Annals of Anesthetic History

How "Indian Arrow Poison" Curare Became a Useful Drug

*A. E. Bennett, M.D.**

In spite of the many publications on how curare was developed into a useful neuromuscular relaxing drug, its historical evolution has been inaccurately reported in much of the literature. At the suggestion of a number of my collaborating colleagues that the record be made clear, this historical resume was prepared. I would like to dedicate this paper to the memory of Richard C. Gill and pay tribute to his great contribution to medicine in making curare available to the numerous investigators who aided in the perfection of this useful muscular relaxant.

This is not an attempt to review the extensive history of curare, which extends back to the time of Columbus. A complete history of early investigations and botanical problems is available in a recent book *Curare: Its History and Usage* by K. Bryn Thomas; it also covers physiological and chemical investigations. Clinical studies are given in detail with few inaccuracies.

Curare had been known for centuries in primitive cultures associated with the livelihood and witchcraft of South American Indians, and other aboriginal tribes. It is used on arrows and spears to paralyze small mammals and birds. Curare with its many synonyms is a nonspecific term used by Indians to designate a varied group of arrow poisons.

Physiologists and pharmacologists have long employed specimens of curare in the study of nerve-muscle preparations. Prior to 1940, most authorities believed that its application to clinical medicine was not practical. Pharmacologic texts[1, 2] published several years after standardization and successful use in thousands of patients, continued to state: that the action of curare was unreliable that it paralyzed striate musculature and its only use was experimental for paralyzing skeletal muscles. Lack of knowledge, varying potency and preparations having toxic impurities produced inconstant results; many thought the drug was lethal thus too dangerous for clinical use. All of this changed when for the first time larger amounts of pure curare became available for experimental work, through the efforts of Richard C. Gill. Mrs. Ruth L. Gill described[3] their ranch life in the jungles of Ecuador and how they procured curare in 1934. More successful was the second expedition in 1938. Gill reported on his long months of jungle work and field research to procure large amounts of curare.[4-7] He also cleared up many misconceptions about the botanical species and the pharmacologic actions of the various curare preparations.[8] It first became accepted in pharmacology as an infusion, later alkaloids were extracted from the plant *Chondodendrom tomentosum* with a specific action on the neuromuscular junction, through its blocking action of acetylcholine. The drug was standardized and successfully introduced into clinical medicine in 1939. The story of how this came about follows.

Claude Bernard, in 1844 in his classic experiments proved that the action of curare took place at the myoneural junction. A number of French clinicians attempted use of the drug clinically in the latter half of the nineteenth century, in such conditions as rabies, tetanus, epilepsy and chorea. No attempts were made to standardize the preparations. West[10] in 1934 tried curare for pyramidal

* The A. E. Bennett Neuropsychiatric Research Foundation, Berkeley, California.
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and extrapyramidal rigidity and also in parathyroid tetany. However, no clinical use for curare was developed.

The successful introduction of curare to clinical medicine began with a search for a means of mitigating the convulsive seizures of metrazol shock therapy. From 1936 until 1938 the problem of traumatic complications became so serious that this valuable treatment was about to be abandoned. The incidence of serious fractures of the extremities had been 1.5 to 2 per cent, dislocations 17 per cent and compressive spinal fractures 43 to 51 per cent. All preventive methods had failed and spinal anesthesia [11] was used in desperation prior to shock treatment. The principle of neuromuscular relaxation or curarization (blocking the neuromuscular junction) appeared in theory to meet the situation ideally. A complete review of the literature was not encouraging however, except for the work of Burman,[12] who showed curare to be a safe relaxant in spastic states. This article started me on a search for an amount sufficient for experimental purposes. None was available in the commercial markets. After discussing with Doctor Walter Freeman the problem and my desire to obtain curare for experimental purposes, he told me of Richard C. Gill who had just returned in December 1938 from an expedition to Ecuador, where he had procured a large amount of crude curare. After corresponding with Gill, a meeting was arranged at his New York Hotel in May 1939. At that time, I explained to him my plan to attempt standardization of the drug and for a clinical trial on spastic children at the Orthopedic Hospital in Lincoln, Nebraska. Finally I expressed the hope that I could use it in preventing the traumatic complications of shock therapy. Mr. Gill immediately made available to me a large quantity of the crude material. This material was then turned over to the Department of Pharmacology at the University of Nebraska, College of Medicine, under the direction of Doctor A. R. McIntyre, who first standardized the drug. The A. E. Bennett Neuropsychiatric Research Foundation financed all of the early investigational work with the drug. A joint venture was arranged with Doctor McIntyre with the understanding that he would take full responsibility for all pharmacological and physiological research and that I would carry on all the clinical investigations. Doctor McIntyre started his studies on the lethal dosage of curare in mice and established a dosage of 3 to 4 mg. per kilogram as a standard unit. This seemed adequate to establish a physiologic dose for use in patients. Spastic patients were treated for about five months with this preparation, using about one-sixth of the established lethal dose as the amount necessary to produce complete flaccid paresis of body musculature without marked respiratory embarrassment.

