THE NEW YORK SCHOOL OF REGIONAL ANESTHESIA

Hadzic's TEXTBOOK OF Regional Anesthesia AND ACUTE PAIN MANAGEMENT

Second Edition

Admir Hadzic

Mc Graw Hill Education

The New York School of Regional Anesthesia

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SECOND EDITION

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This book is dedicated to Dr. Steven Dewaele (1974–2016), for he, the Ironman and essential marine of NYSORA's team, has inspired many by his zeal for life and the dedication with which he pursued everything he aimed at.

"The most dangerous risk of all is the risk of spending your life not doing what you want on the bet that you can buy yourself the freedom to do it later."

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PREFACE

The first edition of *NYSORA's Textbook of Regional Anesthesia and Acute Pain Management* (McGraw-Hill, 2007) was a compendium of knowledge in regional anesthesia and acute pain medicine that quickly became a gold standard for students, practitioners, and test-takers alike. Yet, clinical practice marches on, and over 200 key opinion leaders and the worldwide community of NYSORA's educators worked diligently over the past 4 years to update the first edition. It is now my privilege to present the second edition of the textbook.

The material in this edition has been organized into thematic sections. Writings on history of local and regional anesthesia is often unjustly limited to its very beginnings in the late 1800s and early 1900s. However, a great deal of innovative and pioneering work has taken place in more recent history, that is now featured in the current edition. We have added numerous new anatomical dissections, diagrams, and functional anatomy illustrations developed by the NYSORA team for practitioners of regional anesthesia and pain medicine. NYSORA's teaching of these techniques is based on the principles of injecting local anesthetics within connective tissue sheaths; consequently, significant effort was invested in functional regional anesthesia anatomy and in illustrations that demonstrate the importance of this concept. Sections on connective tissues and the ultrastructural anatomy of the neuraxial meninges were contributed by a group of Spanish collaborators, led by Dr Miguel Angel Reina. Their sections represent a collection of uniquely educational electron microscopic images that offer insights into the mechanisms of neural blockade, causes of failures and the anatomical basis for vulnerability of neural structures to anesthesiology interventions. I believe that these sections and their timeless images will be remain relevant for generations of students to come.

The section on pharmacology features exciting information that is emerging on controlled-release local anesthetics that extend the analgesic benefits of neural blockade. New knowledge on this topic is being published as this textbook is being printed; the reader is suggested to check the latest relevant literature to complement the information that was available at the time of publication.

The section on equipment for peripheral nerve blocks features an expanded chapter on new equipment, such as the development of needles and catheters and novel equipment for needle-nerve and injection monitoring. For instance, Chapter 14 gives an overview of the role of peripheral nerve stimulation in modern practice of ultrasound-guided peripheral nerve blocks and step-by-step algorithms to facilitate understanding of this often-confusing topic.

New to the second edition is an entire section on patient management considerations and regional anesthesia pathways. In Chapter 15, Dr Barrington's team contributes a didactic outline of the steps and processes toward evidence-based clinical pathways that incorporate big data, such as building pathways for specific surgical populations. The section also features two chapters on the effect of local anesthetics and regional anesthesia on cancer recurrence. The immune system and how it can be influenced by surgery and anesthesia are evaluated for possible mechanisms by which regional anesthesia could confer benefits in patients with cancer in Chapters 17 and 18.

Part 3B discusses the clinical practice of regional anesthesia, starting with local and infiltration anesthesia. Dr Raeder's team describes the use of local anesthetics for intra-articular and periarticular infiltration (Chapter 19), and Dr Imran Ahmad shares a wealth of clinical and teaching experience on the use of local anesthetics and ultrasound technology for airway management (Chapter 20).

Intravenous regional (Bier) blocks are still practiced worldwide. A revised chapter on intravenous regional anesthesia for upper and lower extremity surgery was contributed by Dr Alon Winnie and his former students. The chapter features an updated reference list and step-by-step guidance for clinical practice.

In Part 3C, the chapters on neuraxial and epidural anesthesia have been thoroughly updated and feature a wealth of anatomical, practical, and clinical considerations, including complications and their management. A new chapter on the etiology and management of failed spinal anesthesia is highly practical and will be of interest to both students and practitioners of anesthesiology (Chapter 23A). The chapter on epidural anesthesia contributed by Drs Toledano and Van de Velde features vast amount of physiologic, pharmacologic, and practical management information, and it is a good example of the efforts invested in making this edition of the textbook up-to-date.

Chapter 27 on postdural puncture headache now includes a number of electron microscopic images that facilitate understanding of the underlying pathophysiology and instructional diagrams that guide treatment.

Part 3D focuses on the latest techniques and information pertaining to ultrasound-guided nerve blocks. Beginning with equipment and the physics behind image optimization and artifact reduction, the chapters progress to the practical aspects of ultrasound-guided techniques for peripheral nerve blocks of the upper and lower extremities (Chapters 33A–33H) and for truncal blocks (Chapters 34 and 35). The techniques of locoregional anesthesia for maxillofacial and eye surgery have also been updated with highly illustrative, all-new NYSORA illustrations that we developed over the past 3 years. Chapters 39 and 40 focus on ultrasound imaging of the paravertebral and neuraxial space.

The sections on pediatric regional anesthesia and the utility of ultrasound have been greatly expanded by some of most

respected practitioners and educators in pediatric anesthesiology and perioperative care.

Part seven features updated and much expanded chapters on the practice of regional anesthesia in patients with specific considerations and comorbidities.

The etiology of and avoiding complications of regional anesthesia are topics of great interest for practitioners of regional anesthesia. Part 9 discusses the mechanisms of and evidence-based recommendations on how to improve the management of patients with neurologic complications, including sections on advances in monitoring and medicolegal documentation.

Medical care is increasingly driven by evidence-based and cost-effectiveness considerations. Consequently, several chapters address the principles of pharmacoeconomics as they relate to regional anesthesia, rehabilitation, and postoperative outcome.

Part 12 of the book discusses the principles and practice of acute pain management, organization of the acute pain service, the role of intravenous patient-controlled analgesia and perineural catheters, and the epidemiology of pain. Special consideration was given to multimodal analgesia and pharmacologic interventions that increase patient's experience of anesthesia and surgery may have a role in preventing persistent postoperative pain (Chapter 75).

Part 13 focuses on education in regional anesthesia and the development of regional anesthesia fellowship programs in the United States.

