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FROM ARROW TIPS TO SYRINGE NEEDLES

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With a piercingly fast exhale, the dart rips down the hollow of the zarabatana, nicking the Amazonian spider monkey only along its flank. But it's enough. The animal quickly loses the steadfastness in its flee. Within minutes, it becomes fully paralyzed, toppling limp out of the canopy as its last breath is lost to the surrounding air.

Smothered in a dark viscid paste prepared from the Strychno toxifera plant of the Amazon rainforest, this dart symbolizes one of the earliest uses of curare. Little could anyone have predicted that this poison would one day serve as the basis for one of the most important drugs in modern anesthesia. In fact, it was a Canadian anesthesiologist who first demonstrated the perioperative use of curare—a discovery that revolutionized the operating room. This paper will take the reader on a journey through time, describing the clinical development of modern-day muscle relaxants from curare.

500 YEARS AGO, the first written account of curare was made by Pieter Martyr, an Italian gossip columnist of his time.[1] He wrote fantastical accounts of the travels of explorers, recently returned from the New World. Amongst these chronicles were descriptions of curare being prepared by elderly people, who in the process, risked being found "lying on the ground half dead from the fumes of the poison."[2] A potent concoction, this arrow poison was used for thousands of years by South American indigenous peoples for hunting and witchcraft.[3] While the active ingredient was the boiled-down bark of the Strychno toxifera or Chondrodendom tomentosum plants, it was also laced with animal venoms and other plant products.[4,5]

Throughout the 19th century, curare began to emerge in the scientific realm, as naturalists and explorers grew increasingly interested in studying its physiologic effects. A series of macabre experiments involving small animals injected with the toxin described how the heart continued to beat even when respiration ceased. If air was forced into the lungs artificially, the animal could be kept alive until the drug wore off.[6] In 1856, Bernard hypothesized that this occurred because the drug antagonized transmission at the neuromuscular junction of voluntary muscles, without affecting the heart or smooth muscles.[7] This principle would be key to its later applications.

It was not until the late 1930s that curare was first used in clinical medicine as an adjunct for psychiatric treatments.[8] Incostrin, the purified pharmaceutical form, was given during electroconvulsive therapy to soften seizures and reduce trauma, with good results.[9] An American anesthesiologist, Dr. Lewis H. Wright, took interest in this development and began contemplating an application for Incostrin in the operating room. At the time, common anesthetics, like cyclopropane, ethylene, and barbiturates, did not achieve adequate muscle paralysis. As a result, unconscious patients exhibited unintentional muscle contractions, which compromised operating conditions. If muscle relaxation was indeed required, this could only be achieved with deep inhalational anesthetics—a dangerous technique associated with prolonged cardiac and respiratory depression. Wright reasoned that using a separate drug like Incostrin might resolve this issue. However, in 1940, many of his colleagues scoffed at the suggestion of using an indigenous arrow poison in the operating room.[10] The few who initially entertained the idea soon abandoned it after early animal trials.[3,10]

Dr. Harold Griffith was a Canadian anesthesiologist who would see things differently. As one of the anesthetists approached by Wright in 1940, Griffith started putting serious consideration into curare over the next few years. A quiet, humble, and highly accomplished anesthesiologist practicing in Montreal, Griffith always found himself at the frontiers of the field. He was the first to administer cyclopropane anesthetic in Canada,[11] and would soon be the first to introduce postoperative recovery rooms into Canadian practice.[9] With this pioneering resumé, it is no surprise that after two years of discussion with Wright, Griffith courageously decided to begin clinical trials of perioperative Incostrin in 1942. He reasoned that if psychiatrists had been using it safely, so too could anesthetists who were trained in managing its most common side effect, namely respiratory paralysis.

On January 23, 1942, Griffith and his resident [Enid] Johnson introduced the surgical world to the paralyzing properties of curare. They administered Incostrin to a 20-year-old man undergoing surgery for chronic appendicitis. Complete relaxation of the abdominal muscles was achieved safely and reversibly. Griffith proceeded to use Incostrin in 24 more patients before publishing his most famous case series, where he begins memorably with: "Every anesthetist has wished at times that he might be able to produce rapid and complete muscular relaxation in resistant patients under general anesthesia."[12] This report marked the advent of a paradigm-shifting practice: controlled muscle relaxation during surgery. Soon after Griffith's landmark publication, a rush of articles began to fill the literature,[3] until the principle gained widespread acceptance among the global anesthesia community.

There are a number of reasons why muscle relaxation has since revolutionized surgery. It has minimized muscle rigidity, facilitating both intubation and surgical working conditions.[13]

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In intra-abdominal surgery, paralysis has assisted with surgical exposure; in delicate procedures like ophthalmic or neurosurgery, it has prevented potentially detrimental patient movement. In addition to eliminating the need for dangerously high dose inhaled anesthetics, muscle relaxants have enabled the dawn of longer and more complex surgery, including cardiothoracic and organ transplant procedures. Therefore, some 100 years after the famous demonstration of ether anesthesia by Morton at Massachusetts General Hospital, Dr. Griffith's use of Incostrin emerges as the next historical pillar in the formative years of anesthesiology. Arguably the greatest Canadian contribution to the specialty and one that has vastly expanded the surgical horizon, it is no wonder that historians divide anesthesiology into eras "before and after Griffith."[14]

It is noteworthy, however, that the acceptance of curare into everyday anesthetic practice was not without resistance. Two years after Griffith's milestone, a controversial audit published in 1954 by Beecher and Todd stands out as a prominent example. Beecher and Todd studied surgical outcomes at ten major North American hospitals and showed that muscle paralysis was associated with a six-fold increase in anesthetic mortality.[15] Some argued that this increase in mortality reflected the improper use of mechanical ventilation and reversal agents available at the time. Nonetheless, this early paper identified the real dangers of paralysis and led to some important corollaries. Anesthesiologists had to reassess their practice of muscle relaxation and address risks, which continue to shape the practice today. New curare-like drugs with more favourable pharmacological properties have replaced Incostrin and practice guidelines have been established to standardize administration and post-operative care.[16,17] These improvements have now made muscle paralysis a widely accepted tool in the operating room, albeit one that requires significant training and skill.