The McIntyre preparation was used from curare supplied by Gill, from June until August 1939. Gill then turned over to E. R. Squibb & Sons his entire supply. On August 7, 1939, Doctor Sidney Newcomer wrote me that they hoped to standardize it for clinical trial and offered to continue to supply to McIntyre desiccated material—for him to assay, so that I could continue the clinical investigations. On October 2, 1939, I wrote Richard Gill that Doctor Newcomer had visited McIntyre and me, and assured us that he would continue to supply crude curare until their laboratory was able to standardize the drug. On October 28, 1939, I wrote Doctor Newcomer that we had successfully used curare to prevent traumatic complications for metrazol convulsive treatment and that we were preparing a preliminary report to submit to *The Journal of the American Medical Association*.

Within a few months, refinements of the technique of standardization were made by A. H. Holaday and E. R. Squibb & Sons, by his ingenious rabbit head-drop test. This proved to be a highly accurate dosage, directly transferable to man.

The first clinical applications of the McIntyre preparations were upon spastic, athetoid children at the Orthopedic Hospital, from June to December, 1939. After that time the Squibb preparation standardized by Holaday's method, and known as "Intocostrin," was used exclusively in our clinical experimental work until Wintersteiner and Dutcher developed the alkaloids in 1942.[23]

Credit should be here given to Doctor H. Sydney Newcomer, Associate Medical Direc-

tor of E. R. Squibb & Sons, who arranged to take over the Gill material and who cooperated fully with us in our work. We carried out a regular interchange of correspondence for years with frequent conferences also with the Board of Directors of E. R. Squibb & Sons to obtain finally a marketable preparation of curare. (All of the original communications with Richard Gill and Doctor Newcomer have been given to the Arthur E. Guedel Memorial Anesthesia Center of which Doctor W. B. Neff is chairman.) We interchanged material and ideas for publication, scientific exhibits and motion pictures to further the research activities. Every new batch of standardized Intocostrin and later the alkaloid *d*-tubocurarin was tested by my staff, clinically, before being released to others. In 1940 we began to supply the drug to many other investigators and institutions such as The Mayo Clinic, The New York Psychiatric Institute, The Menninger Clinic, St. Luke's Hospital in Chicago, Colorado Psychopathic Hospital, The Shephard and Enoch Pratt Institute in Baltimore and The Milwaukee Sanatarium. We required either a personal demonstration or that a worker come to Omaha to be trained in the technique. In 1940 we submitted to the Federal Food and Drug Administration a report on 1,000 treatments with Metrazol-curare and prepared a teaching film on its use.

The first paper [13] on the use of shock therapy with curare in depressions was given in February, 1940, before the Missouri-Kansas Neuropsychiatric Society. At that time E. R. Squibb & Sons were still undecided about its commercial usefulness and in February, 1940, I wrote as follows:

> We have established the value of a new therapy that is going to rescue shock therapy from being abandoned, as soon as the medical profession becomes fully informed. We have an ideal shock absorber for convulsive shock therapy and I strongly urge Squibb & Sons to push for its acceptance as a standardized drug for medical use.

