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EDITORIAL

From cocaine to lidocaine

Great progress with a tragic ending

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Although Simpson[1] first used the term local anaesthesia in 1847, and Arnott[2] pioneered refrigeration anaesthesia soon after, Carl Koller's 1884 recognition of the utility of the numbing effects of cocaine was the great discovery.[3] Unfortunately, it soon became apparent that cocaine is not the ideal local anaesthetic, especially for injection, and a search for better agents began. Other plant alkaloids were sought, and tropacocaine was used clinically, but it is less potent as well as less toxic than cocaine and neutralises the action of adrenaline.[4] Thus, it was not until synthetic alternatives became available that any significant advance took place. Niemann,[4] the first to isolate (and name) pure cocaine, showed that it is an ester of benzoic acid,[5] the finding that was the basis for the search for a better agent. Many worked on this, but it was not until the early 20th century that new drugs appeared, Einhorn synthesising procaine, ultimately to become the standard drug, in 1904.[6]

With synthetic drugs available, the German surgeon, Heinrich Braun,[6] defined criteria for their assessment. In modern terms, local anaesthetics should:

(1) Have a better therapeutic ratio than cocaine and
(2) Penetrate tissues more readily, as well as being
(3) Well absorbed without irritant effects,
(4) Chemically stable when heat sterilised in water and
(5) Compatible with adrenaline.

Braun compared three new compounds: alypin; amylocaine (Stovaine); and procaine (Novocaine). Pain on injection and tissue irritation led Braun to suggest that alypin should not undergo clinical trial, and the local hyperaemia that followed amylocaine might have had the same result, but Braun[6] accepted the opinion of August Bier, the pioneer of spinal anaesthesia, that it was the best drug for that indication.

Braun gave procaine only qualified approval, perhaps recognising that it does not meet requirements (2) and (4). Then, in 1909, Le Brocq[7] published a more detailed study of a larger number of drugs (including alypin), concluding that procaine was the 'most satisfactory'. Definitively, he found that amylocaine produced tissue necrosis after subcutaneous injection, this leading to its decline in spite of Bier's recommendation and Barker's uneventful use of it in studies of spinal anaesthesia.[8] However, one of procaine's deficiencies is its short duration of action, and subsequent developments looked to overcome that. Both cinchocaine and tetracaine were synthesised in the late 1920s,[9,10] but a longer duration of action is closely related to greater systemic toxicity, thus limiting the major use of both to spinal anaesthesia.

Local anaesthetic development had always been an active process because even Koller, inspired by his teacher Ferdinand Arlt,[11] had sought an effective agent. However, the next step was precipitated by one of those 'accidents' in chemistry that have momentous consequences, with the focus moving from Germany to Sweden in 1934.[12] In the Stockholm laboratory of Hans von Euler, a postdoctoral student, Holger Erdtman (Fig. 1) was working on the structure of an obscure alkaloid, gramine. To prove his conclusions, he attempted to synthesise the compound, but actually produced an isomer, isogramine (Fig. 2), which was 'analysed' like all new compounds, by 'tasting', one of the very few methods available. The significance of the localised numbness produced by isogramine was recognised, and a limited programme of research to find a less toxic derivative was funded by Astra, then a small company.

In 1935, Nils Lofgren (Fig. 3), an undergraduate working with von Euler, offered to help with the project as a way of developing his interest in the new field of structure/activity relationships. They synthesised 16 compounds and selected (again by tasting) the 10 'best' for more formal study, but none was found to perform as well as procaine

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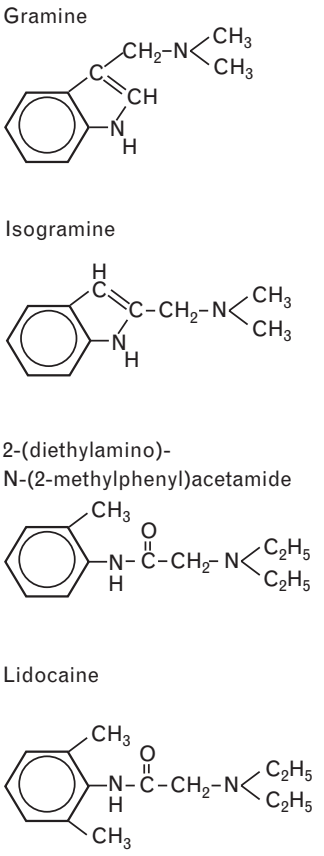
Fig. 1

Holger Erdtman.

