aldrich (1861–1939) (Aldrich 1901), did isolate the compound, which Takamine called "adrenalin" (from the Latin *ad* and *renal* "near the kidney") and for which Aldrich determined the correct molecular formula, namely $C_9H_{13}NO_3$. In 1904, German Friedrich Stolz (1860–1936) synthesized adrenaline or epinephrine in its two isomeric forms levo (L) and dextro (D) (Stolz 1904). At present, only the more powerful levo form is used.

The clinical application of adrenaline as a local anesthetic is attributed to Leipzig surgeon Heinrich Braun (1862–1934) (Braun 1903a). Braun obtained epinephrine from the London Parke Davies laboratories and added it to a cocaine solution in 1903, achieving a deeper and longer-lasting anesthetic effect, which he called a chemical

tourniquet (Braun 1903a,b). Braun subsequently conducted a series of experiments with animals and patients to evaluate different cocaine and epinephrine concentrations (Braun 1903b).

Today, for reasons traceable to its history, this vasoconstrictor is known as epinephrine in the United States and adrenaline in Europe and the rest of the world. Takamine patented the technique and marketed the product with Parke Davis as "adrenalin" (without the final "e") (Navarro 2003). Inasmuch as Adrenalin was a registered trade name in the United States, the American Medical Association's Council on Pharmacy and Chemistry chose epinephrine as the generic name for the active principle (Smith 1920). Chemists and physicians in the rest of the world, however, not subject to such pharmaceutical company interests, chose the name "adrenaline" (with the final "e"), which is now the term used by the European Pharmacopoeia, the World Health Organization (WHO) and the International Union of Pure Applied Chemistry (IUPAC) (Navarro 2003).

Novocaine or Procaine

As soon as the undesirable effects of cocaine began to appear (such as cardiovascular toxicity and dependence liability), attempts were made to find new drugs with anesthetic properties to replace it. However, none of these attempts were very successful until 27 November 1904, when German chemist Alfred Einhorn (1856–1917) (Link 1959) patented 18 derivatives of para-aminobenzoic acid, developed in the Meister Lucius und Brüning factories at Höchst. Composition number two was to bring radical change (Farbwerke vorm 1904).

Professor Heinrich Braun published the first paper on what he called novocaine (Figure 1.2) in 1905, comparing it to other promising local anesthetics such as stovaine and alypin (Braun 1905). Braun compared different concentrations of novocaine with adrenaline and obtained excellent results (Braun 1905). In 1909, Einhorn and his disciple Emil Uhlfelder published a paper outlining the properties and chemical characteristics of novocaine (Einhorn and Uhlfelder 1909).

Novocaine was introduced in North America by W.S. Schley in 1907 and more specifically into dentistry by Hermann Prinz in 1910 (Rahart 1972). In 1910, German dentist Guido Fischer (1877–1959) published the first book on local anesthesia in dentistry, in which he described the novocaine-based local anesthetic techniques already in use in dentistry as opposed to the anesthetic gases applied until then (Fischer 1910). The book was enormously successful, with a second edition translated into English by Richard Riethmüller in 1912 (Fischer 1912) and the fifth edition translated into Spanish in 1924 (Fischer 1924). A number of editions of Fischer's work were published in the early twentieth century and translated into various languages. The second major text to appear on local anesthesia in dentistry, authored by Kurt Hermann Thoma of Harvard in 1914, was likewise based on novocaine (Thoma 1914). Novocaine replaced cocaine, ushering in the modern era of local anesthesia and allowing for the development of new, more effective, and safer techniques (Matas 1934b).

As the patent for novocaine was German, during the First World War the United States Government provided its chemical industry with the formula to manufacture the drug without having to depend on the German license and, in an attempt to protect their product, changed the name to procaine. When the war ended, Germany lost the patent (Smith 1920; Benedict et al. 1932; Nevin and Puterbaugh 1949; Link and Alfred Einhorn 1959). Today novocaine is more commonly known as procaine (Figure 1.2).