At this time the preliminary report appeared in *The Journal of the American Medical Association*.[14] We were then besieged with so many requests for curare that we were unable to supply them all, but we continued to supply as many as we could through the cooperation of Doctor Newcomer and the generosity of the Squibb Company. Soon we were not able, personally, to pass upon each new batch of curare, so I arranged to have some of it tested at the Lincoln State Hospital where my co-worker, Doctor A. H. Fechner, had helped with the first metrazol-curare treatments before I had given them to private patients.

We established the dosage of 1 ml. of Intocostrin or 10 mg. per 20 pounds of body weight as the average dose for female patients, slightly larger amounts for males, to produce a degree of curarization sufficient to markedly soften a convulsive seizure. At the 1940 Annual Meetings of The American Medical Association and The American Psychiatric Association [15] our teaching films on the use of curare in spastic athetoid states and for prevention of complications in convulsive shock therapy were shown, along with a Scientific Exhibit, which received a Certificate of Merit Award.

Studies on Quinine

Early in our investigations on curare, we were greatly concerned as to whether we could be sure of a continuous supply of crude curare from Ecuador. This caused us to look for possible substitute drugs with curare-like actions. Drugs like β-erthyroidine, magnesium sulfate and quinine all with curariform actions were investigated. We finally decided that quinine methocholoride was the most satisfactory substitute and we worked out a combined metrazol-quinine treatment that was highly effective, and published our results.[16] We also were looking for an oral preparation that could be used as a neuromuscular relaxant in spastic athetoid and involuntary spasmodic muscular disorders. We treated a large number of children, for many months, with this preparation.

When it became certain that curare could be obtained in adequate amounts, these substitutive drugs were not further studied because it seemed improbable to improve upon the curare method in shock therapy, which was our major interest. By 1941 over 30,000 treatments had been reported with only two deaths. Both of these were the result of lack of knowledge of a proper airway, the handling of ob-

structive breathing or not using the antidote, prostigmine.

Myasthenia Gravis

From the beginning of our researches we noted that physiologic manifestations of curarization closely followed in order of appearance and character the progressive symptoms of the disease, myasthenia gravis. The two conditions are almost identical: the rapid fatigue of muscle in the myasthenic appears to produce an agent that blocks neuromuscular transmission, almost the same as that seen upon injection of curare. From this observation we deduced that myasthenic patients would be exceedingly sensitive to curare. This observation led to the development of a specific diagnostic test for the disease.[17]

Curare in Anesthesia

Following an observation made in Nebraska State Mental Hospital that pelvic examinations upon disturbed psychotic female patients could be easily made because of the muscular relaxation after injection of curare,[24] we thought that curare would be useful in producing muscular relaxatoin during general anesthesia.

This matter was discussed with Doctor Lewis H. Wright of E. R. Squibb & Sons, several times. However, he had been trying to gain the interest of anesthesiologists in the drug, for at least two years. Upon his suggestion, Doctor H. R. Griffith of Montreal first reported the use of curare in anesthesia in January 1942.[18] In December 1942, Intocostrin was first supplied to Doctor Cullen of Iowa City who first started investigations in the United States.

In a letter to Doctor Newcomer on November 7, 1942, I stated that we had been in communication with Doctor Cullen and that he was planning its use in anesthesia. On January 20, 1943, Doctor Newcomer wrote me that Doctor Cullen was getting along nicely with Intocostrin anesthesia. Doctor Newcomer proposed having Doctor Cullen make human assays of the new alkaloidal preparation, *d*-tubocurarine methyliodide. Before doing so, he desired to know more accurately what I had observed about its potency. On January 30, I rendered him a comparative analysis of the clinical reactions of the two preparations. On July 26, 1943, Doctor Newcomer wrote: "We are concerned about a statement of Doctor Cullen's to the effect that respiratory depression with *d*-tubocurarine was less marked and of shorter duration than with Intocostrin; that *d*-tubocurarine is 30 to 40 per cent more potent. We are, therefore, sending a solution to cancel out the 25 per cent increase in potency. In order for you to check on this we are sending you a supply. Will you, then, please give us your findings as to which, if either, is more potent on a volume basis?" On July 30, I replied that Doctor Cullen's statement was approximately correct. We were able to secure relaxation with smaller doses of *d*-tubocurarine, which assumed was because of the fact that we had a higher degree of potency in the preparation. Many other anesthetists quickly followed the lead and reported on its safe use with all types of anesthetics, especially cyclopropane. In 1958, Doctor Cullen was given an award by *Modern Medine* for having first introduced curare in the United States as a muscular relaxant. They had overlooked completely our original investigations and publications and also Doctor Griffith's pioneering work. On July 14, 1943, Richard Gill wrote me about Doctor Griffith as follows: "I have just received a heartwarming letter from Doctor H. Griffith and a copy of a paper just delivered. Inasmuch as you have already written about the use of curare in abdominal surgery, I thought you would be interested. Doctor Griffith stated the more experiences we have had with curare in anesthesia, the more enthusiastic we have become. It seems that curare will become more valuable to the anesthetist than to the neurologist. I should like to express the great appreciation of our surgeons, anesthetists, and patients for the very careful work, which you have done in making the drug available to us."

