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Lidocaine: The Origin of a Modern Local Anesthetic

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Xylocain, a New Local Analgesic. By Torsten Gordh. *Anaesthesia* 1949; 4:4-9. Abstract used with permission.

Abstract: Before the introduction of lidocaine, the choice of local anesthetics was limited. Procaine was most commonly used and offered less toxicity than cocaine, but it had a short duration of action. Tetracaine had substantial systemic toxicity, limiting its use largely to spinal anesthesia. An agent with low toxicity, a quick onset, and a longer duration of action was needed. This article reports the initial clinical trials with the newly synthesized lidocaine. The first trials were wheel tests on the forearms of human

volunteers. Lidocaine anesthesia duration was markedly longer than that produced by procaine. Lidocaine was first tested for infiltration anesthesia in many short procedures performed in the emergency department, followed by major procedures, including those for goiter and hernia in the operating room. Consistent success was observed in both environments. Lidocaine was then tested for conduction anesthesia using brachial plexus and mandibular, sacral, and paravertebral blocks. Its onset was again substantially faster and longer lasting than that of procaine. Lidocaine also provided good spinal and surface anesthesia of the cornea.

THIS article is based mainly on an interview with Torsten Gordh (1907-2010), M.D., Sweden's first anesthesiologist; Gordh was educated in Madison, Wisconsin, from 1938 to 1940 by Ralph Waters, M.D.¹ Gordh was chief anesthetist at Karolinska Hospital, Stockholm, Sweden, from 1940 until his retirement in 1974 (fig. 1). Gordh conducted the first clinical evaluations of the new local anesthetic lidocaine (Xylocaine®; AstraZeneca, London, United Kingdom) from 1944 to 1947. Gordh died on June 25, 2010, at the age of 102 yr. He participated in the preparation of this monograph in the few months before his death. The first three paragraphs in this article were originally written by Prof. Martin H. Holmdahl, M.D., Department of Anaesthesiology and Intensive Care, Uppsala University Hospital, Uppsala, Sweden, and were copied with the kind permission

of Prof. Holmdahl and the publisher.² In addition, personal memories from Gordh were collected, and relevant lecture manuscripts were studied.

Basic Research Behind the Discovery of Lidocaine

Lidocaine was discovered from systematic investigations at the Institute of Chemistry at Stockholm University (Stockholms Högskola), Stockholm. In the early 1930s, Hans von Euler-Chelpin, Ph.D. (1873-1964, Nobel Prize winner in 1929 for studies on the fermentation of alcohols), wanted to investigate how genes and enzymes were chemically related and to map out the actual process of inheritance in purely chemical terms. He tried to find chemical differences between normal barley and some chlorophyll-defective mutants resistant to certain pests. From the mutants he had obtained from the famous Swedish plant geneticist, H. Nilsson-Ehle, Ph.D. (1873-1949), von Euler-Chelpin *et al.* isolated an alkaloid, an indole, that they named gramine after the Latin name of the grass family Gramineae (see figure, Supplemental Digital Content 1, <http://links.lww.com//ALN/A649>). They made a correct elemental analysis ($C_{11}H_{14}N_2$).

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Fig. 1. Torsten Gordh, M.D., gives his last anesthetic before retiring as professor at Karolinska Hospital in 1974. As a history lesson, he demonstrated an open ether anesthetic for a patient undergoing an acute appendectomy. Most of his staff had never seen this procedure take place. Everything went well.

Local Anesthetic Action of Isogramine

In von Euler-Chelpin's laboratory, Holger Erdtman, Ph.D. (1902–1989), was given the task to synthesize 2-dimethylaminomethylindole, which was not identical to gramine; instead, it was an isomer, called isogramine. As usual, he tested the substance on his tongue, which he found anesthetized. Gramine was inactive in this respect. Erdtman, in association with a young chemistry student, Nils Löfgren, Ph.D. (1913–1967), prepared several analogs, working with the starting material for the synthesis of isogramine, dimethylamino acetotoluidide. Pharmaceutical tests of these compounds were performed in von Euler-Chelpin's laboratory with the assistance of his son, Ulf von Euler (1905–1983, Nobel Prize winner in 1970 for the discovery of noradrenalin and prostaglandins). None of the compounds was considered able to compete with procaine, and the investigations were discontinued.