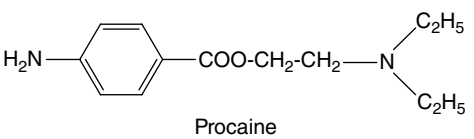


Figure 1.2 Structural formula for novocaine, labeled procaine.

The Development of Local Anesthesia in Dentistry

Much progress has been made since local anesthesia first came into general use. The following discussion, not intended to be exhaustive, highlights the major twentieth and twenty-first century developments in anesthesia, vasoconstriction, instruments, and techniques used in dentistry.

Local Anesthetics

As discussed above, the first local anesthetic was cocaine, but the risks it entailed soon prompted the pursuit of other drugs. In 1890 Eduard Ritsert (1859–1946) developed benzocaine, sold under the trade name "Anësthesin." As it is scantly water-soluble however, it was used as a topical anesthetic (Nueve Arneimittel 1902). Novocaine, as noted earlier, was synthesized in 1904. It was safe, but since its effects were weak, it called for the addition of large quantities of adrenaline, especially for infiltration. To overcome the problem, in 1919 Alfred Kneucker of Vienna began to use 4% instead of 2% novocaine (Kneucker 1919). These concentrations were marketed in the United States beginning

in 1941 (Dobbs 1965). In 1944, however, the American Dental Association's Council on Dental Therapeutics disallowed them (Council on Dental Therapeutics 1944) on the grounds that toxicity increased geometrically with linear increases in concentration. In other words, 1 ml of 2% novocaine is four times as toxic as 1 ml of a 1% solution (Waters 1933). Their decision was also influenced, no doubt, by the reminiscence of the tragic consequences in the late nineteenth century of high concentrations (10–30%) of cocaine and the safety afforded by diluted doses (Pernice 1890; Schleich 1892; Reclus 1895). In 1949, Frank Everett not only showed that 4% novocaine solutions were indeed more effective than 2% solutions (both mixed with epinephrine) but that the 50% lethal dose (LD50), administered intravenously in rabbits and subcutaneously in rats, varied very little with concentration and, in fact, only depended on the total dose administered (Everett 1949). The Council on Dental Therapeutics has accepted the use of 4% novocaine ever since (Dobbs 1965).

In 1928, Otto Eisleb (1887–1948) synthesized a new local anesthetic, tetracaine, distributed under the trade name Pantocaine (Eisleb 1934). Tetracaine is very powerful but unfortunately also very toxic and its effects are delayed. The 2% novocaine and 0.15% tetracaine solution introduced by Cook-Waite in 1940 was intended to prolong and intensify the effects of the anesthetic (Dobbs 1965).

Novocaine, however, posed new problems, in the form of allergic reactions in patients and dentists (Guptill 1920; Klauder 1922). Since cartridge syringes were not in use at the time and dentists did not use gloves, the skin on their fingers was frequently in contact with the anesthetic. In 1920, Arthur Guptill reported the first case of allergic dermatitis in one such professional (Guptill 1920).

These developments led to a search for an alternative to novocaine, but of the many developed in the first half of the twentieth century, none proved to be clearly better. In 1943, Swedish chemists Nils Isak Löfgren (1913–1967) and Bengt Lundqvist (1922–1953) synthesized a xylidine derivative called lidocaine, chemically very different from novocaine, but safe, more powerful, and virtually allergy-free (Löfgren and Lundqvist 1946; Gordh et al. 2010). On the grounds of the studies conducted by Hilding Björn (1907–1995) and Sven Huldt, it came to be considered the standard local anesthetic and remains the standard to this day (Björn and Huldt 1947). Around that time Björn authored another breakthrough, a method to assess the efficacy of local anesthetic solutions in dental practice by electrically stimulating teeth with a pulp tester, which delivers objective data on pulpal anesthesia and its duration, overcoming the bias inherent in earlier, more subjective methods (Björn 1946, 1947). In 1948, Astra Pharmaceutical Products Inc. introduced lidocaine in the United States and Sweden (Gordh et al. 2010). New amide-type anesthetics began to make their appearance soon after. In 1957, for instance, mepivacaine and bupivacaine were developed by Bo af Ekenstam et al. (1957) and the former was marketed in the United States by Cook-Waite in 1960 (Dobbs 1965). Nils Löfgren and Cläes Tegner synthesized prilocaine in 1960 (Löfgren and Tegner 1960) and in 1972 Adams et al. developed etidocaine (Adams et al. 1972). Articaine was synthesized in 1969 (Frenkel 1989; Rahn and Ball 2001; Malamed 2004) by Roman Muschaweck (Rahn and Ball 2001; Vogel 2007) at Hoechst AG, Frankfurt, and Winther and Nathalang (1972) published the first paper on the substance in 1972.