The following are several quotations from Doctor Griffith's numerous publications[19]: "Clinical medicine has made it possible for us to obtain complete muscular relaxation at anytime during anesthesia with nontoxic controllable anesthetic agents." He reported several times that he first learned of the potenti-

alities of curarization from Doctor Lewis H. Wright of E. R. Squibb & Sons, who in 1940 told him of our use of Intocostrin to alleviate convulsions in shock therapy. "When the idea of its use was first suggested in 1940, I passed off the idea as fantastic and laughed at the idea, but again in October, 1941, when he told me that Doctor Bennett had administered the drug to hundreds of psychotic patients without harmful effects, I decided that an anesthetist could control respiration and gave it a trial." He states that he gave the first injection on January 23, 1942, and found relaxation of the abdominal muscles, under light anesthesia, without any complications. Then in July, 1942, he reported on the successful use in 25 cases during anesthesia.

At first, others condemned the procedure. Those who were persuaded to try it were unanimous in support of it. On January 23, 1943, Doctor S. C. Cullen [20] published results in a large series of cases, followed by Knight, Baird, Hudon, Scott Smith, Cecil Gray and others.

In 1951 [21] in his report entitled "Evolution of the Use of Curare in Anesthesiology," Doctor Griffith states that the advent of curare in 1942 made possible the elimination of deep anesthesia with the risks of hypoxia, to produce complete muscle relaxation without any harm to the patient. This had a revolutionary effect upon the practice of anesthesiology. In 10 years it has become routine in all operating rooms throughout the world. He further adds that great credit should be given to Richard C. Gill who spent years in the jungles of Ecuador and had the vision, perseverance and knowledge of botanical, identifiable specimens with the knowledge of curare manifestations. He mentions Gill's book, "White Water and Black Magic" [22] published in 1940 and states that Professor A. E. Bennett of the University of Nebraska began to use Intocostrin in order to minimize the traumatic effects of violent muscular contractions in patients undergoing shock therapy with Metrazol. The first large scale tests of curare on the human subject were made by Professor Bennett and the use of curare in both Metrazol and electroshock therapy has become widely spread in mental hospitals. "It was Doctor Bennett's use for minimizing of trauma in convulsive shock therapy that led us to the cautious trial in a patient under cyclopropane anesthesia."

After the twenty-first anniversary celebration of the introduction of curare to anesthesia, given by McGill University and honoring Doctor Griffith, he wrote me as follows: "I have always felt that I got a little more credit for curare than was really due me because it was your work with psychiatric patients which made me accept Lew Wright's suggestion to bring curare into the operating room."

In May 1942, a real advance in the chemistry was made by Wintersteiner and Dutcher [23] of E. R. Squibb & Sons, when they developed a crystalline alkaloid with the properties of a quaternary base, identical to the *d*-tubocurarine originally isolated by H. King in 1935. They called the new alkaloid *d*-chondocurine. They were able to markedly increase the physiological activity through a process of methylation.

Myasthenia Gravis

We had reported [24] in 1942 that myasthenia gravis must be caused by a chemical intoxication with a quaternary base similar to curare and that research along this line, possible linking it with activity of thymus gland could establish the etiology of the disease. In 1943, E. R. Squibb & Sons authorized financial support through my Research Foundation for combined investigational activities by Doctor A. R. McIntyre and myself. The funds were used mostly to carry on studies on myasthenia gravis and publications, a scientific exhibit and a second Scientific Award at the American Medical Association Meeting in 1946.

