By the 1930s localanaesthesia had become a much broader discipline. Many different nerve blockswere being used including splanchnic and paravertebral blocks, caudal blocksand even diagnostic and therapeutic sympathetic blocks. In a review of localanesthesia in 1934, Matas wrote … the local anesthetist has outgrown his nameand primitive functions. He has now stepped into a new world of complex andvaried medical and surgical relations in which simple analgesia for theprevention and suppression of surgical pain stands only as a symbol for theprimitive trunk of a tree which is now overshadowed by the foliage of its innumerableramifications. But the choice of drugs remained restricted. Procaine, beingrelatively safe, was the most acceptable. Nupercaine and amethocaine had founda place in spinal and topical anaesthesia but there was still no safe, longacting drug with wide application. And there were no signs that anyone wasgoing to discover one. The next major development, the discovery of lignocaine,happened completely by accident. In 1896, a 23-year-old German chemist, Hansvon Euler, moved to Stockholm to work with the famous Professor SvanteArrhenius at Stockholm University. In 1929 he was awarded the Nobel Prize withSir Arthur Harden from London for their work on fermentation. His subsequentresearch focused on genetics, trying to find chemical solutions to physiologicalproperties. His research focused on mutant barley strains that appeared to bemore resistant to insects. The result of this research was the isolation of acompound named gramin which von Euler believed could have application as aninsecticide. He gave the task of synthesizing gramin to a young chemist, HolgerErdtman. There were two isomers of gramin, and Erdtman, to his disappointment,created the wrong one with his initial experiments. However he tested the newcompound, isogramin, for completeness. During the testing he tasted it anddiscovered that his tongue went numb. While he quietly filed away this piece ofinformation the gramin project was unravelling. A German group published thediscovery before them and then others showed that gramin did not really conferresistance to insects. Erdtman was now free to explore his new discovery.Isogramin proved to be extremely poisonous but Erdtman felt that the localanesthetic properties may also be found in the precursors used in itsmanufacture. Further experiments concluded that an anilide produced as anintermediate also produced anaesthesia of the tongue. In 1935, Nils Löfgren,another young chemist, came to work with Erdtman. They produced sixteenanilides with anaesthetic properties but none appeared to be superior toprocaine. They published their results in 1937 and Erdtman left the universityshortly after that. Löfgren continued his research, making compounds, numberingthem and testing them on his tongue. Compound LL30 probably went on the shelfwith all the others in about 1942. At this time an adventurous young chemistrystudent, Bengt Lundqvist, joined Löfgren’s team. He realized that testing onthe tongue was not ideal and that the substances should be tested by injection.Their laboratory did not contain experimental animals so he subjected himselfto all these experiments. He borrowed some articles on local anaesthesia from amedical student friend, took some LL30 from the laboratory and performed aseries of digital and spinal blocks on himself in his home. He concluded thatcompound LL30 was the best local anaesthetic substance that existed.

Toxicologytests were then carried out by Leonard Goldberg at the Karolinska Institute.Fourteen days and hundreds of mice later, he had concluded that LL30 was farsuperior to procaine. It was less toxic, more effective and seemed to have alonger duration of action. Things moved fairly rapidly from there. Löfgren andLundquist applied for a patent on the July 15, 1943. In August they licensedthe product to Pharmacia for a two-week trial, but at the end of the two weeks,no-one had contacted them. A great deal of indecision followed. The scienceattaché to the US embassy offered them $15,000 for an immediate takeover, othercompanies began to show an interest and reportedly ICI flew Löfgren in the tailof a Mustang, a plane transporting ball bearings to England by night during thewar. Clearly Löfgren was acquiring his pupil's sense of adventure. Eventuallythey sold the patent to Astra on November 22, 1943. As part of the deal,Löfgren and Lundquist retained a 4% royalty on all sales for seventeen yearsand a payment of 15000 Swedish crowns. Astra was then faced with the problem ofmass production, which was difficult during wartime as there was a shortage ofraw materials. They chose the name Xylocain for the product and patented it in27 countries. The initial testing was carried out by Torsten Gordh at theKarolinska Hospital in Stockholm in 1945. At the conclusion of these tests,Xylocain was registered on the November 21 1947 and released on to the marketin early 1948. Gordh summarized his findings in a Swedish medical journal: Itwill fulfill the classic requirements of an ideal local anaesthetic, as it haslow toxicity, is nonirritant to tissues, is water soluble, can be sterilizedand permits storage with adrenaline. Lidocain has further, a fast and efficienteffect with sufficient duration and is, in my opinion, the most ideal ofhitherto-known local anaesthetics. It is further remarkably useful in allareas, where any form of local anaesthesia can be performed. Unfortunatelyneither of the designers of this drug really reaped its rewards. Löfgren becamewealthy but found himself excluded from many research grants as a result. Hesuffered from many bouts of depression and eventually took his own life at theage of 53. Lundqvist fractured his skull during a fall down some stairs at theInstitute. Later he bought a yacht with his royalties and, after a day ofdiving under the boat to clean it, died of a cerebral haemorrhage at the age of30.

LOCAL ANAESTHETICS—THE ORIGINS OF LIGNOCAINE

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