CURARE AND CURARE LIKE COMPOUNDS: A REVIEW

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N. B. The label on the Squibb ampule reads, in part, "Each cc. has a potency equivalent to 20 units of Standard Drug." And, to quote from the Journal of the American Medical Association, October 13, 1945, page 517: "The physiologic activity of intocostrin is determined on rabbits; the provisional unit is equivalent to the potency of 0.15 mg. of d-tubocurarine chloride." Therefore, each cubic centimeter of intocostrin has a potency equivalent to 3 mg. of d-tubocurarine chloride (0.15 : 20 = 3.0). This information is important in the future use of other brands of curare, the label on which may read in milligrams rather than in Squibb units.

In the present review, doses have been given exactly as the original authors gave them in their papers. In some instances, however, it appears that an author spoke of "milligrams of curare" when he actually meant "units of intocostrin."

Curare in Anesthesia.—The introduction of the use of curare as an adjunct to anesthesia came in logical sequence to the earlier use of curare in other conditions in which relaxation of voluntary muscle was indicated. The basic facts of the mechanism of action of curare had been elucidated in the experimental animal, and curare had been used in a sufficient number of patients so that the effects that it might produce in the anesthetized patient could be predicted with a fair degree of accuracy.

So far as the needs of the patient for surgical anesthesia are concerned, the state designated by "stage III, plane 1" is adequate, but in order that relaxation may be sufficient for the surgeon to obtain the desired exposure, without the infliction of trauma to the tissues, it frequently is necessary for the anesthetist to increase the depth of anesthesia to "stage III, plane 3 or 4," and this depth of anesthesia may be undesirable so far as the patient's general metabolic processes are concerned.

The conservatism of the first report of the use of curare (in the form of intocostrin) during anesthesia in man by Griffith and Johnson (63), and the conservatism of subsequent reports by Griffith (64-66) have been of the greatest importance in the establishment of curare as a valuable aid in anesthesia.
In the first report (1942) by Griffith and Johnson (63) of the use of curare, they said they had used a dose of about 100 mg., contained in a 5 ec. solution, for the average adult person, and this amount was administered in a single injection. Approximately the same size of dose (60 to 100 mg.) was still being used by Griffith in 1945. Griffith and Johnson preferred to use curare only when the desired degree of relaxation could not be obtained without too deep a plane of anesthesia (63). They have used curare almost exclusively for patients under the influence of cyclopropane anesthesia because in most cases they produced anesthesia with cyclopropane. Griffith (65, 66) was of the opinion that curare can be used to advantage with other inhalation anesthetic agents, and particularly with nitrous oxide and ethylene, when adequate relaxation is not the rule with a mixture containing 20 to 25 per cent oxygen.

The curare is injected intravenously. Its maximal effect is observed in two to three minutes after the injection; this effect gradually diminishes in fifteen to twenty minutes. A second injection may be needed if the action of the first dose is of too short duration.

In a series of 478 abdominal operations Griffith (65) found it desirable to administer curare to only 16.5 per cent of the patients. In a more recent report (66) he said that he was using it in 38 per cent of abdominal operations. Griffith thought that curare is "of value to the expert anesthetist by affording a better surgical field for abdominal operations with light and non-toxic anesthesia."

Cullen (67-69) has reported his experiences with the use of curare during anesthesia in about 1,000 cases. Although in the great majority of instances curare was administered to patients who were under the influence of cyclopropane, Cullen has used it when nitrous oxide, ethylene or ether were the anesthetic agents. He said he prefers to use a smaller initial dose—40 to 60 mg.—than that employed by Griffith, and then to add additional amounts of curare as needed. In a series of 129 cases the average total dose was 92.5 mg., with 240 mg. being the maximal amount used. This maximal total dose of 240 mg. was administered during an operation that lasted three hours. Paralysis of the intercostal muscles occasionally was produced, but was compensated for by manual compression of the rebreathing bag. As a rule, there were no changes in the blood pressure or pulse rate.

The combination of curare with nitrous oxide or ethylene anesthesia provides a degree of relaxation that it is not possible to achieve with either agent alone in the presence of adequate oxygen.

