CURARE: ITS PAST AND PRESENT *†

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It is beneficial at times and particularly during a rising tide of enthusiasm for a new therapeutic agent to read its past history and to submit current practices with it to objective study. A review of the history of curare and an investigation of the geneology of the preparations in clinical use today is fascinating and humbling. It is fascinating because so much is learned of the witchcraft and daily lives of the South American Indians and the exploits of the early explorers. It is humbling because it is evident that the Indians were aware of the powers and the limitations of those powers possessed by the crude curare. It is humbling also because, although we have succeeded in securing a predictable product and have learned a little more of the details concerning its action, we have not altered the conception of the drug's fundamental properties that was held by investigators and clinicians of the early 19th Century. It will be evident as the review of the literature concerning-curare unfolds that very little has been added to an understanding of the basic action of curare by current clinical and laboratory research. It will also be evident that although we are able to apply the drug satisfactorily in clinical practice, we have probably not extended the scope of its usefulness over that proposed by the clinicians of the 19th Century.

M. Webster Brown (1) of New York wrote an interesting short historical article about the magical and mysterious drug. Curare, then known as wourali, was brought to good Queen Bess by Sir Walter Raleigh in 1584. Raleigh had been on a visit to British Guiana and had obtained the specimen of wourali from the Indians in the Orinoco basin (2). This early source of crude curare has led many to believe that all crude curare comes from this region. Richard Gill (2, 3), a famous explorer and author about whom there will be discussion later, emphasizes that although the Orinoco basin is a source of curare, major portions of northern and western South America and particularly regions of Amazonian drainage are productive of plants from which current prepara-

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tions of curare are derived. The specimen of wourali that Raleigh presented to Queen Elizabeth was contained in a small, elaborately and grotesquely carved wooden vial. The tales of witchcraft and extreme irrevocable damage that accompanied the presentation must have discouraged any investigation of the properties of the black mass because nothing more is recorded about curare until 1745.

On May 16, 1859, William A. Hammond, an assistant surgeon in the United States Army, and S. Wier Mitchell, who at that time was lecturer in physiology in the Philadelphia Medical Association, read a paper before the Academy of Natural Sciences in which they gave a comprehensive review of the published material concerning wourali and spoke of experiments with two new varieties of the South American arrow poison (3). They related that in 1745, De la Condimine (4), a French investigator, was probably the first reliable physiologic experimenter with the drug. He killed chickens with wourali and used sugar and salt as an antidote, with some success. The combination of sugar and salt was apparently an empirical and mildly satisfactory panaceal antidote of those days. It is interesting to note that in these experiments and in many experiments in later years, the investigator introduced the drug by making a wound with a spear point covered with the crude preparation. It is not evident from the accounts whether this method of introduction was used because it was the method employed by the Indians or because it was recognized that the drug had to come in contact with the blood stream. De la Condimine claimed that the wourali, known by him as the ticunas poison, came from about thirty species of plants. Apparently the most widely used plant was the bindweed or mavaure.

Investigations were made in 1781 by Fontana (6), a curator of an Italian museum, who found that the vapors arising from the extraction process were not deleterious. It had long been established by the Indians that curare taken by mouth was innocuous and Fontana corroborated this elemental truth by noting that wourali given by mouth was less effective. The effect was delayed even more and was less pronounced if the stomach contained food. He determined also that acids and alkalies were ineffective antidotes. He found that wourali prevented the coagulation of the blood. It is pertinent to point out, in the light of later and even current experimentation, that he found no poisoning of nerve tissue when the drug was applied directly to it. He made another fundamental observation, which is still tenable, that the ticunas or wourali destroys the irritability of the voluntary muscles but does not affect that of the heart.

In 1811, during some experiments and observations on the different modes by which death is produced by certain vegetable poisons, Sir Benjamin Brodie (5), an English scientist, conducted rather fundamental research into the action of some wourali brought to him by Bancroft, a naturalist. Brodie was probably the first to observe that the drug
affected the respiration primarily and that the heart continued to beat for some time after respiratory activity had ceased. He performed artificial respiration and was able to revive some of the experimental animals. He also made the astute observation that it was essential to have an intact circulation in order that the drug might produce its effect. It was his belief that the brain was influenced by the wouralí only after the substance got into the blood stream. He, however, was mistaken in that he thought death was caused by poisoning of the brain. These are facts unrefuted by subsequent experimental and clinical experience.