One characteristic development in the history of local anesthetics is the steady downward trend in the recommended doses used in dentistry. Thus, for instance, the maximum dose of novocaine recommended by Fischer in 1910 was 500 mg (Fischer 1910), whereas today it is 400 mg (American Dental Association 1984). The 1000 mg maximum dose of lidocaine initially recommended (Lozier 1949; Gordh et al. 2010) has now been lowered to 300 mg (American Dental Association 1984). With mepivacaine the original recommendation for 7.9 mg/kg was later reduced to 6.6 mg/kg (Zinman 1976) and today stands at 4.3 mg/kg (American Dental Association 1984).

Vasoconstrictors

The first and to date the best vasoconstrictor, epinephrine, continues to be widely used, although maximum concentrations and doses have changed. In 1910, Fisher recommended maximum doses of 312 µg (Fischer 1912) and Mayer no more than 1000 µg (Mayer 1924). The concentrations used in those days were on the order of from 1:20 000 (50 µg/ml) to 1:40 000 (25 µg/ml) (Fischer 1912; Thoma 1914; Hein 1917; Smith 1920; Steadman 1923). The aim of these high concentrations was to strengthen the weak effects of novocaine.

In 1938, Tainter showed that 2% novocaine solutions together with 1:25 000 (40 µg/ml) epinephrine caused nervous reactions such as shaking and sweating in 42% of patients and dizziness in 9%,due to high concentrations of epinephrine. Reducing the concentration to 1:50 000 (20 µg/ml) led to a significant decline in such reactions (Tainter et al. 1938). In 1953, the Council of the New York Institute of Clinical Oral Pathology sought an official report from the New York Heart Association (NYHA) on the administration of epinephrine to cardiovascular patients. In October 1954, the NYHA recommended a maximum concentration of 1:50 000 (20 µg/ml) and an absolute maximum dose of 200 µg (Report of the Special Committee of the New York Heart Association 1955). In 1964, the

American Dental Association, in conjunction with the American Heart Association, confirmed the NYHA recommendations for the maximum epinephrine concentration and dose (ADA-AHA 1964).

Until 1931, epinephrine was the only vasoconstrictor allowed by the Council on Dental Therapeutics (1931), although nordefrin hydrochloride (cobefrin, corbadrine, or corbasil) was introduced in 1933 at concentrations of 1:10 000 (100 µg/ml) by Cook-Waite laboratories (Dobbs 1965). In 1940, Mizzy Laboratories Inc. introduced phenylephrine (neosynephrine) at concentrations of 1:2500 (400 µg/ml) (Dobbs 1965). Levonordefrin, the levo isomer of nordefrin, was proven to be more powerful than the dextro form in 1957 (Moose 1959). In 1946, Swedish researcher Ulf Svante von Euler (1905–1983) (Gordh et al. 2010) was the first to isolate norepinephrine (Von Euler 1946a, 1946b), the more potent levo form of which was introduced in the 1950s (Dobbs and de Vier 1950; Epstein et al. 1951; Berling and Björn 1951). In the end, however, of all the sympathomimetic vasoconstrictors developed, the original, epinephrine, has proved to be the safest and most powerful. Noradrenaline is not only less effective in anesthetizing pulp with different local anesthetics (Berling and Björn 1951; Brown 1968), but more dangerous insofar as it may provoke blood pressure spiking (Boakes et al. 1972; Okada et al. 1989).