Discovery of a Potent Anesthetic, Initially Labeled LL30

After some years, Löfgren continued the interrupted work. Early in 1943, he gave one compound to his assistant, Bengt Lundqvist (1922–1953), who, in self-experiments, found it was active and had a longer duration of action than procaine. It was originally labeled LL30 after the initials of the two main coworkers (fig. 2). It differed from one of the compounds prepared by Erdtman and Löfgren only by the addition of an extra methyl group in the 6 position of the benzene ring.

Problems of Local Anesthetists before Lidocaine

According to Gordh, the problems with local anesthesia at the time were its duration of action and the fact that the



Fig. 2. At the start of the testing period, LL30 was supplied in small glass syringes packed in small, blue, cardboard containers, shaped like a cylinder. It was in this form that physicians and dentists first became acquainted with lidocaine.

preparations were difficult to preserve. The agent of choice was the ester procaine (Novocain or Ethocaine). However, procaine had a short duration of action. The powder had to be dissolved before being injected, and it was not possible to store it with adrenaline because then it degraded. Adrenaline had to be added drop by drop to the procaine solution just before the injection. Therefore, handling it was a somewhat lengthy process.

In the 1940s, hernias, for example, were operated on under local anesthesia, as was goiter. All the so-called minor surgery on the hands and varicose veins was performed with local anesthesia. Thoracoplasty surgery was performed with paravertebral anesthesia.

In the 1940s, one third of surgical procedures in Sweden were performed with local or regional anesthesia. It was less traumatic for the patient. The major risk with local anesthetics came from having to inject in an area rich in blood vessels, presenting risk of a toxic effect leading to cardiac arrest. Surgeons had to watch for spasms and convulsions. They wanted a substance with a low toxicity and a rapid onset; this substance should also last a long time and be kept in bottles. Xylocaine® was introduced and met these demands of efficacy and safety. It was like a godsend.

First Contact with the New Local Anesthetic

Please note that the remainder of this article is written from the perspective of Torsten Gordh.

In the spring of 1943, we had dinner at a restaurant, Stallmästaregården, after a staff meeting at Karolinska Hospital. Tore Kornerup (1912–1998), who was a colleague of mine and an ophthalmologist, said that he had a friend named Lundqvist, who he practiced fencing with and who had a new local anesthetic. I was naturally interested but said that before testing it, I would first like to have its toxicity compared with that of procaine, which was the drug we used

most. I wanted to know whether it was more or less toxic before using it. Only about a year later, when I met Lundqvist and Löfgren, did I realize that they actually had something to offer. However, at the time, I was busy with my thesis about circulatory and respiratory impairment during ether and intravenous anesthesia in rabbits, so I had other things to think about.

Someone else who was partly involved in the story of lidocaine was Bengt Lagergrén, who was also a fencer. He knew Lundqvist and Löfgren, and when Lundqvist wanted to perform some tests with finger anesthesia, they talked to Lagergrén, who had studied under me for approximately 3 months at the beginning of the 1940s. I had given him a book about local anesthesia. They asked him to demonstrate anesthesia of the finger because they were to give a presentation to Pharmacia in Uppsala.

Lidocaine: First Clinical Tests

We started the official clinical trials of LL30 in 1944. Because I had close contact with Astra AB in other affairs, it was natural that I was asked to handle the clinical investigations of lidocaine. Furthermore, I was the only educated anesthesiologist in Sweden at that time. I tested it on my colleagues, students, and patients. The patients each received 5 Swedish crowns (\$1), whereas the students could choose between a packet of cigarettes or my thesis. Most of them chose a packet of cigarettes (Camel or Lucky Strike). I had some good US connections in Sweden, so I had access to cigarettes, which were hard currency then.