In the 1830's there was considerable investigation by a number of men of the properties of curare. This was made possible by the return from South America of several explorers and naturalists who brought with them specimens of the crude preparation and some botanical material. Sir Robert Schomburgk (7), an English naturalist, was one of the more active of this group and it was he who maintained that the source of the wouralí was chiefly from the bark of a plant which he termed Strychnos Toxifera. By so naming the plant, he precipitated an argument among scientists relative to the nature of curare. The apparent stimulant or convulsive effects of the crude preparation of those days prompted many to consider that strychnia was a constituent of wouralí. As a matter of fact, it was this very action of large doses of the current preparation in dogs that delayed the advent of curare into clinical use in anesthesiology. In 1828, two French physicians, Roulin and Boussingault (8), concluded from their experiments that wouralí action was independent of the action of strychnia. They isolated an active principle to which they gave the name curarin. They stated that "the curarin was a solid transparent mass, of an excessively bitter taste, and possessed in an eminent degree of all the virulence of the wouralí. It was not crystallizable, was of a pale yellow colour, and strongly attractive of moisture from the atmosphere. It formed salts with sulphuric, nitric, hydrochloric, and acetic acids, none of which were crystallizable." Thenceforth the argument about the inclusion of strychnia declined.

Hermann Beigel, physician to the Metropolitan Free Hospital in London in 1868 (9), wrote that he was in possession of some notes of a Dr. Francis Sibson. Dr. Sibson was apparently an English investigator to whom Charles Waterton, an English naturalist, had given some urari obtained in travels in South America. Waterton (11, 12), in experiments superintended by Sibson and performed at the medical school in Nottingham, noted that animals could be revived by means of artificial respiration with an ingenious device made by Sibson. Sibson, in 1839, experimented with urari and arrived at conclusions that were, many years later, observed and published by Bernard, the great French physiologist.

Beigel, from whom the above history was obtained, stated that he thought it possible that the name curare came from a river in Guiana.
called Curwara. Prior to this more or less final definition, the preparations had variously been designated as woorari, wourali, urari, ticunas, and a number of other names derived mostly from the plant, the particular locality, and the Indian tribe from which the drug was secured. In 1855, Dr. Cogswell (12), a prominent English scientist, discussed, at a meeting of the Physiological Society of London, the different names applied to curare extracts and came to the conclusion that wourali or perhaps curari was the most representative name. He thought it possible that the extract might have contained snake venom, poison ant residue, and so forth. He pointed out that the physiologic action of curari was such that it was not likely that the preparation contained strychnia. He added that curari acted primarily as a stimulant but secondarily as a "sedative" and paralyzed the functions of the nervous system. It is of considerable interest to anesthesiologists that Dr. John Snow, the pioneer English anesthetist, presided at the meeting of the Society at which Cogswell spoke. Snow related at the meeting that he had conducted experiments which convinced him that wourali had no anesthetic action even up to the moment of death. This observation, made about 100 years ago, was only recently confirmed by Scott Smith who was the subject of a singular experiment in which he permitted colleagues to administer curare to him in doses sufficient to cause complete respiratory paralysis.

In 1844, Claude Bernard, the eminent French physiologist, and his associate Pelouze were the first to demonstrate the physiologic effect of urari (10). These experimentalists established the fact that urari paralyzed the motor nerves and from that fact concluded the existence of an irritability peculiar to the muscles. These researches were extended by Virchow and Munter, the German investigators (14), who found that curare was not a tetanic poison but that it induced a stupor and a paralysis of voluntary muscle while not interfering with involuntary muscle. They found that curare did not produce death by absorption from external surfaces but only through introduction into a solution in continuity with animal tissues. It will be recalled that this was an observation made by Brodie about forty years earlier. Virchow and Munter concluded that death was a consequence of paralysis of respiratory muscles and not due to central nervous system poisoning as Brodie had thought.