Felypressin (octapressin), a vasopressin (a hormone produced by the posterior lobe of the pituitary gland) derivative synthesized by Vigneaud et al. in 1953, constitutes a wholly different approach to vasoconstrictors (Du Vigneaud et al. 1953). As a polypeptide unrelated to sympathetic-mimetic substances governed by an entirely different mechanism, it can be used where the latter are contraindicated. Felypressin is used at concentrations of 0.03 International Units, i.e. a concentration of 1:1 850 000 (0.54 µg/ml), with 3% prilocaine. It was studied in 1966 by Cläes Berling with satisfactory results, although not as good as 2% lidocaine with 1:80 000 (12.5 µg/ml) epinephrine (Berling 1966). Felypressin is presently marketed in a number of European countries, but not in the United States.

Instruments

Early in the use of local anesthesia, and especially in the first few decades of the twentieth century, needles were re-usable, thick (Fischer 1912; Smith 1920), and made of platinum, steel, or a platinum–iridium alloy (Fischer 1912; Thoma 1914; Tompkins 1921). They broke easily (Blum 1919; Tompkins 1921) and the steel models corroded with use (Fischer 1912; Thoma 1914; Tompkins 1921). Needles made of new stainless-steel alloys were introduced in the 1940s and were not only stronger but finer in caliber, down to 25-gauge (25G) (Harrison 1948; Bump and Roche 1973). In 1959, the Cook-Waite and Roehr laboratories introduced disposable, sterilized needles to prevent viral hepatitis (Dobbs 1965). Modern disposable needles with new alloys are highly resistant to breakage and come in even finer calibers, 27G or 30G, although they tend to bend rather easily (Robison et al. 1984).

Becton and Dickinson glass syringes appeared in 1897 and glass ampoules of novocaine and epinephrine solution were introduced in 1914 (Dobbs 1965). Prior to their appearance, dentists had to mix the solution themselves by dissolving anesthetic tablets in distilled water with salts (Fischer 1912). Around 1920, military surgeon and World War I veteran Harvey S. Cook devised the cartridge system (a cartridge containing the anesthetic attached to a syringe) which, much like a rifle cartridge, could be loaded and injected into a single patient (Dobbs 1965), enhancing safety, sterilization, and speed (Nevin and Puterbaugh 1949). Later, Cook-Waite introduced a cartridge he called a "carpule," a name that became so popular that even today cartridges are known as carpules in many dental clinics (Nevin and Puterbaugh 1949). In 1935, the Novocol Chemical Company brought out vacuum-packed cartridges, extending the shelf life of solutions, and in 1947 the same company introduced a kind of screw at the upper end of the syringe plunger and a thumb ring for aspiration (Nevin and Puterbaugh 1949; Dobbs 1965).

The first papers on aspiration prior to injection appeared at the end of the 1950s (Harris 1957; Seldin 1958) and in 1957 the Council on Dental Therapeutics recommended routine aspiration before any injection (Council on Dental Therapeutics 1957). Self-aspirating, cartridge-type syringes appeared in the early 1970s (Evers 1971; Cowan 1972; Corkery and Barret 1973), although the first self-aspirating cartridge, attributed to Niels Bjorn Jorgensen (1894–1974), was designed in the early 1960s (Monheim 1965).

Anesthetic Techniques

US surgeon William Stewart Halsted (1852–1922) was the first to block the mandibular nerve in 1884 (Hall 1884), although he left no record of whether the technique used was intra- or an extra-oral. In his 1910 book, German dentist Guido Fischer (1877–1959) (Groß 2018) described and popularized the indirect mandibular nerve block, otherwise known as the 1–2–3 technique (Fischer 1912) attributed to Braun in 1904 (Lindsay 1929). In 1924, Boris Levitt of New York developed the direct technique (Levitt 1924), also known as the conventional technique because it is the one most commonly used even today. In 1940, Laguardia of Montevideo developed a closed-mouth mandibular block technique (Laguardia 1940), which was rediscovered by

Akinosi of Lagos in 1977 (Akinosi 1977). In 1973, a new mandibular block technique was described by Australian dentist George Albert Edward Gow-Gates (1910–2001), which he had been perfecting since 1947 but which had not been published earlier (Gow-Gates 1973; Gow-Gates and Watson 1989).