Leonard Goldberg (1911–2010), M.D., Ph.D. (Karolinska Institute, Stockholm), performed the initial pharmacological and toxicity work³, and we worked together extremely closely. We knew each other well, having been fellow students and having received our doctorates at the same time. We continued to test LL30 for 3 yr before we were sufficiently convinced. It was so important at the outset to perform a toxicity test for a comparison with procaine.

Superiority of LL30

I did not think that I needed to perform any statistical analysis because LL30 was so overwhelmingly superior. I tried it first with intracutaneous wheals and then subcutaneously. The analgesia was tested with a point of a needle. The solutions we had bore no name, except for a code, and no one knew what they were.

Torsten Gordh's wife, Ulla Gordh, M.D. (1918–2005), at that time a medical student, tells how she raised the first wheals and made the injections from eight different glass syringes containing solutions whose identity she was unaware of (see photo, Supplemental Digital Content 2, <http://links.lww.com/ALN/A650>).

"I injected into the forearm, a milliliter in each wheal; there was a small round mark more or less the size of a mosquito bite. To indicate which injection was which, I took the top of a fountain pen and used it to ring each injection site, putting a number beside the ring. Some of the marks

quickly disappeared, within 15 min or so. But when I injected from one particular syringe, much larger areas were anesthetized, and it turned out to be Xylocaine®. It started working quickly and lasted for a long time. This is what's special about Xylocaine®, plus its low toxicity. I must have tested about 20 people, mostly young men, who were in the hospital for a few weeks following a simple operation (hernia, for example) and who were in good physical shape. At that time during the war, there was a surgical clinic for the military at the Karolinska Institute and the lads were willing to volunteer. So Xylocaine® was only tested on young men, in fact."

"We injected Xylocaine® in concentrations of 2, 1, 0.5, and 0.25%. Novocain, which we made comparisons with, we gave as 1% and tetracaine as 0.1%. The latter was 10 times stronger."

The procaine in the wheal lasted 17 min, whereas 1% lidocaine lasted, on average, 70 min. A huge difference! It was so completely reliable that we thought statistical analysis was unnecessary. Today, though, statistical analysis would certainly have to be performed.

In total, 175 subcutaneous skin wheal tests were performed in volunteers. The lidocaine concentrations varied from 0.1 to 2%, with and without the addition of adrenaline, 1:100,000. The mean duration of effect of 25 tests per concentration was reported. It was compared with the effect of procaine. Seventy-five intracutaneous wheal tests were performed as well. After these initial tests, clinical applications were started.

Surface analgesia of the cornea was attempted; for otolarngology, surgical indications produced good results. Infiltration anesthesia was attempted in 400 cases of superficial surgery in the casualty policlinic, including 17 cases of radius fracture. In 11 cases, the effects were reported as unsatisfactory. A full anesthetic effect was usually seen after 2 min. Lidocaine was effective in mandibular, brachial plexus, sacral, and intercostal anesthesia, showing swift and good effects. It was attempted in 100 cases for pain treatment, with infiltration, extradural analgesia, and blocks of the sympathetic system, in which a long lasting alleviation of pain was obtained, which could not be obtained by means of our usual local anesthetics. Lidocaine was also attempted for spinal anesthesia in a 2% solution. All of these results were described in the original publication from 1949.⁴

During this clinical investigation, lidocaine was simultaneously tested by a group of dentists at the Royal School of Dentistry in Stockholm by Hilding Björn (1907–1995) *et al.*⁵ They established the efficacy of lidocaine for dental use. The analgesia was studied with the aid of an electrical pain stimulator, according to Björn.

Premier at the Swedish Anaesthesia Club

Gordh recalled that his first public appearance talking about lidocaine was at the anesthetists' society in 1947. There, he presented the results of testing. The agenda for

the small Swedish Anaesthesia Club, founded in 1946 (later on converted into The Swedish Society of Anaesthesiology and Intensive Care), may deserve some interest in translation from Swedish (see Supplemental Digital Content 3, <http://links.lww.com/ALN/A651>).

