MUSCLE RELAXANTS IN CLINICAL ANESTHESIA

David R. Bevan
Joan C. Bevan
François Donati

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David R. Bevan, M.B.
Professor of Anesthesia
McGill University
Anesthetist-in-Chief
Royal Victoria Hospital
Montreal, Quebec, Canada

Joan C. Bevan, M.D.
Associate Professor of Anesthesia
McGill University
Montreal, Quebec, Canada

François Donati, M.D.
Assistant Professor of Anesthesia
McGill University
Montreal, Quebec, Canada

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PREFACE

During the last 10 years, there has been an explosion of new information concerning muscular relaxation during anesthesia. In part, this has resulted from the development of new neuromuscular blocking drugs and a reevaluation of drugs used for their reversal. These new agents encouraged the search for sensitive assays to examine their pharmacokinetic profile and to relate these changes to the action of the drugs. This, in turn, encouraged a standardized system of measuring neuromuscular activity, which led to closer evaluation of the action of the agents at different muscle groups. Standardized measurement also allowed improved evaluation of drug interactions, and defined the behavior of the relaxants and their reversal agents at the extremes of age and in states of major organ dysfunction. Simultaneously, many refinements in electrophysiologic and histochemical techniques have allowed greater understanding of the morphology and function of the acetylcholine receptor.

Several questions remain. For example, which are the sites of action of the relaxant drugs? Will it be possible to develop a short-acting relaxant without undesirable side effects? Is reversal of neuromuscular blockade always necessary? The purpose of the present text is to review the current state of knowledge of neuromuscular physiology and pharmacology for the clinician. In particular, attempts have been made to provide an extensive bibliography and to include much of the factual details in a graphical format. The drugs that have been discussed are those currently available in the Western world.

It seemed appropriate to produce a text by a group of anesthesiologists who enjoy clinical investigation from a city, Montreal, that was influential in the introduction of muscle relaxants into clinical anesthetic practice.

David R. Bevan, M.B.
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The Arrival of Curare in Montreal

> We have been so much impressed by the dramatic effect produced in every one of our patients that we believe this investigation should be continued.
>
> H.R. Griffith and G.E. Johnson, 1942[1]

This modest conclusion by Griffith and Johnson revolutionized anesthetic practice. Very quickly, the use of muscle relaxants during anesthesia spread from Montreal around the world. However, many others were involved in transferring the lethal poison from the arrow tips of the South American jungle to the operating room. Medieval explorers, scientists, and medical pioneers of the 19th century were all entranced by the mystique of curare. The purpose of this chapter is to summarize those achievements that culminated in Griffith's success.

BERNARD–SIBSON–SAYRE

Medical uses for curare have been suggested since the mid-1800s. Claude Bernard showed that it produced paralysis only after injection into the bloodstream and by a selective action at the neuromuscular junction. In 1839, Dr. Francis Sibson in Nottingham, England, attempted to treat rabies with crude curare extract, and by 1857 Dr. Lewis Albert Sayre in New York had advocated the use of the drug to relieve the spasms of tetanus. Until the end of the 19th century, curare was

used primarily to produce immobility in animals for physiologic experiments.

BOEHM–LAWEN

It was recognized that the crude curare extract varied in quality. From 1895 to 1897, Rudolf Boehm classified the curare extract as calabash, tube, or pot curare according to the native containers in which it reached Europe. In 1912, he gave Arthur Läwen, a surgeon of Leipzig, some of the curarine extracted from calabash curare. This was injected during surgery to produce relaxation for abdominal closure, while avoiding deep anesthesia.[2] The work went unnoticed for the next 30 years. It needed the enthusiasm of neurophysiologists and psychiatrists to suggest the first practical application for curare; a determined explorer to bring back large quantities from the South American jungle; and careful pharmacologic studies before a purified standardized preparation was available for clinical use. Experience with curare in electroconvulsive therapy encouraged others to suggest a place for it in anesthesia.

RANYARD WEST—SHERRINGTON

In the early 1930s, Dr. Ranyard West of Scotland, at the suggestion of Dr. Hamilton Hartridge, professor of physiology in London, attempted to use curare for its selective relaxing or lissive effect in the investigation of tetany and treatment of neurologic spasticities.[3] However, their supplies of curare were as uncertain as the pharmacologic effects. The curare extracts originated from an unknown source supplied to Burroughs Wellcome Co. from France and some pot curare from the Orinoco region that was a gift from Sir Charles Sherrington at Oxford. Clearly, several groups wished to investigate the properties of curare, but material was scarce.