Although the current trend toward ultrasound guidance is likely to become the most prevalent method of delivering most regional anesthesia techniques in the developed world, surface-based and electrical nerve stimulation techniques will likely continue to be practiced in many geographic areas without expertise ultrasound equipment. Because this edition was envisioned as a standardized text for global education in regional anesthesia and acute pain medicine, for completeness we opted to include principles of peripheral nerve blockade without ultrasound guidance (Part 15). These sections have been thoroughly updated from the previous edition, many practice updates being adopted from what we have learned utilizing ultrasound guidance. These chapters also include fascinating historical perspectives on the development of peripheral nerve block techniques throughout decades passed and how advances in anatomical, pharmacologic, and equipment influenced the their developments. The chapters also contain a wealth of anatomical information, teaching diagrams, and illustrations that add meaningful value to this textbook regardless of the needle guidance and techniques methods.

Finally, the book features two practical appendices. Appendix 1 contains a pragmatic guide for the use of regional anesthesia in the anticoagulated patient adopted for practices in Europe. The Appendix 2 illustrates the principles of disposition of injectates in tissue sheaths in common regional anesthesia techniques, contributed by a true pioneer in this area, Dr Philippe Gautier (BE).

No book is complete or without unavoidable errors regardless of the efforts invested. However, I believe that we have put together one of the most comprehensive texts on regional anesthesia and pain medicine to date and have spared no efforts to accomplish this. I thank and sincerely congratulate all collaborators and cordially invite readers to send along any discrepancies or suggestions to ana.lopez.517@gmail.com. As with the first edition, we will do our best to use the feedback to improve the textbook in a future edition to come a few years from now.

Respectfully,
Prof. Admir Hadzic

ACKNOWLEDGMENTS

Writing a textbook is an overwhelming endeavor; only those who have undertaken the work on a book can understand the efforts and the sacrifice that it entails. Throughout the couple of years it took to compile the new information and collaborate with such a large group of opinion leaders, researchers, and educators, a number of outstanding individuals were crucial to its successful completion.

Sincerest appreciation to my wife, life and work partner, Dr Catherine Vandepitte, without whose wisdom, advice, and esthetic guidance this book would not see the light of the day.

Huge thanks go to NYSORA's incredible illustrator, Vali Lancea. Thank you to Dr Monika Golebiewski's impeccable organizational skills, eye for detail, and beyond-describable work ethics, Monika was truly instrumental in tying the loose ends in the final push to complete this project.

A big thank you to the entire NYSORA support team: NYSORA-Europe, NYSORA's new CREER (Center for Research, Education, and Enhanced Recovery); our top surgeons and nurses at ZOL Anesthesiology; and more. Many thanks to Dr Alex Visan for his advice on the economics of regional anesthesia as well. Thank you to all current and former NYSORA fellows who have inspired much of the work.

The current NYSORA-Europe research team deserves a resounding thank you: Ingrid Meex, Gulhan Ozyurek, Aysu Emine Salviz, Marijke Cipers, Max Kuroda, and Greet Van Meir. You really rock!

Finally, thank you to the amazing managing editor, Brian Belval; your professionalism, common sense, and experience have provided the crucial guidance for this book to come together. Combined with co-managing editor Christie Naglieri, the production supervisor Catherine H. Saggese, and production manager Sonam Arora, we had the best team possible to make this book the gold standard it inspires to be.

Prof. Admir Hadzic

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PART 1

HISTORY

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CHAPTER 1

The History of Local Anesthesia

Alwin Chuan and William Harrop-Griffiths

INTRODUCTION

The history of local anesthesia lacks a distinct *Eureka moment.* It can be argued that regional anesthesia does not have in its history a pivotal day that signified the wholesale change from an era before local anesthesia to the dawn of a new and wonderful age that included parts of the body being rendered insensate for therapeutic reasons. We do not have the equivalent of October 16, 1846, and the trembling hands of William Thomas Green Morton. What we have is a remarkably slow concatenation of the three elements necessary for the administration of the vast majority of local anesthetics: a syringe, a needle, and a local anesthetic drug. Many, however, would argue that to these three need be added several other factors: a detailed knowledge of anatomy and an appreciation of the body's pain mechanisms and more objective methods to localize peripheral nerves and monitor administration of local anesthetics. We make no excuse for concentrating in this chapter on the early history of local anesthesia to dissect the development of these three vital components.

BEFORE COCAINE

The origins of the first attempts at some form of local analgesia or anesthesia are lost in the mists of time. Direct nerve compression and the direct application of ice to peripheries before surgery have distant origins but were certainly in regular use from the latter half of the eighteenth century. The first detailed appreciation of the benefits of local anesthesia was written by James Young Simpson and published in 1848, decades before local anesthesia became a practical possibility (Figure 1–1). In this paper, he also described his own unsuccessful experiments with the topical application of a variety of liquids and vapors in an attempt to produce local anesthesia. The paper was published less than 2 years after Oliver Wendell Holmes had coined the term *anesthesia,* and it therefore almost certainly represents the first use of the term *local anesthesia,* although Simpson would have used the (arguably more correct) English spelling *anaesthesia.* However, Simpson was well aware that his were far from the first attempts to produce peripheral insensibility, for he refers to some ancient methods, which he considered "apocryphal," and also to Moore's method of nerve compression (Figure 1–2).[1]

Another distinguished British physician and president of the Medical Society of London in 1868 was Sir Benjamin Ward Richardson. He spent many years in the attempt to alleviate pain by modifying substances capable of producing general or local anesthesia. He brought into use no fewer than 14 anesthetics and invented the first double-valved mouthpiece for the administration of chloroform. He initially experimented with electricity before turning to the effects of cold as an anesthetic. Cold was known to produce a numbing effect and was used as far back as Napoleon's time when his surgeon, Baron Larrey, used its effects to alleviate pain. He introduced a method of producing local insensibility by freezing the part with an *ether spray,* which became the most practical method of using local anesthesia until cocaine's actions became apparent. The ether spray was utilized as a local agent until it was replaced in 1880 by ethyl chloride[2] (Figure 1–3).