Clinical application of curare was first attempted in 1866 by two French physicians, Tiercelin and Benedict (15). They tried to allay and prevent the convulsions of epilepsy in human beings but their project was interrupted for lack of a continued supply of curare. Voison and Lionville, two other French physicians (16), also used curare for the same purpose. The results obtained by these men were inconsistent but they reported a few cures at a meeting of the Academy of Paris. In 1878, H. Hunter, a British physician, wrote a book (17) on British Guiana in the preface of which he described the use of curare for the
treatment of the spasticity of tetanus and hydrophobia. A study by Lucas (16) of the electrical properties of the nerve, nerve endings, and muscle made it possible to determine a differential action of curare. This study seemed to indicate that curare was capable of influencing the response of muscle to different optimal electrical stimuli. Boehm (19), a German chemist, described three separate alkaloids as being present in "pot" curare, two further ones in "tube" curare, and two, different again, in "gourd" or "calabash" curare. These varied greatly in their paralyzing properties. There is good reason to doubt, as Gill (32) pointed out, that the container in which the curare is placed by the Indians has anything to do with the type of alkaloid present.

Ranyard West, an English physician, was stimulated by the clinical experiments of the four French physicians, Tiercelin, Benedict, Voison and Lionville, and attempted to corroborate their results in 1932 (20). West used curare in the treatment of spastic disorders, such as Parkinson's disease, parathyroid tetany, epilepsy and hemiplegia. His results were not encouraging because the effects of the drug were transitory and accompanied by unpleasant subjective sensations and a fall in blood pressure. Because of this latter effect, West also attempted to treat hypertension with curare. In the course of these various clinical endeavors, West noted that with doses which produced the desired relaxation of the spastic muscles, there was a rather consistent and definite reduction in pulse rate. West was much intrigued by the peripheral action of curare and, in the light of current speculation about the action of curare on the autonomic nervous system, it seems pertinent to quote the following from West. "Secondly there is the possibility of the myoneural junction being a more selective apparatus than it is usually considered to be. I have in mind a structure upon which curare could actually act selectively, removing discharges of certain electrical patterns, while allowing others to pass. Dale and Gaddum (21) have shown with great clearness that stimulation of the nerves to the blood vessels of the tongue, by the local production of acetylcholine, can cause contraction of this organ when its motor innervation has been removed. If such an action is upon the remaining myoneural junctions (as it seems it may be), these would appear to have become sensitized by denervation to the peculiar form of stimulation presented. Whether some such mechanism could involve the autonomic nervous system as offering to these pathologic rigidities a contribution which is specifically removed by an action of curare on the myoneural junction, is entirely speculative. But the relationship of curare—or rather of the active principles which it contains—to the autonomic nervous system deserves investigation."

F. Huidobro, a pharmacologist in the Catholic University of Chile, in a recent report (22) indicated that he was also interested in the action of curare on neural transmission. He studied the action of metrazol, strychnine and picrotoxin on neuromuscular junctions influenced by
prostigmine and curare and concluded that the classical concepts of the action of acetylcholine fail to explain his results. It seems quite likely that in the future, as in the past, curare may be useful in delineating the functions and components of neuromuscular transmission.

Current enthusiasm for clinical application of curare is largely owing to the efforts of A. E. Bennett, a psychiatrist in Omaha (23). He popularized the use of curare to control the convulsions associated with metrazol or electric shock therapy. He was aided by the introduction in 1939 of a new, predictable and stable preparation of curare known as intocostrin, marketed by the E. R. Squibb laboratories. Bennett suggested that curare might be used as a means of improving muscular relaxation to facilitate the reduction of fractures.