AMAZON, ORINOCO, AND THE ROYAL BOTANICAL GARDENS

The Amazon basin was the site of a number of expeditions, but none of the treks was successful in obtaining adequate supplies. Eventually, links with Indians in the Orinoco region were made through the

forestry service in the British colony of Guiana. In 1932, T. A. Warren Davis, the conservator of the forests, collected rare plants from the Mayarum River. These included *Strychnos toxifera, cogens,* and *pedunculata,* which were used by the natives in the preparation of curare arrow poison: "the flying death." The botanical specimens were authenticated by N. Y. Sandwich of the Royal Botanical Gardens at Kew.

HAROLD KING AND THE BRITISH MUSEUM

Chemical analysis was delayed while Burroughs Wellcome Co. awaited supplies of the plants. So, Ranyard West sought help from Dr. J. H. Daly of the Medical Research Council, a physiologist investigating the action of acetylcholine in neuromuscular transmission. In Daly's laboratory, Harold King, a chemist who studied alkaloids, was interested in "the flying death" and knew that curare interfered in some way with the action of acetylcholine. In the British Museum, a bamboo tube labeled "Ucayali River, 1871," containing 25 gm of tube curare was found, from which Harold King isolated pure *d*-tubocurarine chloride in 1935.[4] Later King extracted considerable supplies of crude curarine from the abundant supplies of bark of the *Strychnos toxifera* tree from Guiana. These extracts often produced bronchospasm. At this time, although the chemistry and pharmacology of curare had been determined, the botanically identifiable source remained elusive.

RICHARD GILL

Eventually large supplies of the plants used in curare making by the Indians in Ecuador[5] were obtained by Richard C. Gill. This allowed the first authenticated variety of curare to become commercially available. Born in 1901, the son of a Washington physician, Gill adopted an unconventional life-style. He abandoned medical studies to teach English, and then, in 1927, he followed his love of the wilderness to become a salesman for the American Rubber Company in Lima, Peru. Leaving the business life, he bought land on the eastern slopes of the Andes in the valley of the Rio Pastaza, a tributary of the Marañón and Amazon rivers. Here, he and his wife, Ruth, built a ranch, cultivated coffee, and learned the ways of the jungle.

MULTIPLE SCLEROSIS—WALTER FREEMAN

In 1932 the Gills returned to Maine on vacation. A few days before leaving, Gill was thrown from a horse, a fall which later he blamed for the development of bizarre symptoms of numbness, tingling, and clumsiness. He became paralyzed, and the illness, which was diagnosed as multiple sclerosis by the New York neurologist Dr. Walter Freeman, confined him to Washington for the next 4 years. As his health improved, he became obsessed with this doctor's notion that curare might relieve some of the symptoms of his spastic neurologic disease. He was determined to return to Ecuador where he knew he could locate supplies of curare.

MERCK—SQUIBB—ECUADOR

Gill approached the pharmaceutical firm, Merck & Co., Inc., which had shown an interest previously in collecting plants in South America. Their botanist, Dr. Boris A. Krukoff, taught him how to identify, collect, and preserve botanical specimens. Financial backing for his expedition was offered by a Massachusetts businessman, Sayre Merrill, who was impressed by Gill's jungle tales. Gill returned to Ecuador in 1938 during a remission of his disease, after organizing a 5-month jungle expedition. He became a jungle "brujo," or medicine man, learned the secrets of native manufacture of curare, and observed its use in blowguns to kill birds and small animals. He collected lianas from which he extracted the sticky tar-like, crude curare and returned to the United States later the same year with 25 lb of the substance. Unfortunately, Merck had turned its attention to the investigation of a different plant with curariform properties that yielded the alkaloid erythroidine. However, with characteristic persistence, Gill persuaded another pharmaceutical company, E. R. Squibb & Sons, Inc., to buy his supplies in 1939.

BURMAN—BENNETT—McINTYRE

Meanwhile, Michael Burman, an orthopedic surgeon, influenced by Ranyard West's work, attempted to relieve spastic paralysis with curare and erythroidine and found the responses promising but unpredictable.[6] This encouraged A. E. Bennett, a neuropsychiatrist in Omaha, Nebraska, to use curarization to prevent the fractures and dislocations associated with convulsive shock therapy. Bennett, a col-

league of Dr. Walter Freeman, had learned of Gill's successful expedition and obtained supplies of curare from him. The drug was standardized by A. R. McIntyre, chairman of pharmacology at the University of Nebraska, by traditional methods using frog muscle and mice. First, Bennett repeated Burman's work on spastic children and then applied curarization successfully to convulsive shock therapy. The incidence of extremity fractures and vertebral dislocations associated with unmodified treatment was drastically reduced from 40% to 50% to less than 1%.[7]

