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By the 1930s local anaesthesia had become a much broader discipline. Many different nerve blocks were being used including splanchnic and paravertebral blocks, caudal blocks and even diagnostic and therapeutic sympathetic blocks. In a review of local anaesthesia in 1934, Matas wrote ... the local anaesthetist has outgrown his name and primitive functions. He has now stepped into a new world of complex and varied medical and surgical relations in which simple analgesia for the prevention and suppression of surgical pain stands only as a symbol for the primitive trunk of a tree which is now overshadowed by the foliage of its innumerable ramifications. But the choice of drugs remained restricted. Procaine, being relatively safe, was the most acceptable. Nupercaine and amethocaine had found a place in spinal and topical anaesthesia but there was still no safe, long acting drug with wide application. And there were no signs that anyone was going to discover one. The next major development, the discovery of lignocaine, happened completely by accident. In 1896, a 23-year-old German chemist, Hans von Euler, moved to Stockholm to work with the famous Professor Svante Arrhenius at Stockholm University. In 1929 he was awarded the Nobel Prize with Sir Arthur Harden from London for their work on fermentation. His subsequent research focused on genetics, trying to find chemical solutions to physiological properties. His research focused on mutant barley strains that appeared to be more resistant to insects. The result of this research was the isolation of a compound named gramin which von Euler believed could have application as an insecticide. He gave the task of synthesizing gramin to a young chemist, Holger Erdtman. There were two isomers of gramin, and Erdtman, to his disappointment, created the wrong one with his initial experiments. However he tested the new compound, isogramin, for completeness. During the testing he tasted it and discovered that his tongue went numb. While he quietly filed away this piece of information the gramin project was unravelling. A German group published the discovery before them and then others showed that gramin did not really confer resistance to insects. Erdtman was now free to explore his new discovery. Isogramin proved to be extremely poisonous but Erdtman felt that the local anaesthetic properties may also be found in the precursors used in its manufacture. Further experiments concluded that an anilide produced as an intermediate also produced anaesthesia of the tongue. In 1935, Nils Löfgren, another young chemist, came to work with Erdtman. They produced sixteen anilides with anaesthetic properties but none appeared to be superior to procaine. They published their results in 1937 and Erdtman left the university shortly after that. Löfgren continued his research, making compounds, numbering them and testing them on his tongue. Compound LL30 probably went on the shelf with all the others in about 1942. At this time an adventurous young chemistry student, Bengt Lundqvist, joined Löfgren's team. He realized that testing on the tongue was not ideal and that the substances should be tested by injection. Their laboratory did not contain experimental animals so he subjected himself to all these experiments. He borrowed some articles on local anaesthesia from a medical student friend, took some LL30 from the laboratory and performed a series of digital and spinal blocks on himself in his home. He concluded that compound LL30 was the best local anaesthetic substance that existed.

Toxicology tests were then carried out by Leonard Goldberg at the Karolinska Institute. Fourteen days and hundreds of mice later, he had concluded that LL30 was far superior to procaine. It was less toxic, more effective and seemed to have a longer duration of action. Things moved fairly rapidly from there. Löfgren and Lundquist applied for a patent on the July 15, 1943. In August they licensed the 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 science attaché to the US embassy offered them \$15,000 for an immediate takeover, other companies began to show an interest and reportedly ICI flew Löfgren in the tail of a Mustang, a plane transporting ball bearings to England by night during the war. Clearly Löfgren was acquiring his pupil's sense of adventure. Eventually they 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 years and a payment of 15000 Swedish crowns. Astra was then faced with the problem of mass production, which was difficult during wartime as there was a shortage of raw materials. They chose the name Xylocain for the product and patented it in 27 countries. The initial testing was carried out by Torsten Gordh at the Karolinska Hospital in Stockholm in 1945. At the conclusion of these tests, Xylocain was registered on the November 21 1947 and released on to the market in early 1948. Gordh summarized his findings in a Swedish medical journal: It will fulfill the classic requirements of an ideal local anaesthetic, as it has low toxicity, is non-irritant to tissues, is water soluble, can be sterilized and permits storage with adrenaline. Lidocain has further, a fast and efficient effect with sufficient duration and is, in my opinion, the most ideal of hitherto-known local anaesthetics. It is further remarkably useful in all areas, where any form of local anaesthesia can be performed. Unfortunately neither of the designers of this drug really reaped its rewards. Löfgren became wealthy but found himself excluded from many research grants as a result. He suffered from many bouts of depression and eventually took his own life at the age of 53. Lundqvist fractured his skull during a fall down some stairs at the Institute. Later he bought a yacht with his royalties and, after a day of diving under the boat to clean it, died of a cerebral haemorrhage at the age of 30.

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