COCAINE ANESTHESIA

The Origins

If local anesthesia has a Eureka moment, then it may have happened in the forests of South America. Centuries ago, an unnamed inhabitant of these climates may have been experimenting by putting leaves of various plants into his mouth and giving them a good chew. We can imagine that this would be a largely unrewarding hobby, but let us focus on the moment when he first placed a coca leaf into his mouth and masticated

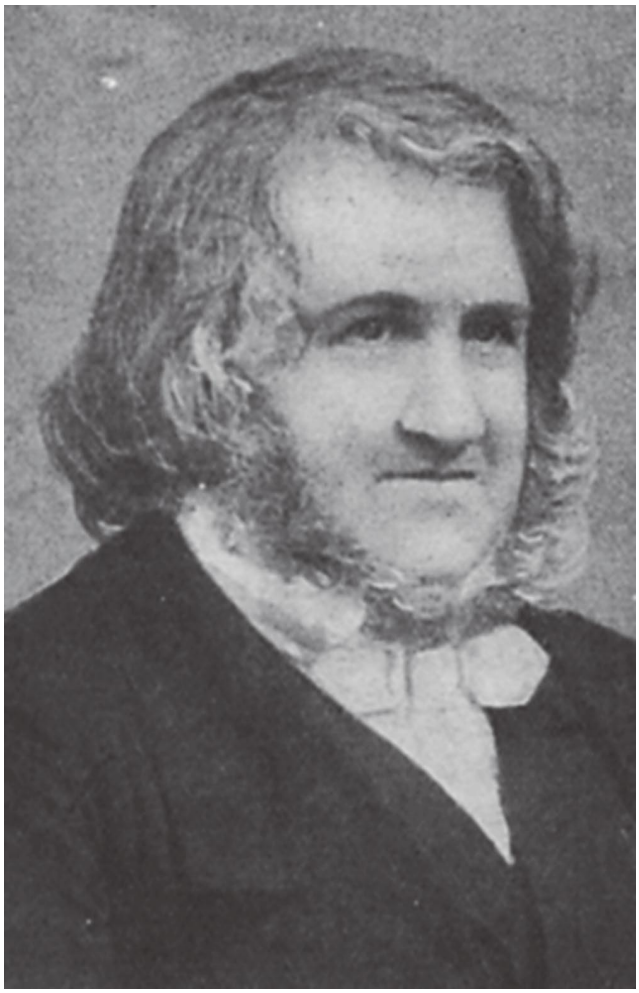

FIGURE 1–1. James Young Simpson.

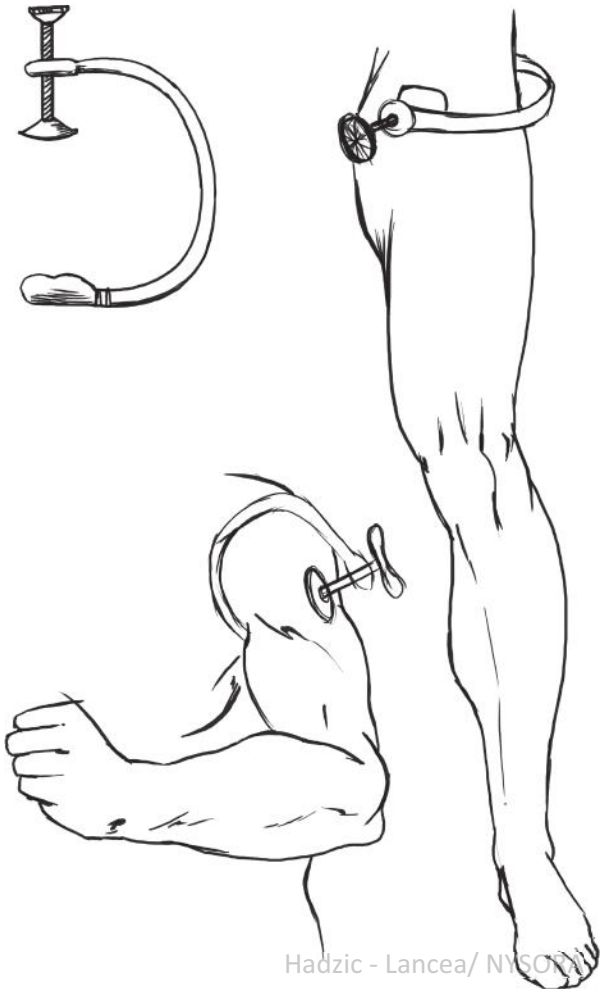

FIGURE 1–2. Nerve compression technique.

vigorously. Did he fall to his knees and shout in wonderment: "My lips have gone numb—surely this is the dawn of a new age of painless surgery!"? Almost certainly not—although he might have later told his friends that he felt somewhat excited, energetic, and euphoric while he chewed the leaves.

For thousands of years, South American peoples have chewed the coca leaf. It is a remarkable plant in that it contains vital nutrients as well as numerous alkaloids, most notably cocaine. The coca leaves are taken from a shrub of the genus *Erythroxylon coca,* named by Patrico Browne because of the reddish hue of the wood of the main species.[3] Many species of this genus have been grown in Nicaragua, Venezuela, Bolivia, and Peru since pre-Columbian times. *Erythroxylon coca* contains the highest concentration of the alkaloid known as cocaine in its leaves[3,4] (Figure 1–4).

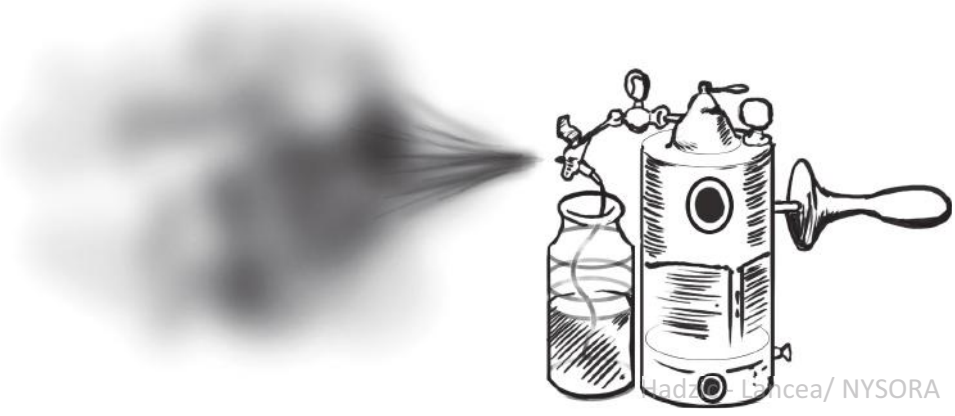

FIGURE 1–3. Ether spray.

FIGURE 1–4. Coca leaf.

Traditionally, the leaves were chewed for social, mystical, medicinal, and religious purposes. The Florentine cartographer Amerigo Vespucci (1451–1512) was arguably the first European to document the human use of the coca leaf.[5,6] In his account of his voyage to America on the second expedition of Alonso de Ojeda and Juan de la Cosa from 1499 to 1500, he reported that the inhabitants of the Island of Margarita chewed certain herbs containing a white powder.[7] 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. Pedro Pizarro (1515–1571), Francisco Pizarro's cousin, who played a leading role in the capture of the last king of the Incas, described coca consumption by the nobles and high officials of the Inca Empire.[8] After the fall of the Inca Empire in the early 1500s, coca consumption spread to the population at large, creating a drastic change in the entire social system.