HOLADAY—DUTCHER—WINTERSTEINER

The active principle of the purified curare had not yet been isolated, but the plant source was identified as *Chondodendron tomentosum* by Squibb's chemist, Horace Holaday. He devised an accurate biologic assay, the rabbit head-drop test,[8] to assess the potency of the new drug Intocostrin. Supplies were sent to McIntyre, who held a research grant from Squibb, and Bennett. They found that its action was uniform and predictable in 1,500 psychiatric patients, which encouraged its widespread use by other psychiatrists. Squibb then distributed ampules of Intocostrin to selected doctors and sought Food and Drug Administration permission for its sale. This approval was not forthcoming until 1945.[9] In 1942 James Dutcher and Oskar Wintersteiner, working with Gill's supplies, established with certainty that the origin of the *d*-tubocurarine chloride, previously isolated by King from a 65-year-old museum specimen, was *Chondodendron tomentosum*.[10]

WRIGHT—ROVENSTINE—PAPPER—CULLEN

The idea to use curare in anesthesia originated with Lewis H. Wright, who had used curare in the physiology laboratory, practiced as an obstetrician, and then joined Squibb to advise in anesthesia. At the 91st annual meeting of the American Medical Association held in New York in 1940, he watched a film on the use of Intocostrin in shock therapy by Drs. A. E. Bennett and A. R. McIntyre. It seemed logical to him to extrapolate this method of relaxation to supplement the action of the newer anesthetic agents that he promoted. Usually his suggestions were greeted with ridicule, but two anesthetists, Dr. Emery A. Rovenstine and Dr. Stuart C. Cullen, left that meeting to return to New York and Iowa with several ampules of Intocostrin, while Dr. Griffith left for

Montreal with only his thoughts. Rovenstine's research assistant, Dr. E. M. Papper, experimented with the drug in etherized cats, and it provoked severe, sometimes fatal bronchospasm. Following the injection of a dose, thought to be safe, to two patients, he was horrified to have to resuscitate them overnight. Cullen fared no better with his attempts to use the drug in dogs and categorically asserted that there was no possibility of introducing Intocostrin into anesthesia.[11]

HAROLD GRIFFITH—MONTREAL HOMEOPATHIC HOSPITAL

When Harold Griffith next met Wright at a meeting in Montreal in 1941, he learned the outcome of Papper and Cullen's efforts. However, his certainty that Intocostrin could be used safely, as a result of Bennett's work in psychiatry, persisted. Griffith decided to try it. Harold Griffith was well established as an anesthetist practicing in Montreal at the Homeopathic Hospital (now the Queen Elizabeth Hospital) where his father had been its first medical director and his brother was chief surgeon. His interest in anesthesia began as a medical student and lasted through years of general practice and war service. He was influenced by the principles of homeopathy and believed in the use of the smallest effective dose of any drug. He wanted to use less toxic amounts of anesthetic agents and curare might allow him to do this. Unlike Papper and Cullen, he was familiar with cyclopropane, a drug which he saw used by Ralph Waters in Wisconsin in 1933 and he introduced it into Canada that same year. Unlike ether, cyclopropane had no hypotensive effect or marked peripheral muscle relaxant action and so lacked synergism with curare. Moreover, Griffith remembered that one of his patients had died from laryngeal spasm in 1925 and was conscious of the possible need for endotracheal intubation and artificial ventilation in an anesthetized patient. When he first gave an intravenous injection of 5 ml of Intocostrin, an unauthenticated extract of curare, to a 20-year-old plumber during cyclopropane anesthesia for appendectomy (see Frontispiece), it was as a caring doctor rather than as a controversial medical pioneer. Griffith was satisfied.

Harold Griffith's report of the administration of curare to 25 patients under cyclopropane anesthesia was published in July 1942.[1] Without the constraints of ethics committees and peer reviews, this information was disseminated to an eager readership of clinical anesthetists within 6 months of its first clinical trial!

COLUMBUS—MARTYR—KEYNES—RALEIGH

Griffith knew nothing of Lawen's earlier use of curare for abdominal relaxation. Curare's reputation as a poison, surrounded by superstition and mythology, was centuries old and could not be dispelled prematurely. Soon after Columbus's explorations of South America in 1498, stories were brought back to Europe of travelers killed by poison arrows. These accounts and descriptions of the preparation of curare were collected by Pieter Martyr, an Italian who lived in Spain, in a book *De Orbe Novo*. Sir Walter Raleigh's expeditions took him to the same region, the Orinoco River in present day Venezuela, in 1554. One of his lieutenants, Lawrence Keynes, described the tribes of Indians they encountered and first used the word "ourari." It is probable that this meant "bird-killer," and variations include urari, woorara, oorali, cururu, ticunas and wourali, as well as the now familiar curare.[12]

TREATY OF TORDESSILES

The wars between the English and Spanish had resulted in the Treaty of Tordessiles in 1494, which gave Portugal sovereignty over part of Brazil and Africa, and Spain took all the lands west of Brazil. This effectively barred travel between Guiana and parts of Brazil in the east and Venezuela, Colombia, Ecuador, and Peru in the west for more than three centuries.