Intraligamentary injection, one of the oldest techniques known, was first described by Emilie Sauvez of Paris in 1905 (Sauvez 1905), but as he did not lay claim to it as an original technique, it may have been in use prior to that date, perhaps in 1904 by Guido Fischer. Although Cassamani of Paris wrote his doctor's thesis on this technique in 1924 (Cassamani 1924), it was not included in the scientific literature until the 1970s, when it was described by Robert Lafargue (1973) and Chenaux et al. (1976). In 1981, a paper by Richard Walton et al. retrieved the method for the English-speaking world (Walton and Abbott 1981). According to Mendel Nevin and Pliny Guy Puterbaugh, the intra-pulp technique was first used in 1895 (Nevin and Puterbaugh 1949).

The foremost technique for blocking the upper maxillary nerve behind the tuberosity (high tuberosity approach) was developed after 1913 by Arthur Ervin Smith and described in 1920 (Smith 1920). The greater palatine foramen technique was first described by Juan Ubaldo Carrea (1883–1956) of Buenos Aires in 1921 (Carrea 1921).

Another technique for administering anesthetic solutions is high-pressure jet injection, based on high-pressure injection of a flow of very fine droplets which penetrate the skin and mucus and get into the tissues. It was used on human beings for the first time in 1947 by Frank Figge et al. (Figge and Scherer 1947). That same year, another paper describing a device called hypospray (Hingson and Hughes 1947) was published, but this device was not used in dentistry until Margetis et al. implemented it in 1958 (Margetis et al. 1958). The dermojet, an instrument specifically designed for dentistry, was developed in 1960 (Roberts and Sowray 1987). New and improved devices continued to be developed, the most prominent of which is the syrijet introduced in 1971 (Bennett and Monheim 1971; Epstein 1971).

Power-operated injection systems constitute another group of techniques for administering anesthetics. The history of the use of electricity has been revised (Kane and Taub 1975; Malamed and Joseph 1987), with the consensus being that the first reference was authored by Scribonius Largus, a Roman physician during the period of Tiberius and Claudius (first century) (Chinchilla 1841). In his treatise *de Compositionibus Medicamentorum* (Scribonii 1529) Largus described the use of an electric fish [the marbled electric ray (*Torpedo marmorata*): Kane and Taub 1975] to alleviate pain. Centuries later, in Wesley 1760, Methodism founder John Wesley (1703–1791) published *The Desideratum*, in which he addressed the application of electrodes to relieve pain. The first reference in the application of electrodes to alleviate tooth-related pain was penned by another British scientist, James Ferguson, in 1770 (Ferguson 1770). In 1858, Jerome B. Francis reported 164 cases of electricity-mediated painless tooth extractions after the application of electrodes to the teeth in an article published in *The Dental Reporter* (Francis 1858). The impact of Francis's paper in the United States and Europe was enormous in the years thereafter, but its influence declined due to the poor results obtained in the late nineteenth and early twentieth centuries. As early as 1858, the London College of Dentists advised against its use because electricity was found to have no anesthetic effects and heighten pain and the few favorable results were attributable to "distraction" (Kane and Taub 1975). With the description of gate control theory (Melzack and Wall 1965) in 1965 and the mechanisms of pain modulation, truly operative systems have begun to be developed. In medicine, a technique known as TENS (transcutaneous electrical nerve stimulation) is used, whose equivalent in dentistry is called EDA (electronic dental anesthesia) (Malamed et al. 1989). The first practical system to be marketed for use in dentistry was Ultracalm in 1989 (Silverstone 1989) and more recently in 1994, 3M brought out a smaller and more accessible piece of equipment specifically applicable to dentistry, which goes by the name of Dental Electronic Anesthesia System, 8670 3M Dental (Croll and Simonsen 1994).