When the Spaniards conquered South America, they initially ignored the aboriginal claims that the leaf gave them vigor and liveliness. They self-righteously declared the practice of chewing the leaf the "work of the Devil."[5] But, once they found that the claims of the natives were true, they not only legalized the leaf but also taxed it—taking 10% of the value of each crop. The taxes were then used to support the Roman Catholic Church—the main source of revenue for the church to thrive. In 1609, Padre Blas Valera wrote: "Coca protects the body from many ailments, and our doctors use it in powdered form to reduce the swelling of wounds, to strengthen broken bones, to expel cold from the body or prevent it from entering, and to cure rotten wounds or sores that are full of maggots. And if it does so much for outward ailments, will not its singular virtue have even greater effect in the entrails of those who eat it?"[9] If the padre had been blessed with the ability to foresee the future, perhaps his enthusiasm would have been redirected toward limiting the use of the leaf, and the field of anesthesia might have taken a different turn.

Another member of the clergy, Bernabé Cobo, who spent his life bringing Christianity to the Incas, was the first to describe the anesthetic effects of coca. In a 1653 manuscript, he mentioned that toothaches could be alleviated by chewing the coca

leaves. In 1859, an Italian physician by the name of Paolo Mantegazza had witnessed the use of coca by the natives in Peru. He wrote a paper describing the medicinal use in the treatment of "a furred tongue in the morning, flatulence and whitening of the teeth."[10]

Needles and Syringes

If local anesthetic drugs are the bullets used when fighting pain, the gun needed to fire these bullets is made up of a syringe and a needle. Without the bullets, the gun is useless, and just as certainly, without the gun, the bullets will have little effect. The development of the hypodermic syringe and needle was therefore an important prerequisite for the use of cocaine for anything but topical application. A thorough sifting of the available historical evidence and independent reexamination of the sources support the following outline of the facts: In 1845, Francis Rynd described the idea of introducing a solution of morphine hypodermically in the neighborhood of a peripheral nerve to alleviate neuralgic pain.[11] He introduced the solution by means of gravity, passively through a cannula once the trocar had been removed.

Several centuries passed before the development of a syringe to deliver medicine was described by Alexander Wood (Figure 1–5). Wood, a contemporary of James Young Simpson, in 1855 was the first to combine needle and syringe for hypodermic medication. He used the equipment manufactured by a gentleman by the name of Ferguson, who had developed the graduated glass syringe and hollow needle for the purpose of treating aneurysms by injecting ferric perchloride into the aneurysm to form a coagulated mass. Wood, a physician interested in the treatment of neuralgia, reasoned that morphine might be more effective if it were injected close to the nerve supplying the affected area. Although morphine may have some peripheral actions, and the effect of Wood's morphine was almost certainly central, he was nevertheless the first to think of the possibility of producing nerve blockade by direct drug injection. Thus, he has been called the "father-in-law" of local anesthesia—all he lacked was an agent that worked locally. Wood's contribution was therefore his procedure of subcutaneous injection. This technique was subsequently adopted by C. Hunter and renamed hypodermic injection, presumably because Hunter's purpose was to provide systemic absorption of medications injected.[12,13]

The Introduction of Cocaine

The growth in Western science and technology exploded during the nineteenth century. Six years after Charles Darwin's controversial book, *On the Origin of Species by Means of Natural Selection,* Joseph Lister was an important figure in changing the face of surgery. He applied Pasteur's principles of bacterial growth in eliminating sepsis in the operating theatre. Other prominent figures contributed to the understanding of human physiology, such as Sydney Ringer's discovery of the need for calcium and potassium to maintain cardiac excitability, significantly advancing medical care. And then—there was cocaine.

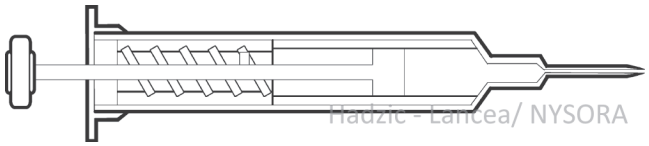

FIGURE 1–5. Early syringe.

Although the stimulant and hunger-suppressant effects of coca had been known for years, the isolation of the cocaine alkaloid was not achieved until 1855. Scientists attempted to isolate cocaine, but no one was successful for two reasons: Coca did not grow in the colder environment of Europe, and the chemistry involved was unknown at that time. Finally, in 1855, the German chemist Friedrich Gaedcke was able to isolate the cocaine alkaloid and publish the description in the journal *Archiv der Pharmacie*. In 1856, Friedrich Wöhler asked a colleague to bring him a large amount of coca leaves from South America. Wöhler then gave the leaves to Albert Niemann, a PhD student at the University of Göttingen in Germany, who then developed an improved purification process. His dissertation, *On a New Organic Base in the Coca Leaves,* published in 1860, earned him his doctoral degree. Of interest, he described cocaine as having "a bitter taste, promotes the flow of saliva, and leaves a peculiar numbness, followed by a sense of cold when applied to the tongue."[14,15]

Following Niemann, the first experimental study on cocaine was conducted by a former naval surgeon from Peru, Thomas Moreno y Maiz. He discovered that the injection of cocaine solutions caused insensitivity in rats, guinea pigs, and frogs. But, it was not until 1880, when Basil Von Anrep experimented on himself, that the application of cocaine for surgery was appreciated. Von Anrep injected a small amount of cocaine under the skin on his arm and noted that the area became insensitive to pinpricks. He did the same to his tongue with the same effect. He published his findings with the caveat "the animal experiments have no practical application; nevertheless I would recommend trying cocaine as a local anesthetic in persons of melancholy disposition."[16]

The groundwork was in place, but the final step toward the clinical use of cocaine had yet to be taken. Viennese ophthalmologist Karl Koller (1857–1944) rose to the challenge (Figure 1–6). Koller was an intern working in the Viennese General Hospital, where he was befriended by Sigmund Freud[17] (Figure 1–7). Freud wanted to know more about the stimulating action of cocaine, which he hoped might prove useful in curing one of his close friends of morphine addiction. This friend was a pathologist and had developed an agonizingly painful thenar neuroma secondarily to cutting himself during the performance of an autopsy. Freud was able to obtain a supply of cocaine from the pharmaceutical firm Merck. He shared it with Koller, who during the spring of 1884 helped him investigate its effects on the nervous system.[18]

Koller had dreams of achieving an appointment to assistant and knew his chances would be greatly enhanced by the creation of a respectable piece of research. The research he produced proved worthy enough, but interpersonal animosity intervened, and he was not awarded the position. Deeply disappointed, he moved first to the Netherlands, then to the United States.[19] In July 1884, Freud published a review of