The more reliable curare preparation that was made available to Bennett was the result of the coordination of the activities of an author, explorer and naturalist and the men in the research laboratories of the University of Nebraska and the E. R. Squibb company. The explorer, naturalist and author was Richard Gill. One learns from a book of his, White Water and Black Magic (24), that on one of his early expeditions into the Ecuadorian jungles, he was thrown from a horse and suffered an injury that resulted in a spastic paraplegia. As he lay in bed beset with the annoyances of the paraplegia, he chanced one day in a discussion to think about the possibilities of utilizing curare to relieve the spasticity. Upon further deliberation, he became enthused with the prospects of the satisfactory clinical application of the South American Indian arrow poison. In spite of limiting physical infirmities, Gill organized another expedition into South America for the purpose of determining the source of curare and the methods of its extraction. After many months in the jungle during which time he gained the confidence of the Indians, Gill learned the various plants from which the curare was extracted. He learned also the secret methods by which the Indians brewed the crude mass with which they tipped their poison arrows. Gill brought back with him several botanical specimens which have since been deposited in the New York Botanical Garden and in the Arnold Arboretum at Harvard. He was confronted with considerable skepticism among manufacturing chemists as to the practicability of curare in clinical medicine but, with a singleness of purpose that has characterized his whole experience with curare, he finally succeeded in interesting Dr. McIntyre, pharmacologist at the University of Nebraska, in developing a dependable product. After initial experimentation in the laboratory by McIntyre and in the clinic by Bennett, the psychiatrist, the drug was turned over in 1939 to the Squibb laboratories for commercial preparation. Intocostrin, now officially accepted, is said by the representatives of the Squibb company to be prepared from the plant Chondodendron tomentosum. The trade name is, in fact, partially derived from this plant name. Gill believes that the ethnobotany of curare is still complex and is not confined to the species Chondodendron.
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It is, on the other hand, quite evident that the current product, intocostrin, and its active principle, d-tubocurarine, are preparations that allow the research worker and the clinician to rely upon them for consistent action.

At the 1940 meeting of the American Medical Association, Bennett had an exhibit dealing with the employment of curare during metrazol shock therapy. This exhibit prompted several anesthesiologists to consider the possibility of using curare as a means of improving muscular relaxation during inhalation anesthesia. Dr. Lewis Wright was impressed with its potentialities and endeavored to interest several anesthesiologists in the drug. As mentioned earlier, one anesthesiologist did administer the drug to dogs, with undesirable convulsive effects and as a consequence abandoned the clinical application of curare. Wright, however, in convincing Harold Griffith of Montreal that intocostrin might be a valuable adjunct to anesthesia. Griffith and Enid Johnson, his associate, reported in 1942 that they had used curare in 25 patients to improve muscle relaxation during cyclopropane anesthesia (25). Following this publication, other investigators and clinicians soon began expanding the laboratory and clinical knowledge of intocostrin (26).

The rational and safe utilization of curare in anesthesiologic practice was defined by the anesthesiologists who were among the first to employ curare in volume. These fundamental principles emphasized that curare was to be used only as a means of providing muscular relaxation and that some anesthetic or analgesic agent must be administered to provide pain relief. It was emphasized, also, that the drug was selective in action as Lucas, the early 20th century pharmacologist, had shown. Therefore, graded doses were recommended as being capable of producing the desired relaxation without interference with respiratory efficiency. It was also emphasized that the principal advantage of curare in anesthesiology is to provide muscular relaxation and permit the anesthesiologist to effect anesthesia with low concentrations of potent anesthetic agents. It is also possible to extend the usefulness of the impotent agents. Phyllis Harrown, California anesthesiologist (27), has demonstrated the possibilities of expanding the usefulness of impotent agents in a paper in which she shows how nitrous oxide can be used for anesthesia for surgical procedures requiring excellent muscular relaxation.

The laboratory investigations that accompanied the introduction of curare into anesthesiologic practice established the principle that the dose of curare is influenced by the anesthetic agent because some of the anesthetic agents have curariform properties of their own. Other research indicated that curare in therapeutic doses is capable of lowering the blood pressure in a few patients, thus corroborating Ranyard West's findings in patients with epilepsy. It was determined during further research that curare does not alter cardiac rhythm, does cause relaxa-
tion of the small intestine, and does not interfere with certain elements of tissue metabolism (28).

Curare was not immune from the practice accorded most new therapeutic agents and increasing familiarity with its action and its apparent minimal toxicity prompted several clinicians to administer very large doses without concurrent anesthesia. It appeared that the patients to whom these large amounts were given lost consciousness and were analgesic. The doses required to produce this pseudo-anesthetic state caused complete respiratory paralysis and artificial respiration was necessary to maintain oxygenation. As pointed out earlier in connection with John Snow's observations of the anesthetic properties of curare, Scott Smith (29), in a courageous experiment, confirmed the lack of anesthetic or soporific properties of curare. In those patients in whom apparent anesthetic states were developed, a large share of the anesthesia must have been the result of drugs used for premedication. Fortunately, the use of intocostrin in excessive amounts is a dwindling practice.