Power-driven injection systems are yet another technique for administering anesthetic solutions. Spring-driven or gas-actuated syringes introduced in the 1970s were designed to inject solutions while maintaining a constant pressure and hence a more uniform injection flow (Roberts and Sowray 1987). In 1997 a new, even more sophisticated apparatus called "the Wand" appeared, a computerized injection system developed by Dr. Mark Hochman of New York that automatically adapts the pressure to ensure a slow and constant flow at all times (Friedman and Hochman 1997) and separating injection rate from pressure. All these systems have built-in aspiration.

Twenty-First Century Developments

Oraqix® gel was introduced to the market in 2005. As a derivative of eutectic mixture of local anesthetic (EMLA) cream it contains 5% topical anesthetic in a 1:1 eutectic blend of 2.5% lidocaine and 2.5% prilocaine, but designed for use in the oral cavity. It is a noninjectable, thermoreversible anesthetic gel characterized by low viscosity at ambient temperature. When introduced into the

periodontal pockets, however, the body temperature converts it into an elastic gel that remains at the application site, which it anesthetizes with low risk of dissemination to other areas of the mouth (Friskopp and Huledal 2001; Friskopp et al. 2001; Herdevall et al. 2003; Magnusson et al. 2003) (see Chapter 12).

In 2008 the US Food and Drug Administration (FDA) authorized the inclusion of phentolamine mesylate in dentistry cartridges under the trade name *OraVerse*® for administration in standard syringes to reduce the duration of anesthesia in soft tissue (Tavares et al. 2008; Malamed 2008).

As a nonselective α-adrenergic antagonist, phentolamine neutralizes the vasoconstrictive effect of epinephrine and the other vasoconstrictive sympathomimetics (norepinephrine and levonordefrin). It was synthesized in 1950 at the CIBA laboratory in Basel, Switzerland, by Urech et al. (1950) and marketed in the United States in 1952 (Hersh et al. 2008) under the trade name Regitine® (Weaver 2008).

Phentolamine is injected into the same site as the vasoconstrictive sympathomimetic-bearing local anesthetic to block the effect on the α-adrenoreceptors. The outcome is vasodilation that increases the local blood flow, carrying the local anesthetic from the oral submucosa into the bloodstream to restore normal sensation in the oral and perioral tissues much more quickly, reducing the duration of soft tissue anesthesia by half (Hersh et al. 2008; Tavares et al. 2008) (see Chapter 6).

The *pH Onset System* developed by Dr. Mic Falker (Malamed and Falkel 2013), appeared in the United States in 2010, although much earlier papers on the method can be found in the literature (Davies 2003). Automated, speedy, and sterile, this device is highly practical for alkalinizing local dental anesthetic cartridges bearing sympathomimetic vasoconstrictors such as epinephrine, which usually have a pH of around 4 (Annex 14). The device raises the pH to a value very close to the physiological 7.4, reducing the burning, stinging, or pain attendant on the initial insertion of these solutions. It also aims to reduce anesthetic latency (Malamed et al. 2013) (see Chapter 11).

Intranasal maxillary local anesthesia Kovanaze™ (intranasal 3% tetracaine and 0.05% oxymetazoline spray) is a needle-free means of achieving dental local anesthesia and was approved by the US FDA in June 2016 for anesthesia of the anterior teeth and maxillary premolars (Saraghi and Hersh 2017). Kovanaze® is a formulation of two well-known medications: local anesthetic (tetracaine) and vasoconstrictor (oxymetazoline) for intranasal administration were combined based on the fact that these medications have been used for many years to provide local anesthesia for surgical and diagnostic procedures in the nasal cavity (Hersh et al. 2017) (see Chapter 20).

Frequency of Use of Local Anesthesia in Dentistry

In the United States the number of cartridges/injections per year grew from 30 million in 1950 to 300 million in 2010, while worldwide the number rose from 730 million in 1980 to 1 billion in 2000. Around 30% can be estimated to consist of mandibular blocks (Annex 1).

According to these data, local anesthesia is the most prominent tool at dentists' disposal to control the pain induced by their treatments. The anesthetics involved are widely used by dentists the world over and in their absence, practice of the profession is simply unthinkable.

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