“Swedish Anaesthesia Club meets Friday November 21 1947 at 8 PM, in the conference room at Karolinska Hospital.

Agenda:

1. Last protocol revisited.
2. Fil lic. Nils Löfgren (guest): On the discovery of xylocaine.
3. MD Torsten Gordh: Clinical experiences with xylocaine.
4. MD Sven Rune Johnson: Experimental investigations on blood glucose levels during anesthesia.
5. MD Olle Friberg: To the 100 yr memorial of chloroform anesthesia.

The meeting is followed by food and drinks.

Dinner speech: “Impression from visits to anesthesia clinics in England- T Gordh”

After that, Gordh gave a talk at the Nordic Association of Surgeons. Goldberg (with the collaboration of Gordh) wrote the first article in 1948, published in Swedish; and the first international publication appeared the following year in the English journal *Anaesthesia*.⁴

Registering lidocaine was a roundabout procedure, which is why publication took so long. The patent was not granted until 1948, despite application as early as 1943.

Rumor Spreads

After Pharmacia rejected lidocaine, many other pharmaceutical companies were interested, including ICI in England and Bayer in Germany. However, Löfgren did not want to let lidocaine go to Germany and Bayer. The story goes that Löfgren traveled in the tail of a Mustang one night to London from Göteborg, Sweden, which was how they transported ball bearings to England. However, he was supposed to have to leave London in a hurry because there was a bombing raid on the city. This story has been denied by Ingrid Löfgren, who said that her husband never went to England during the war and that the story probably came from Löfgren himself, who liked to spread it abroad that everyone wanted to have lidocaine.

However, the rumor spread like wildfire that lidocaine was an excellent preparation and that most large pharmaceutical firms wanted to obtain it, *via* embassies and the like. Because there was a war that continued, local anesthetics were especially sought because they allowed surgical procedures to be performed without the need for general anesthesia equipment. *Via* Lagergrén, who helped Löfgren and Lundqvist as a medical consultant and acted as a go-between

in their contacts with the companies, the message got through to Astra AB that it was important to act if lidocaine was to remain in Sweden. Lagergrén's father-in-law was related to the Wallenberg Swedish industrialist family, which explains why lidocaine came to the notice of Jacob Wallenberg and the Astra AB board, which realized that it would have to make a move. This it did in September 1943. Bertil Sjögren, the head of the laboratory at Astra AB, took charge.

It is even said that when Löfgren and Lundqvist were on their way by train to Astra AB in Södertälje, Sweden, Lundqvist suddenly remembered that they had not tried the mandibular nerve. Therefore, he went into the bathroom and injected himself in the jaw to see how it worked. When he emerged, the corners of his mouth were drooping a little. It was all exciting!

The name *xylocaine* was created as a union of its most important raw product, xylidine, and the general suffix used for local anesthetics, “-caine.” On May 11, 1948, the patent for Xylocaine® was approved in Sweden, supported by the reports of Goldberg (toxicology) and Gordh (clinical results), claiming that lidocaine had a pronounced and unexpected anesthetic action. In November 1948, Xylocaine® was approved by the Food and Drug Administration for use in the United States.

Discoverers

Löfgren himself was a fantastically gifted and energetic individual. Simply to have done all this with lidocaine is proof of this. However, he was also a bit of an eccentric character. I met Lundqvist a few times now and then, and I remember him as a small man who gave the impression of being energetic and intelligent. At all events, Löfgren and Lundqvist got along extremely well together. Later on, Lundqvist performed experiments on himself. He is even said to have performed spinal anesthesia on himself with the help of a mirror! He was bold to the extreme, reckless even! It is almost incredible that anyone should anesthetize his or her spine by himself or herself. Löfgren and Lundqvist were also supposed to have sought advice from a veterinarian instead of a physician, although I do not know whether that is true.