To date there has been a minimum number of disadvantages and dangers accompanying the rational use of curare. It is obvious that means for providing prompt and efficient artificial respiration must be at hand when curare is administered, but no competent anesthesiologist will practice anesthesia of any type without these means available. A few patients have exhibited varying degrees of bronchospasm, but there is reason to believe that at least a few, if not all, of these patients had had prostigmine, which may have caused or contributed to the bronchospasm. The indiscriminate employment of prostigmine to overcome the effects of improper use of curare should be discouraged. The bronchospasm may be relieved by the administration of additional curare. In a few patients to whom curare has been given in large doses and particularly in those patients to whom curare has been given in large doses for long periods, there appears to be a deterioration of the peripheral circulation with subsequent circulatory failure and death. Fortunately, this does not seem to occur with doses ordinarily employed during anesthesia. In spite of laboratory and considerable clinical evidence that curare has little or no influence on the heart and peripheral circulation, it will be well to avoid using large doses over long periods.

Edward B. Schlesinger, of New York (30), is attempting to advance the knowledge of the influence of curare upon spastic states by using a preparation of curare in oil. The oil delays the absorption of the drug and may serve to lengthen the effective blood level. It is hoped that his experience will be more fruitful than those of the four early French physicians and Ranyard West, the contemporary Englishman. There is currently developing a new use for intocostrin. A few years ago Scott Smith, the fearless anesthesiologist, made a few preliminary trials with curare in attempts to relax the spasm associated with acute an-
terior poliomyelitis. He achieved some success but was unable to continue his investigation. Lately, Ransohoff (31) has employed curare in patients with poliomyelitis with apparent significantly good results. The curare is used to effect relaxation of the spastic muscles so that more effective and earlier intensive physical therapy can be instituted. Experience with this approach to the treatment of the deformities and pain of poliomyelitis is not yet sufficient properly to evaluate its effectiveness.

It can be seen from the foregoing review that curare has secured a respectable position in the compendium of therapeutic agents. There is much to be learned about the drug. There is much that curare can do to enhance the knowledge of fundamental physiologic processes. It can be anticipated, however, that this jungle poison will justify the faith in it that all its ancient and contemporary patrons have had.

REFERENCES

1. Brown, M. Webster: Curare the Magical and Mysterious, Medical Record 140: 149-150, 1924.
2. Sir Walter Raleigh: Hakluyt's Voyages III 649, "Discovery of the Large, Rich and Beautiful Empire of Guiana."
15. Ticelein and Benedict: Wiener Presse, No. 32-33, 1866.
JOINT MEETING OF THE AMERICAN SOCIETY OF ANESTHESIOLOGISTS, INC., AND THE OHIO SOCIETY OF ANESTHESIOLOGISTS

(Continued from page 463)

FRIDAY—2:00 p.m.

1. Business Meeting.
   American Society of Anesthesiologists.

2. Intravenous Pentothal Sodium for Thoracoplasty.
   William H. Stiles, M.D., Dayton, Ohio.
   Discussion to be opened by L. E. Larrick, M.D., Cincinnati, Ohio.

3. Recent Contributions of Research to Anesthesiology.
   John S. Lundy, M.D., Rochester, Minn.
   Discussion to be opened by Charles F. McCuskey, M.D., Los Angeles, Calif.

4. The Intravenous Use of Pentobarbital Sodium.
   Stuart C. Cullen, M.D., Iowa City, Iowa.
   Discussion to be opened by R. M. Crane, M.D., Cleveland, Ohio.

5. The Therapeutic Uses of Procaine.
   Milton C. Peterson, M.D., Kansas City, Mo.
   Discussion to be opened by J. K. Potter, M.D., Cleveland, Ohio.

   Ohio Society of Anesthesiologists.
   6:00 p.m.—COCKTAILS—CARTER HOTEL
   7:00 p.m.—DINNER—CARTER HOTEL

Speaker: Charles F. McCuskey, M.D., Los Angeles, Calif., President-elect of The American Society of Anesthesiologists.

Subject: Plans for The American Society of Anesthesiologists for 1948.

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