FIGURE 1–6. Carl Koller.

cocaine and his experiments with the drug, again noting, but without lending any particular attention to, the alkaloid's anesthetic effect on mucous membranes.[20] It was Koller who grasped the importance of this observation. His discovery was no accident, for he was keenly aware of the limitations of general anesthesia in ophthalmic surgery. Because of his past experience in the field of ophthalmology, Koller understood what others had failed to recognize. Many eye surgeries at that time were still being performed without anesthesia. Almost four decades after the discovery of ether, general anesthesia by mask had a number of limitations for ophthalmic surgery (eg, the anesthetized patient could not cooperate with the surgeon, the anesthesiologist's apparatus interfered with surgical access). At that time, many surgical incisions in the eye were not closed, as fine sutures were not yet available. Vomiting from chloroform or ether threatened to cause extrusion of the internal contents of the globe, markedly increasing the risk of permanent blindness. As a medical student, Koller had worked in a laboratory searching for a topical ophthalmic anesthetic to overcome the restrictions posed by general anesthesia. The medications available at that time had proved to be ineffective.

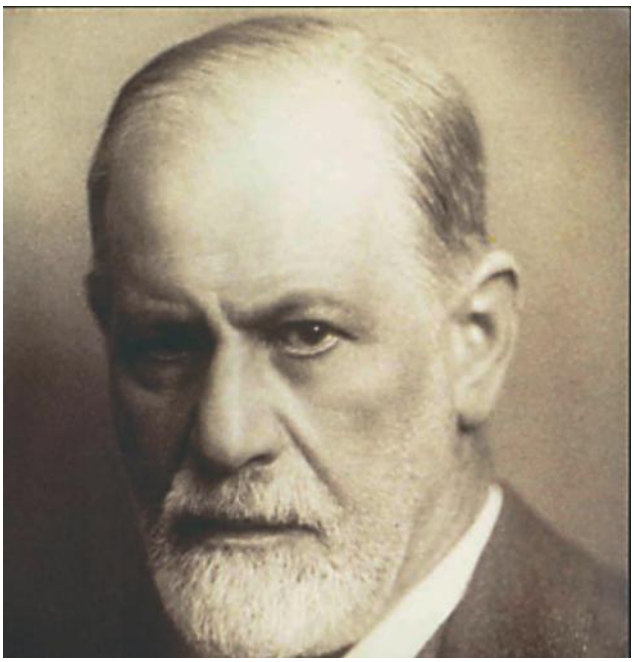

FIGURE 1–7. Sigmund Freud.

One day, Freud gave Koller a small sample of cocaine in an envelope, which he slipped into his pocket (an everyday occurrence in many American and European cities to this day). When the envelope leaked, a few grains of cocaine stuck to Koller's finger, which he casually licked with his tongue. His tongue became numb—if he had been able to mouth the word *Eureka* with a numb tongue, he may well have done so at this precise instant. At that moment, Koller realized that he had found what he had been searching for. He immediately created a suspension of cocaine crystals in his laboratory.[2] Koller realized that this had been noted by all who had worked with cocaine and that "in the moment it flashed upon me that I was carrying in my pocket the local anesthetic for which I had searched some years earlier."[1] In Freud's absence, he and another colleague, Joseph Gartner, dissolved a trace of the white powder in distilled water and instilled the solution into the conjunctival sac of a frog. After a minute or so, "the frog allowed his cornea to be touched and he also bore injury to the cornea without a trace of reflex action or defense." Koller wrote: "One more step had yet to be taken. We trickled the solution under each other's lifted eyelids. Then we placed a mirror before us, took pins, and with the head tried to touch the cornea. Almost simultaneously we were able to state 'I can't feel anything.'"[21,22] Then, he experimented with dog and guinea pig corneas with 2% to 5% cocaine solutions.[23]

Koller soon achieved the extraordinary notoriety he had longed for when in September 1884 he performed the first ophthalmologic surgical procedure using local anesthesia on a patient with glaucoma. The German Ophthalmologist Society Congress was to meet in Heidelberg in September 1884 and Koller was going to present his findings. Unfortunately, he was unable to attend. He asked Dr. Joseph Brettauer, an ophthalmologist from Trieste, to present his paper at the Congress. The effect of his work was immediate. Koller was able to present his findings in October of that year to the Viennese Medical Society. In late 1884, he published his findings.[21]

Physicians in the United States soon heard about Koller's amazing work. Dr. Henry Noyes of New York, an attendee of the Heidelberg Congress, published a summary of Koller's work in the *New York Medical Record*.[24] Another American physician, Dr. Bloom, translated Koller's article into English and published it in *The Lancet* in December of that same year. Koller's work was the trigger for the development of regional/local anesthesia. In the subsequent year, more than 60 publications on local anesthesia with cocaine appeared in the United States and Canada.

One of the most significant publications was that of N. J. Hepburn, an ophthalmologist from New York.[15] Self-experimentation was the standard for drug trials in those days.

To determine whether a drug was safe or effective, the researcher or physician commonly tried the drug personally. It takes courage to try a new drug on a patient, but it takes a particular and much greater form of courage to try that drug on yourself. Hepburn was no different from his colleagues. He gave himself a succession of subcutaneous injections of 0.4 mL (8 mg) of cocaine at 5-min intervals. By the eighth injection, the stimulating effects of the drug were strong enough that he decided it was best to stop. Unfortunately, Hepburn did not stop with those initial injections. He repeated the "experiment" 2 days later and 4 days after that, each time increasing the total amount of cocaine injected. Most likely by this time, he was hopelessly addicted.