In the studies of Gross and Cullen (37) on the effect of different anesthetic agents on the tone of skeletal muscle, they found that ether itself had a marked curare-like effect. Because of this specific action exerted by ether, they wrote, a smaller quantity of curare—a third of that used with cyclopropane—is used when ether is the anesthetic agent.
Knight (70) reported the administration of curare during anesthesia to 250 patients. He found that it was of value in relieving laryngeal spasm as well as in producing abdominal relaxation. Knight wrote that curare will replace the need for deep ether anesthesia and also the need for spinal anesthesia, in certain conditions.

Cole (71) stated that impaired renal function is a relative contraindication to the use of curare because the kidney is one of the routes of elimination of curare.

In the report of Whitaere and Fisher (30) it was shown that curare administered in large doses will cause loss of consciousness, and that this loss of consciousness may persist for a few minutes after normal respiratory activity has returned. These authors also reported the administration of a large amount of curare (intocostrin)—405 mg.—in divided doses to a patient over a period of one hour and forty-five minutes, during which time no anesthetic agent was used. Likewise, a second patient received 280 mg. in a period of twenty minutes. By maintenance of artificial respiration for these patients during the period of complete curarization, the pulse rate and blood pressure were kept near normal. These observations are of interest because they show that if an overdose of curare is given, the condition of the patient can be returned to normal by maintenance of an adequate gaseous exchange during the time necessary for the patient to destroy or eliminate the excessive dose.

Whitaere and Fisher, like Cullen, said they preferred to use a small initial dose of curare and to repeat the dose until the desired effects have been produced. Usually, they found, a total dose of 100 mg. or less was sufficient when the patient was in the first plane of anesthesia. Most of the patients in their report were anesthetized with cyclopropane.

Lenahan (72) used curare in association with pentothal-nitrous oxide-oxygen anesthesia as well as in association with cyclopropane anesthesia for patients who underwent genito-urinary surgery, and he found that curare used thus produced good relaxation. He used small doses and repeated the doses when necessary.

Brody (73) reported the use of curare in association with pentothal-nitrous oxide-oxygen anesthesia for abdominal operations. His technic was to induce anesthesia with pentothal sodium and then to use nitrous oxide-oxygen, 2 liters of each per minute in a semiclosed carbon-dioxide absorption system. Small amounts of pentothal sodium were administered during the operation. Sixty to 80 units of curare was administered at the time of the incision in the skin, and this amount usually provided adequate relaxation for twenty to thirty minutes, after which time a second dose of 20 to 40 units was injected. By the use of curare the amount of pentothal sodium required was about a third less than in similar cases in which curare was not employed.
Mallinson (74) used curare as a relaxing agent for patients under the influence of pentothal-nitrous oxide-oxygen anesthesia and pentothal cyclopropane anesthesia. He said he prefers to have the patient in anesthesia of plane 2 at the time the curare is injected in small repeated doses, until the desired degree of relaxation has been obtained. He observed no decrease in blood pressure in his studies, nor was paralysis of the diaphragm produced by the amounts he used.

Waters (75) used curare to produce the relaxation needed for surgical procedures on the upper part of the abdomen with the patient under the influence of nitrous oxide-oxygen anesthesia. He used small doses of morphine sulfate—4 to 8 mg.—and of scopolamine—0.16 to 0.33 mg.—because he felt that by the use of such small doses it was possible to obtain saturation with nitrous oxide more readily than when larger doses of morphine sulfate and scopolamine were used.

Harroun, Beckert and Hathaway (76) reported the administration of curare to patients who were under the influence of nitrous oxide anesthesia for surgical procedures in the upper part of the abdomen. After anesthesia had been induced with nitrous oxide-oxygen mixture and a pharyngeal airway was in place, the patient received an amount of curare—150 to 200 mg.—that was certain to produce complete curarization. An orotracheal tube with an inflatable cuff was inserted, and anesthesia was continued with the closed carbon-dioxide absorption technique. During the period of apnea, which usually was of twenty to thirty minutes’ duration, “controlled respiration” was employed. After the patient had regained adequate respiratory activity, curare was administered as needed to produce relaxation of the muscles of the abdomen. The average duration of the operation in the series of 38 patients concerned was three hours and ten minutes, and the average amount of curare employed was 237 mg. Complications occurring during the operation, such as an increase in the heart rate, a decrease in blood pressure to less than 80 mm. of mercury and frank shock, were definitely fewer when curare was used in association with nitrous oxide-oxygen than when other agents were used for similar types and duration of surgery.