Toxic Overdose

I gave two patients doses that were a little too large, and they began to exhibit convulsions and spasms. However, we knew how to treat this with barbiturates, so the toxic reaction subsided and everything was fine. We concluded that the maximum dose was 1 g. The patients in question had been given 3 g!

Later, when lidocaine was introduced abroad, there were toxic reactions. However, in these cases, a 2% solution had generally been injected, whereas I had been content with a 0.25% solution. In my view, the 2% solution is rather risky—it might be all right for dentists who inject

only 1 mL. However, if a 2% solution is used for goiter or hernia, an overdose can easily occur. A 0.25% solution is enough in such cases. I tried to impress this on people.

The only problem that occurred with lidocaine initially was among dentists who used metal injection syringes. Traces of metal from the syringe irritated patients' tissues. However, in the hospitals, we used glass syringes, so we did not have this problem.

Conclusions

In a lecture on the clinical development of lidocaine by T. Gordh in 1985, he finished with the following words: "To one who took part in the pioneering research in the pharmacological and clinical action of Xylocaine®, it is gratifying to find that the original observations, may be simple according to modern requirements, stands up so well when appraised in the light of later findings and critiques. In the last analysis, only long documented clinical fitness for use can assure the survival of a drug. Xylocaine® has,

for more than three decades, stood the test as a reliable and highly efficient local anesthetic" (see Supplemental Digital Content 4, <http://links.lww.com/ALN/A652>).

The authors compiled information, in part, from the first reference, with permission; this article was published to celebrate the 50-yr jubilee of the original synthesis of lidocaine. The present publication also contains excerpts from an interview with T. Gordh, at the time 86 yr.

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In Memoriam

Torsten Gordh (1907–2010)

KAROLINSKA⁰ Institutet Professor Emeritus Torsten Gordh passed away peacefully June 25, 2010, in Stockholm, Sweden. He was born in Örebro, Sweden, and grew up in Skara, a city in western Sweden. Torsten Gordh nearly reached the age of 103 yr, and his life was in many ways exceptional. He leaves four children: Elisabet Humlesjö, Gunilla Dahlman, Torsten Gordh, Jr., and Josefina Gordh, all with families of their own. His dearly loved wife, Ulla, died in 2005.

In the 1930s, Torsten Gordh planned to pursue a career in surgery after obtaining his medical degree at Karolinska Institutet (Stockholm, Sweden). However, his interest in anesthesiology—a specialty that did not exist in Sweden at the time—was actively encouraged by the institute's surgeon in chief, Gustav Söderlund. From 1938 to 1940, Torsten Gordh worked in Madison, Wisconsin, where he studied and trained with the legendary Ralph Waters. There, he joined a cutting-edge faculty consisting of, among others, Virginia Apgar and Emery A. Rovenstein.

When Torsten Gordh returned to Sweden in April 1940, the new Karolinska University Hospital was built. A major advancement of the new hospital was a permanent position

for anesthesiology—the first of its kind in Sweden and other Nordic nations. Torsten Gordh was appointed to a post at the new hospital. The clinical result of this hiring decision did not take long; within a few years, mortality in connection with major laparotomies was reduced by more than 50%.

Subsequent decades of success further demonstrated that Torsten Gordh was the ideal choice. He started educational programs for physicians and nurses. He initiated Swedish and Nordic societies of anesthesiology and was involved in establishing an internationally prominent scientific journal, *Acta Anaesthesiologica Scandinavica*.

In 1945, Torsten Gordh defended his postdoctoral thesis at Karolinska Institutet and inspired an important development of research in anesthesiology. He was the first to introduce lidocaine in human medicine—an especially significant development for the then-young Astra pharmaceutical company. He was also involved in the final design of the Gordh-Olovson cannula for intravenous use.

In 1964, Torsten Gordh was appointed the first professor of anesthesiology in Sweden. In 1974, he stepped down as clinical chair of the hospital's Department of Anesthesiology, a position he had held for more than 30 yr. At the same time, he was named professor emeritus.

As an anesthesiologist, Torsten Gordh was extremely skilled, but he also displayed an impressive level of dexterity throughout

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