By November 1884, the ophthalmologist C. S. Bull reported that he had been able to use cocaine to produce anesthesia of the cornea and conjunctiva in more than 150 cases.[25] He was enthusiastic about the advantages of the drug in that he saved time required for complete anesthesia with ether; patients were less nauseated, the engorgement of the ocular blood vessels (caused by ether) was eliminated, and he was less hampered by the anesthesia equipment required for inhalation anesthesia. Cocaine revolutionized eye, nose, and mouth surgery. Operations that had been exceedingly difficult or painful became routine when topical or injectable cocaine was used. Koller did not forget the contribution of his friend, Freud. He gave him the credit as his muse. Despite his disillusionment at not being foremost with the discovery, Freud is considered by many to be the founder of psychopharmacology because of his initial use of cocaine. He is considered the predecessor in the discovery and experimentation with mescaline, LSD, and amphetamines to modify behavior and to attempt to cure mental illness.[20]

Dangers of Cocaine

The "wonder drug" cocaine was soon sold everywhere and in almost everything. Following its isolation from the coca leaf, cocaine emerged as an ingredient in wine both in the United States and in Europe in amounts up to 7 mg/oz. In the original recipe for Coca-Cola (1866), coca leaves were included in the ingredients. It was not until 1906 when the Pure Food and Drug Act was passed that the Coca-Cola company began using decocainized leaves.[14] Until 1916, cocaine could be purchased over the counter at Harrods in London. It was found in tonics, toothache cures, and medicines (Figure 1–8). Coca cigarettes were sold with the promise of lifting depression. Those who purchased cocaine were promised in ads by the pharmaceutical firm Parke-Davis that it could "make the coward brave, the silent eloquent, and render the sufferer insensitive to pain." In the operatic world, it became commonplace to use cocaine to ease the pain of sore throats and to shrink nasal mucous membranes to enable the singers to improve the resonation of their voices.

Had cocaine's use been restricted to enhancing opera singing and local anesthesia, it would have become the achievement of nineteenth-century medicine. As had happened earlier with brandy, tobacco, morphine, and other drugs, cocaine was administered in too high concentrations and with too few precautions. In 1886, William Hammond, a former US Army Surgeon General, assured an audience of physicians that cocaine addiction did not exist. Based on self-experimentation, he concluded that regular use of cocaine was as easy to stop as quitting coffee. It did not have the addictive qualities of drugs like opium. But, when Hammond finished his lecture, an addiction specialist named Jansen Mattison offered a rebuttal. He related incidences of fierce addictions in patients under his care. He described cocaine's damaging effect on nerves and its ability to produce hallucinations, delusions, and emaciation. Many other practitioners began to encounter serious side effects.[26,27]

Mattison knew what he was talking about. Over the next several years, medical journals published hundreds of case reports of "cocainism." Unfortunately, many of the addicts were medical practitioners who had experimented on themselves, most notably Freud and William Stewart Halsted.[28,29] The opiate

FIGURE 1–8. Cocaine toothache drops.

addicts, promised a cure for their addiction, switched to cocaine, but continued to use both drugs, further compromising their health.

Several researchers deserve the credit for making the infiltration of cocaine safer. Maximillian Oberst, Ludwig Per-nice, and Carl Ludwig Schleich, all from Germany, described the use of low concentrations of cocaine as effective means of local anesthetia.[30] The Parisian surgeon Paul Reclus described the use of very low concentrations of cocaine as effective anesthesia without harmful side effects for tooth extractions and pulpotomies.[31]

About the same time, Halsted was experimenting with low concentrations of cocaine applied by compression devices. Unfortunately, he also became addicted to both cocaine and morphine and could not publish his results.[12,17,29] Over time, the maximum "safe" cocaine dosage for infiltration anesthesia was established at 50 mg.

AFTER COCAINE

As the undesirable effects of cocaine, most notably addiction and toxicity, gradually became known, new anesthetic drugs were sought to replace it. Local methods to provide anesthesia had to await the development of less-toxic drugs. Once the clinical usefulness of cocaine became evident, efforts were made by various researchers to identify the active portion of the cocaine molecule and to create new substances that possessed local anesthetic activity without the adverse side effects. Most of the chemical work involving the creation of local anesthetics took place in Germany from 1900 to 1930.[32]

Niemann, as part of his pioneering work on purifying cocaine, had hydrolyzed benzoic acid from cocaine. In the search for other benzoic acid esters with local anesthetic properties, amylocaine (stovaine) was introduced in 1903. It became popular for spinal anesthesia until it was shown to be an irritant. But, it was the development of procaine in 1904 by the German chemist Alfred Einhorn that revolutionized local anesthetics.[33] On November 27, 1904, Einhorn (1856–1917) patented 18 *para*-aminobenzoic acid derivatives that had been developed in the Meister Lucius and Brüning plants at Höchst, in Hesse, Germany. His compound Number Two was to bring about a radical change in local anesthetic practice. He named the new anesthetic Novocain.[11] Procaine (Novocain) was introduced into clinical practice by Professor Heinrich Braun in 1905. Braun published a study comparing this new anesthetic to stovaine and alypine, two other promising local anesthetics.[34] Procaine was found to be safe and quickly became the standard local anesthetic drug. Within a short time, procaine completely replaced cocaine as the most commonly used local anesthetic. But, because of the short duration of action and prominent allergic potential limiting its clinical effectiveness, the search for longer-lasting compounds continued.[11,18,26,35]

In the years that followed, several local anesthetics were synthesized and used in clinical practice until side effects or other unfavorable characteristics were noted. In 1925, Karl Meischer synthesized dibucaine, and in 1928 Otto Eisleb synthesized tetracaine. Both were effective local anesthetics and had the desirable qualities of longer duration and potency, but systemic toxic effects limited their usefulness for regional techniques other than for spinal anesthesia. Most of the compounds developed during this time were amino ester derivatives, similar to cocaine, with similar allergic potential.

A major breakthrough came in the mid-1940s when the Swedish chemists Nils Löfgren and Bengt Lundquist developed a new local anesthetic they called lidocaine. Lidocaine was an amino amide derivative, a stable compound not influenced by exposure to high temperatures and, most importantly, one that did not have the allergic potential of the ester-type local anesthetics. With the development of this amide-type anesthetic drug, a whole new class of local anesthetics was synthesized. In 1957, Af Ekenstam developed mepivacaine and bupivacaine, and in 1969 Löfgren and Claes Tegnér developed prilocaine. Prilocaine's synthesis began because of a desire to produce a local anesthetic with a potency similar to that of lidocaine but without lidocaine's systemic toxic effects. Unfortunately, it was soon discovered that large doses of prilocaine produced a metabolite that caused methemoglobinemia. Although probably not clinically significant, this discovery severely limited its use in clinical practice.[36] In 1972, etidocaine was introduced to the clinical scene but was soon discovered to lack a differential sensory–-motor blockade. Its clinical usefulness was therefore limited.

The only new ester local anesthetic developed in more recent times is chloroprocaine. Its rapid hydrolysis reduced the possibility of systemic toxicity, but its usefulness was restricted to procedures of short duration that did not produce a high degree of postoperative pain. In modern regional practices, it has been used both in spinal anesthesia and in nerve blocks for short, relatively painless procedures.

Two goals of modern pharmaceutical research have been development of amide anesthetics with lower toxicity and modification in the delivery of local anesthetics. Levobupivacaine and ropivacaine were both introduced commercially in 1996 as purified S-enantiomers rather than racemic solutions, with less risk of cardiac and central nervous system toxicity. More recently, liposomal delivery systems that allow slow release of commonly used local anesthetics have extended the duration of effect beyond 48 hours.