Today, muscle relaxation is achieved with a class of pharmaceuticals known as the neuromuscular blocking agents (NMBAs). While curare was the only option some 70 years ago, the modern day anesthesiologist faces a choice among various designer drugs of curare-like origin: cisatracurium, rocuronium, pancuronium and succinylcholine to name a few. Each has a differing pharmacokinetic, pharmacodynamic, and side effect profile, allowing drug selection to be customized to the operation at hand. To add to this armamentarium, there are reversal agents known as anticholinesterases, which can be used to minimize the risks of residual paralysis. Nerve stimulators are further employed to monitor the degree of muscle relaxation and best titrate effects.

In spite of this complexity, it is not to be forgotten that the modern era of muscle relaxation stems from a story that is much more profound and long-standing. The history of curare lends itself to vivid portrayal, from South American hunting poison to mainstay medication in the current operating theatre. Its use in anesthesiology has allowed patients to undergo increasingly complex procedures more safely and with faster recovery. Today, new pharmaceutical research and improved monitoring techniques continue to shape the anesthetic practice of neuromuscular blockade, but the journey of this medication thus far, from arrow tips to syringe needles, must not be overlooked.

The 21st century anesthesiologist gently places the oxygen mask on the patient's face, as instructions are given to "take a few deep breaths in". Syringes approach the intravenous line, through which various medications are injected, one after the other like the pistons in a car. The last of these syringes is a translucent fluid labelled 'Rocuronium 10 mg/mL'. A seemingly innocuous mixture, this powerful intubating dose of muscle relaxant paralyzes the patient and allows the anesthesiologist to assume full responsibility for their care—to subsequently regulate their breathing and vital functions. This power and extreme responsibility is a privilege few other physicians experience and one that has been hundreds of years in the making.

1 *Raghavendra, T. Neuromuscular blocking drugs: discovery and development. J R Soc Med. 2002 Jul;95:363-367*

2 *Martyr Pd'A. De Orbe Novo (1516 Latin). Translation by FA Mainutt. New York, GP Putnam's Sons, 1912, vol 1, p 75*

3 *Betcher, AM. The Civilizing of Curare: A History of Its Development and Introduction Into Anesthesiology. Anesth Analg. 1977 Mar-Apr;56(2):305-19*

4 *Bisset, NG. War and hunting poisons of the New World. Part 1. Notes on the early history of curare. J Ethnopharmacol. 1992 Feb;36(1):1-26*

5 *Shibamoto T, Bjeldanes LF. Introduction to Food Toxicology. 2nd ed. Oxford: Elsevier; 2009*

6 *Brodie, BC. Further Experiments and Observations on the Action of Poisons on the Animal System. Phil Trans R Soc Lond. 1812 Jan;102:205-227*

7 *Bernard C. Analyse Physiologique des Proprietes des Actions de Curare et de la Nicotine sur Systemes Musculaire et Nerveux au Moyen du Curare. Compt Rend. 1856;43:305-319*

8 *Bennett, AE. A history of the introduction of curare into medicine. Anesth Analg. 1968 Sept-Oct;47(5):484-92*

9 *Bennett, AE. Preventing traumatic complications in convulsive shock therapy by curare. JAMA. 1940;114(4):322-324*

10 *Sykes, K. Harold Griffith Memorial Lecture. The Griffith Legacy. Can J Anaesth. 1993;40(4):365-74*

11 *Griffith, HR. Cyclopropane Anesthesia: a clinical record of 350 administrations. Can Med Assoc J. 1934 Aug;31(2):157-160*

12 *Griffith HR, Johnson E. The use of curare in general anesthesia. Anesth. 1942 Jun;3(4):418-420*

13 *Ledowski, T. Muscle relaxation in laparoscopic surgery: what is the evidence for improved operating conditions and patient outcome? A brief review of the literature. Surg Laparosc Endosc Percut Tech. 2015 Aug;25(4)281-5.*

14 *Cohen, L. An anesthetist of a different order. Can Med Assoc J. 1999 Jan;160(1):160*

15 *Beecher, HK, Todd, DP. A study of the Deaths Associated with Anesthesia and Surgery. Ann Surg. 1954 Jul;140(1):2-34*

16 *Merchant R, Chartrand D, Dain S, et al. Guidelines to the Practice of Anesthesia – Revised Edition 2016. Can J Anesth 2016;63:86-112*

17 *Apfelbaum JL, Silverstein JH, Chung FF, et al. Practice guidelines for postanesthetic care: an updated report by the American Society of Anesthesiologists Task Force on Postanesthetic Care. Anesth. 2013 Feb;118(2):291-397.*