Many lay magazines began to publish sensational articles about the use of curare. *Life* and *Collier's* both wanted photographs of patients; these requests were refused. Problems arose from this publicity largely because false hopes were raised in the treatment of spastic disorders and the real value of curare in shock therapy and anesthesia was not understood. One damaging article was published over my vigorous protest.

Electroshock Therapy

With the introduction of electroshock therapy in the United States in 1940, it was first claimed that through regulation of the amount of electric current one could soften the convulsive seizure and prevent complications. This soon proved to be untrue and traumatic complications became even more serious especially in the upper extremities. Preliminary curarization [25] became necessary and finally mandatory from a medicolegal standpoint. Treatments without the use of neuromuscular relaxants were considered to be malpractice by a number of court decisions.

Misconceptions About the Drug's Action

Probably no other drug has raised more fears and misconceptions concerning its action and safety than curare. Many considered it a dangerous drug and feared to use it. For example, such a leading authority as Doctor Edward Strecker then Professor of Psychiatry at the University of Pennsylvania wrote me in 1940, that he would hesitate to use curare clinically and that his department of pharmacology was dubious about its value. A number of reports of its hazards were made: cardiorespiratory reactions, medullary depression, respiratory paralyzing action and death. All of these reports were studied in detail and answered in a publication entitled "Misconceptions Concerning Hazards of Curarization with Electroshock." [26] These erroneous opinions were discussed fully and answered as follows:

(1) Curare does not increase the hazards of treatment.
(2) Curare is not a cerebral, cardiac or respiration depressant. Electroshock or sedative drugs may cause the cardiac or respiratory depression, but not curare.

Such symptoms as asystole and bradycardia do not arise from curare. Cardio-respiratory failure following curarization is secondary to asphyxia and not from a central respiratory or cardiac action. Curare is the only safe and effective means we have of eliminating traumatic complication of shock therapy.

There is relatively little danger in its use in competent hands. Prostigmine is a complete antidote against action of the curare, and with proper management of respiratory difficulties, no fatalities need occur. There is only one proved contraindication to the use of curare and that is myasthenia gravis.

After reading this report, Richard Gill who was understandably very enthusiastic about curare and subject to expansive moods wrote me as follows: "It's a grand piece of work. Every once in awhile I read over your archives and mentally wind up with the thought, if anyone ever deserved a Nobel Prize for a sound, lasting contribution in medicine, you surely do. After all, it has been given to a very few to make a drug functional and useful as you have done with curare and more. I just had to tell you how I feel."

Summary

The blocking of neuromuscular transmission of nerve impulses was first demonstrated by Claude Bernard. One hundred years elapsed before it became a clinically useful drug.

King,[31] West and Burman paved the way for its first practical application. Next Richard C. Gill made available to me sufficient amounts of the drug for standardization and clinical investigation. McIntyre, Holaday, and Wintersteiner and Dutcher of E. R. Squibb & Sons' pharmacological, physiological investigations perfected the drug.

Curare was successfully introduced in clinical medicine, first as a preventive of traumatic complications (1940) in metrazol convulsive shock therapy and then electroshock therapy. Next it became a useful neuromuscular relaxant in anesthesia. It proved then to be a specific diagnostic test in myasthenia gravis.

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Medical Practice

SPECIALTY CHOICE Of 178 residents, 37 per cent made their specialty selection during internship, 23 per cent as senior medical students, 17 per cent sometime after internship, and 15 per cent as junior medical students, with a few choices made prior to the third year of medical school. The use of certain abilities and skills was most highly emphasized by the various surgical fields and anesthesiologists. Pediatricians were most highly influenced by the variety their specialty offers, with anesthesiologists least affected by this factor. Desire for leisure time and family activities was an important consideration to radiologists and dermatologists in their career plans, with anesthesiologists and ophthalmologists also ranking these factors relatively high. (*Nesbitt, L. T.: Study of Factors that Influence the Choice of the Various Medical Specialties, Bull. Tulane Med. Faculty 25: 219 (Aug.) 1966.*)