Fig. 2



Chemical formulae of gramine, isogramine, the single ortho-methyl precursor of lidocaine (studied by Erdtman and Lofgren) and lidocaine.

and the project was abandoned. The results,[13] including one compound very similar to lidocaine (Fig. 2), were published, but Erdtman left research for teaching in 1939. He later returned and was appointed to a Chair of Organic Chemistry in 1949, but never worked on local anaesthetics again. Lofgren continued with his degree and, after graduation, worked with Pharmacia to develop an alternative to procaine because war-time conditions were limiting its supply from Germany. The result, amoxecaine (Lokastin), was considered to be no better than acceptable.

In 1941, Lofgren returned to von Euler's department as an assistant lecturer with major teaching duties, but he also established an undergraduate research group to help with his doctoral thesis. His topic, perhaps prompted by the work at Pharmacia, was local anaesthetics, but Lofgren's primary interest was their structure–activity relationships, not the search for a new drug. Many homologous series were synthesised for study, the project eventually earning him the maximum possible marks

Fig. 3

Nils Lofgren (left) and Bengt Lundqvist.

for his thesis,[14] but that was well into the future. In early 1943, an enthusiastic student called Bengt Lundqvist (Fig. 3), who was also a fencer of international standard, joined Lofgren's group, and his sporting contacts were to prove as important as his enthusiasm. He pestered Lofgren to be allowed to test what might be one of the more effective compounds, was given the total supply of 'LL30', and promptly vanished!

Fortunately, he was putting the agent, his enthusiasm and his contacts to good use. One contact, a medical student called Bengt Lagergreen, had been attached to Torsten Gordh, then Sweden's only specialist anaesthetist, and had borrowed a book on nerve block. Lunqvist used this to perform a range of blocks on himself and found that LL30 was a potent agent clearly meriting further study. Another fencer, an ophthalmologist called Tore Kornerup, sought Torsten Gordh's advice and he suggested comparison with procaine in animals (the right advice for the wrong reason; Gordh was later to admit that he suggested this course of action as a delaying tactic because he was too busy with his own thesis at the time!). Leonard Goldberg, a pharmacologist at the Karolinska, undertook the work and quickly established the primary features of LL30,[15,16] these meeting all of the Braun requirements noted earlier. With confirmation of the drug's potential, Gordh's help was sought again, but he remained 'busy' and the necessary volunteer studies were undertaken by his wife, Ulla, who in 1944 showed that a 1% solution was faster in onset than procaine and had four times the duration.

While this evidence was accumulating, Lofgren sought a commercial sponsor, Pharmacia buying an option in August 1943, but this lapsed. Subsequently, Astra was approached (Kornerup was involved again, his wife being related to the Wallenberg family who were shareholders in the company) and they bought the rights in November 1943, the official Swedish names, lidokain (generic) and Xylocain (commercial), being chosen the following January (variant spellings depended on relevant national practices). A 3-year programme was started to secure the patent, develop a commercial manufacturing process, complete clinical evaluation (Fig. 4) and devise the clinical product range. The drug was launched in Sweden in January 1948, and in other countries subsequently. An academic review by Gordh[17] presented its scientific and clinical features to the anaesthetic community, and the drug was an immediate success.

The consequences of such academic and financial success were considerable for Lofgren, the royalty agreement with Astra paying him 4% of sales, one-third of which he shared with Lunqvist for his help in developing the drug. Erdtman received no share, a source of some tension initially because his work had started the project and one of the original compounds synthesised with Lofgren required the addition of only a methyl group

Fig. 4

Container of LL30 produced for clinical trial.

to produce lidocaine (Fig. 2). A bigger problem for Lofgren was that such success while he was, academically speaking, very junior brought jealousy, both real and imagined. To develop his career, he spent a year in the USA, but the teaching was proscribed and there was little research opportunity so it was not an enjoyable experience. Back in Sweden, Lofgren found that the exchequer was taking most of his royalties so, in 1953, he became a tax exile in Switzerland, having his own laboratory in Lausanne. Meanwhile, Lundqvist, having finished his degree, also became a tax exile in 1953 and bought a large sailing boat. Diving to maintain it, he suffered a major stroke (probably related to a head injury some years earlier) and died.

The death of his friend cannot have helped Lofgren's unhappiness, and in 1955, he moved back to Sweden as an Assistant Professor, buying an estate with a laboratory where he studied alkaloids and fish breeding. In 1963, after years of 'anxiety' about his academic status, he was appointed to a Chair of Organic Chemistry, but resigned the following year because of the bureaucracy. Alcohol probably played a part in his spiral downwards and he committed suicide in 1966. Lofgren was a pioneer of structure–activity relationships in chemistry and, with Lundqvist, found a drug that revolutionised local anaesthetic pharmacology, led to the development of a range of agents that advanced the practice of regional anaesthesia and established a major pharmaceutical company. However, with both their lives ending in tragedy, it is no

wonder that Erdtman eventually came to think that he was better off without a share of their wealth.

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