CONDAMINE—BANCROFT—ABEE FONTANA—VON HUMBOLDT

Charles Marie de la Condamine led an expedition to Ecuador in 1735 where he spent 10 years. As a scientist, he was interested in the configuration of the equator and North and South Poles, but he also wrote about a tribe called the Yameos who hunted with blow darts. He noticed that it was not dangerous to eat the meat that they killed. He took the first samples of curare back to Europe, where he demonstrated its lethal effect on chickens. Early investigators of the 18th century, Roger Herrisant, Richard Brockelsby, and the better-known Edward Bancroft, Abee Felix Fontana, and Friedrich von Humboldt also contributed to an understanding of the actions of curare.

BRODIE—WATERTON—"WOURALIA"

Bancroft's son, a physician, later supplied Benjamin Collins Brodie with the curare that Brodie used in 1812 to show that a curarized cat could be kept alive by artificial respiration through a tracheostomy. The eccentric Charles Waterton, Squire of Walton Hall, left England to manage his family's sugar plantation in Guiana. His stories of Indians killing birds with blowpipes and poison arrows, and descriptions of plants, including *Chondrodendron tomentosum*, were told in his book *Wanderings in South America*. When he returned to England in 1812, he took with him supplies of curare sufficient to repeat Brodie's experiments on a larger animal, a donkey, thereafter named Wouralia.[13]

SCHOMBURGK—BERNARD

The mechanism of action of curare, as well as the plants from which it came, remained unknown. Twenty years after Waterton's exploration, the Schomburgk brothers, Robert and Richard, saw the "urari" plant in the same area and described the apples and stems of *Strychnos toxifera*. It was later found that the curare plants from the eastern Amazon region have *Strychnos toxifera* as their chief ingredient. Despite these tentative scientific advances, Claude Bernard's experiments of the 1840s repeating those of Fontana, were needed to allow curare to move out of the laboratory and into clinical use. Perhaps Lawen failed to get acceptance for the paralyzing properties of curare for therapeutic uses only because the active ingredient had not been isolated, and the drug was not yet standardized.

GRAY—HALTON

Although the introduction of curare into clinical anesthesia required a long time, its subsequent acceptance was rapid. Cullen[14] followed Griffith's lead enthusiastically and reported more than 1,000 successful cases in which Intocostrin was used by 1945 removing any remaining impediment to its acceptance. Despite delays due to wartime difficulties in obtaining supplies, the next advances came from England. As a result of King's isolation of *d*-tubocurarine chloride and of its availability from Gill's supplies of *Chondodendron tomentosum*, Gray and Halton introduced this authenticated extract of curare (3 mg of *d*-tubocurarine was equivalent to 1 ml of Intocostrin) clinically. Their

1946 account of its use in 1,000 patients was aptly entitled "A Milestone in Anaesthesia?"[15] More importantly, they dispelled the belief that low doses were necessary so that spontaneous respiration was preserved and they deliberately paralyzed their patients with large doses, necessitating the use of controlled artificial ventilation. Thus, the technique of balanced anesthesia was developed, using minimal doses of drugs to provide unconsciousness, analgesia, and relaxation, the components of the "triad of anesthesia."[16]

BEECHER AND TODD

Inevitably doubts arose. The most damaging to curare's reputation was Beecher and Todd's 1954 report on deaths associated with anesthesia, suggesting a sixfold increase in mortality when curare was used.[17] An inherent toxic effect of curare was refuted, and Dripps,[18] in a critical review of these findings, drew attention to the role of inadequate reversal of paralysis in these deaths. While the need for ventilatory assistance during surgery was apparent, the use of pharmacologic reversal of paralysis at the end of surgery was not widespread. Clinical criteria were subjective, leaving uncertainties about residual curarization.

POLIO—INTENSIVE CARE UNITS—INTERMITTENT POSITIVE-PRESSURE VENTILATION

During these early years, manual compression of the reservoir bag served as a means of artificial ventilation. Satisfactory mechanical ventilators were not available until experience in the poliomyelitis epidemic in Denmark in 1952 necessitated their development. Body respirators were found to be ineffective in severe cases. Ibson instituted the technique of endotracheal intubation and intermittent positive pressure ventilation. Initially it was applied manually and later by mechanical respirators.[19] Once measurements of acid-base state became easier, with the introduction of electrodes to measure blood oxygen and carbon dioxide tensions,[20] control of ventilatory parameters was possible. Respiratory support could then be guaranteed, and curarization became a technique of choice in anesthesia.

The acceptance of muscle relaxants in anesthesia allowed interactions with developments in medicine and surgery and facilitated the treatment of thoracic, cardiac, and neurosurgical conditions previously considered inoperable. By extrapolation to the management of respi-