Harroun and Hathaway (77) used curare in association with nitrous oxide-oxygen anesthesia for patients who underwent thoracic surgery. The authors said that the use of nitrous oxide as the anesthetic agent permits the use of the cautery, and that curare makes controlled respiration easier for the anesthetist. Nine of the eleven patients received doses of curare of 300 mg. or more. By proper timing of the doses of curare with the operative procedure it was usually possible to have the patients breathing spontaneously within five minutes after closure of the pleura.

Baird and Adams (78) reported the use of curare to advantage, particularly for patients of a heavy and muscular build who are heavy smokers and drinkers. The laryngospasm that is frequently noted in
anesthetization of this type of person and the difficulty of obtaining the desired plane of anesthesia usually are relieved by the use of curare. Tnohy, Adams, Mousel, Seldon and one of us (Lundy) (79) found that curare produces good relaxation of patients who have abdominal rigidity caused by perforated duodenal ulcer.

Adams (80) and one of us (Lundy) (81) reported that curare is a valuable aid in direct laryngoscopy in which the patient is anesthetized with pentothal sodium. Curare produced good relaxation and reduced the amount of pentothal sodium necessary for use in the examination.

Curare in Poliomyelitis.—Smith (82) stated that curare relieves spasticity of the muscles in poliomyelitis. Ransohoff (83) reported the use of curare in four cases of acute poliomyelitis. He said that by the intramuscular injection of 0.9 mg. of curare per kilogram of body weight, marked symptomatic relief as well as definite reduction in spasticity was obtained.

Fox (84) used curare in thirty-four cases of acute poliomyelitis. Although twelve patients obtained slight temporary relief of muscle spasm at the peak of action after the intramuscular injection of 0.9 mg. of curare per kilogram of body weight, Fox was of the opinion that the use of curare was not warranted during the acute phase of poliomyelitis.

Curare in Endoscopy.—Cullen and Trapasso (85) reported on the use of curare to produce relaxation of the muscles of the neck and larynx, after the topical application of a 10 to 20 per cent solution of cocaine hydrochloride for anesthesia of the pharynx and larynx. The particular advantages of curare for endoscopic work reside in its effects on patients who are difficult to examine, either because of reflex spasm of the muscles of the larynx or because the patient is not cooperative. By the use of curare in doses of 10 to 60 mg., computed according to the size of the patient, Cullen and Trapasso obtained good relaxation of the muscles of the larynx and neck.

Quinine and Quinine Derivatives

Quinine itself has long been known to exert a weak curare-like action. Several quaternary ammonium derivatives of quinine, formed by the addition of alkyl radicals to the nitrogen in the quinuclidine ring, have recently been prepared and investigated for their curare-like action.

Among the derivatives are quinine methochloride, quinine ethochloride, quinine-n-propyl bromide, quinine-n-propyl chloride, quinine-iso-propyl chloride, quinine-n-butyl chloride, quinine-n-amyl bromide, quinine-iso-amyl chloride and quinine-n-hexyl-bromide.

Experimental Studies in the Laboratory.—Skeletal Nerve-Muscle Studies.—Harvey (86) has shown that quinine has a weak curare-like effect on the nerve-muscle unit, and that it blocks the contraction usually produced by the close-range intra-arterial injection of acetylcho-
line. Harvey had quinine methochloride prepared and reported on his observations of its action in the cat (87). He found that after the oral administration (150 to 200 mg. per kilogram of body weight) or intravenous injection of 15 mg. of quinine methochloride per kilogram of body weight there was a regular order of muscle involvement similar to that which occurs in man after the administration of curare. The extrinsic ocular muscles and the muscles of the jaw were first paralyzed; then the muscles of the extremities were involved and, finally, the intercostal and diaphragmatic muscles were paralyzed. Harvey showed that electrical stimulation of a motor nerve, after the administration of quinine methochloride, failed to cause contraction of the muscle, but that direct electrical stimulation of the muscle elicited the normal contraction.