LOCAL ANESTHESIA TECHNIQUES

Infiltration Anesthesia

In 1895, a then-novel approach, termed *infiltration anesthesia,* had been promoted by Karl Ludwig Schleich (1859–1922).[35] Schleich applied the principle that pure water has a weak anesthetic effect but is painful on injection, whereas physiologic saline is not. In 1869, Pierre Carl Edouard Potain first observed that the subcutaneous injection of water produced local anesthesia. Halsted, a surgeon at Roosevelt Hospital in New York City, in a frank letter to the editor of the *New York Medical Journal* in 1885, declared that the "skin can be completely anesthetized to any extent by cutaneous injections of water."[37] In his own practice, Halsted had begun using water instead of cocaine in skin incisions, noting that the anesthesia did not subside completely when hyperemia reappeared.

In the belief that there was a solution capable of performing as a useful anesthetic that would not cause pain on injection, Schleich mixed 0.2% sodium chloride with 0.02% cocaine.

He used the mixture to produce cutaneous anesthesia for sebaceous cystectomy, hemorrhoidectomies, and small abscesses. Although Braun dismissed Schleich's solutions as "nonphysiologic," Schleich's work was important in advancing the application of small quantities of local anesthetics for surgical procedures. Because of the reported serious toxic reactions and fatalities reported with cocaine, enthusiasm for the utilization of local anesthesia had waned considerably. Paul Reclus undoubtedly understood that the cause of death from local anesthetics was related to overdose. He was able to demonstrate that absorption could be limited with lower concentrations of cocaine, a fact that Schleich obviously supported and implemented.[31] Schleich's approach still seems to be relevant, particularly with the recent European enthusiasm for *tumescent anesthesia,* in which sometimes-huge volumes of very dilute local anesthetic are used for surface surgery.

Conduction Anesthesia

With the excitement generated by Koller's report of cocaine anesthesia in 1884, several US surgeons concurrently entertained the idea of injecting cocaine directly into tissues to render them insensitive. William Burke injected five drops of 2% cocaine solution close to a metacarpal branch of the ulnar nerve and then painlessly removed a bullet from the base of his patient's little finger.[38] However, it was William Stewart Halsted (1852–1922; Figure 1–9) and his associate John Hall at Roosevelt Hospital in New York City who most clearly saw the great possibilities of conduction block.[39] Hall experimented on himself by blocking a cutaneous branch of the ulnar nerve in his own forearm.[41] He and Halsted did not stop with upper extremity injections; they also successfully injected the musculocutaneous (superficial peroneal) nerve of the leg. Hall described the manifestation of systemic symptoms such as giddiness, severe nausea, cold perspiration, and dilated pupils, but these symptoms did not stop these daring scientists from further self-experimentation. Halsted blocked Hall's supratrochlear nerve to remove a congenital cystic tumor. One can assume that both Halsted and Hall had run out of minor surgical ailments in themselves and therefore had to look to others on whom they could experiment. In the days long before ethics committees and informed consent, one is tempted to speculate about the true "volunteer" status of the poor, and most likely unsuspecting, medical students. Hall's report was unequivocal in predicting that this mode of administration of cocaine would find wide application in outpatient surgery once the limits of safety had been determined—remarkably prescient of him.[40]

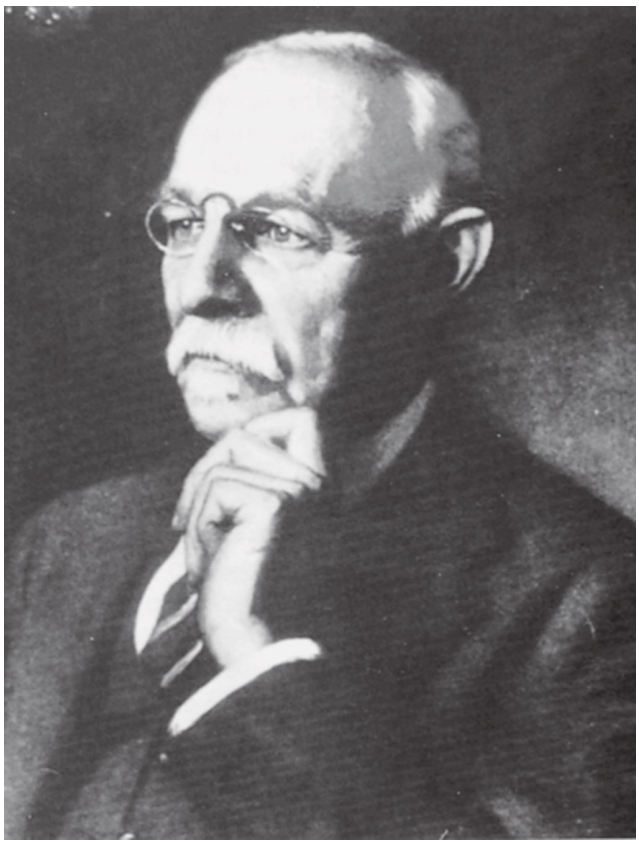

FIGURE 1–9. William Stewart Halsted.

Although the conduction blocks were successful, unfortunately, several members of their group became addicted to cocaine. No further publications about the usefulness of cocaine anesthesia for surgical procedures were presented. It is one of the great sadnesses of the development of analgesic drugs in the history of humankind that two of the most effective agents, morphine and cocaine, are wickedly addictive. They deprived medicine of many of the potential discoveries of its most gifted sons and daughters. However, that Hall and Halsted were the true progenitors of conduction anesthesia can scarcely be doubted.[17,26]

In 1891, François-Franck was the first to apply the term *blocking* to the infiltration of a nerve trunk in any part.[41] He correctly discovered that the effect of the blocking drug was not limited to sensory fibers, but provided blockade of all nerves, both motor and sensory. He noted that sensory anesthesia became apparent more rapidly than the motor paralysis, a fact confirmed by von Anrep's 1880 observations.[16] François-Frank described the action of cocaine as transitory and noninjurious, "physiologic and segmental" anesthesia. He may well have borrowed part of it from J. Leonard Corning, who in 1886 wrote that "the thought of producing anaesthesia by abolishing conduction in sensory nerves, by suitable means, should have been rife in the minds of progressive physicians."[42] Corning most likely got the idea from Halsted because he had frequently observed Halsted and Hall's work at Roosevelt Hospital in New York.

The advantage of utilizing cocaine as a local anesthetic was that it anesthetized only the section of the body where surgery was to be performed, the goal of regional techniques in modern practice. But, the price to be paid was in the duration of action and toxicity, not to mention the more commonly recognized problem of addiction. The dose of cocaine was limited to 30 mg because of rapid absorption. Unfortunately, the duration of anesthesia was therefore no more than 15 minutes. Corning, in 1885, began researching means of prolonging the local anesthetic action of cocaine for surgery. He believed that once cocaine was injected beneath the skin, capillary circulation was responsible for distributing, diluting, and removing the anesthetic substance. In one experiment, he injected 0.3 mL of a 4% solution of cocaine into a cutaneous nerve of the arm and

produced immediate anesthesia of the skin of the forearm. By compressing the extremity proximal to the site of injection with an Esmarch bandage, he was able to intensify and prolong the anesthesia to the forearm.[43]

Corning's successes with prolonging the action of local anesthetic with a physical tourniquet inspired Heinrich F. W. Braun to substitute epinephrine, a "chemical tourniquet," for the Esmarch tourniquet.[44] John Jacob Abel had isolated the pure form from the suprarenal medulla in 1897, and it had been subsequently used in ophthalmology to limit hemorrhage and in the treatment of glaucoma.[45] During its use in ophthalmology and subsequently in ear, nose, and throat surgeries, it was discovered that epinephrine prolonged the effect of cocaine, thereby allowing a reduction in dose and limiting side effects. Braun determined the optimal solution of epinephrine with cocaine by once again experimenting on himself. He discovered that the maximal dose that he could tolerate without side effects was 0.5 mg (0.5 mL of a 1:1000 solution of epinephrine). He coined the term *conduction anesthesia* when publishing the results of his experimentation.[46]

Intravenous Regional Anesthesia

The first reported use of intravenous regional anesthesia (IVRA) can be traced back to August Karl Gustav Bier (Figure 1–10), the originator of the infamous **Bier block**. Bier, a German surgeon (1861–1949), influenced surgery, anesthesia, and general medicine with his contributions through the decades. IVRA was first described by Bier in 1908. His method consisted of occluding the circulation in a segment of the arm with two tourniquets. He then injected a solution of dilute procaine through a venous cutdown in the isolated segment. The injected solution diffused through the entire section of the limb quickly, producing **direct vein anesthesia** in just a few minutes.[47] The anesthesia lasted as long as the upper tourniquet was in place. Recovery of sensation was rapid after the tourniquet was removed.[48] Despite his successes, IVRA was not widely used until the technique was reintroduced in the 1960s by C. M. Holmes.[49]

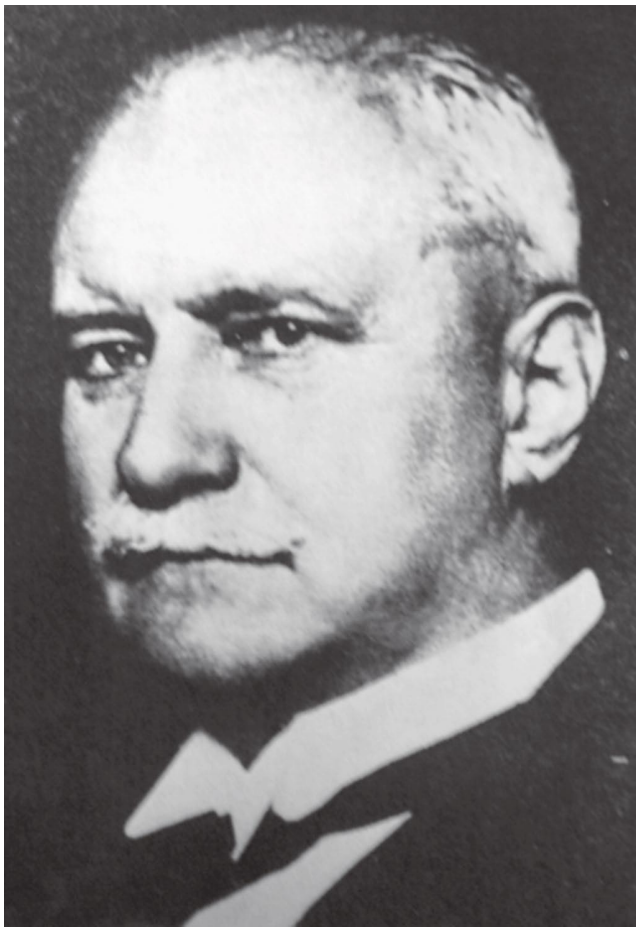

FIGURE 1–10. August Bier.

Spinal Anesthesia

Soon after its introduction in 1884, local anesthesia became popular with surgeons, particularly those in France, Germany, and the United States.[18] This was in large part due to concerns about the safety of inhalational anesthesia, which, increased by the introduction of chloroform, had given rise to significant worries about toxicity. General anesthetic mortality was high at this time, and there was a distinct shortage of personnel trained to administer general anesthesia.[50] In a bizarre twist, the first spinal anesthetic was given some 5 years before the first lumbar puncture. The term *spinal anesthesia* was introduced by Corning, a neurologist, in his famous paper of 1885: "Spinal Anaesthesia and Local Medication of the Cord With Cocaine."[42] He theorized that interspinal blood vessels would carry the local anesthetic (cocaine) via communicating vessels into the spinal cord. He did not mention anything about cerebrospinal fluid or the depth of the needle insertion into the spinal space. It is speculated that he was aiming directly at the spinal cord as he introduced a needle between the 11th and 12th vertebrae. In his paper, he wrote: "I reasoned that it was highly probably that, if the anesthetic was placed between the spinous processes of the vertebrae, it would be rapidly transported by the blood to the substance of the cord and would give rise to anaesthesia of the sensory and perhaps also of the motor tracts of the same. To be more explicit, I hoped to produce artificially a temporary condition of things analogous in its physiological consequences to the effects observed in transverse myelitis or after total section of the cord."[42]

Corning's report was based on a series of two injections: one human and one animal (a dog). After first assessing its action in a dog, producing a blockade of rapid onset that was confined to the animal's rear legs, he administered cocaine to a man who was "addicted to masturbation." It may be that many anesthesiologists have spent much time wondering whether masturbation played any role in local anesthesia—this question can now be answered in the affirmative. Corning administered one dose without effect, and then, after a second dose had been given, the patient's legs "felt sleepy." The man had impaired sensibility in his lower extremity after about 20 minutes. He left Corning's office "none the worse for the experience"—although this experience itself may well have put him off his penchant for onanism. Corning had injected a total of 120 mg of cocaine, about four times the potentially lethal dose, in a period of 8 minutes.