Chase and Lehman and their associates (88–90) have shown, by using a modification of the Thomas and Franke procedure (91, 92) in which records are made of two strips of muscle from the diaphragm, one with the circulation intact and the other without the normal blood supply, that quinine methochloride, quinine ethochloride, quinine-n-propyl chloride, quinine-iso-propyl chloride, quinine-n-butyl chloride, quinine-n-amyl chloride, quinine-n-amyl bromide, quinine-iso-amyl chloride and quinine-n-hexyl-bromide all produced paralysis by peripheral action. They found that the doses of these quinine derivatives necessary to produce paralysis of the diaphragm in dogs varied from 5 to 20 mg. per kilogram of body weight, whereas the dose of curare was 1 to 2 mg. per kilogram of body weight.

Studies on the Central Nervous System.—Harvey (87) placed electrodes on the phrenic nerves of cats and recorded the rhythmic electric discharge down the nerve after the intravenous injection of a full dose of quinine methochloride which would produce a curare-like effect. As asphyxia developed after paralysis of the peripheral respiratory mechanism, the electrical activity increased; this showed that quinine methochloride in the full paralytic dose has no effect on the respiratory center.

Chase and Lehman and associates (88–90) have shown that the activity of the respiratory center is not seriously altered by the action of quaternary ammonium quinine derivatives until the dose is four to ten times that necessary to produce complete paralysis.

Studies on the Autonomic Nervous System.—Harvey (87) showed that by the addition of quinine methochloride to the perfusion fluid the transmission of impulses through the superior cervical ganglion is blocked, but that the normal amount of acetylcholine is liberated as shown by the effect of the venous efferent from the ganglion on the blood pressure of the cat.

Studies of Absorption.—Unlike curare, which is noneffective when it is administered orally, all the quinine derivatives which have been listed previously herein are absorbed by the gastro-intestinal tract at
such a rate that typical effects are observed. The oral dose, however, is much larger than the intravenous dose (87–89).

Quinine and Quinine Derivatives in Clinical Medicine to Produce Curare-like Effects.—Kennedy and Wolf (93) showed that the oral administration of quinine in amounts of 160 to 960 mg. two to three times daily gave marked relief to patients who had myotonia.

Harvey and Masland (26), in their investigation of agents which would produce effects like those of curare in man, found that quinine methochloride administered in doses of 8 to 12 mg. per kilogram of body weight produced signs of bulbar paralysis when the full amount was injected over a period of five minutes. There was a rapid return of normal function of the muscles upon stopping the injection of the drug. In two of their thirteen cases signs of gastro-intestinal disturbances were noted.

Bennett and Cash (94) reported on the use of quinine methochloride to reduce or prevent the occurrence of fractures during metrazol shock therapy. They found that by the intravenous administration of 8 to 10 mg. of quinine methochloride per kilogram of body weight the severity of the metrazol convulsions was reduced. If the dose was too large, a decrease in blood pressure occurred.

**Erythrina Alkaloids**

The presence of a substance, in the seeds of the erythrina plant, which exerts a curare-like action was first recorded by Dominguez and Altamirano (95) in 1877.

Source.—Erythrina plants are widely distributed throughout the tropics and subtropics of North and South America, Asia, Africa and Australia. Seeds from fifty-one of 105 known species of Erythrina from these areas have been shown by Folkers and Unna (96, 97) to contain alkaloids which have curare-like properties.

Lehman (98, 99) was the first to show that seeds from Erythrina americana contained curare-like substances; Cierardo and Hug (100) first demonstrated the curare-like properties of alkaloids derived from the seeds of *E. crista galli*.

Chemistry.—Erythroidine, the first pure alkaloid isolated from *E. americana* by Folkers and Major (101), later was shown by Folkers and Koniuszy (102) to be a mixture of at least two isomeric alkaloids, alpha erythroidine and beta erythroidine, each of which is dextrorotatory. The empirical formula is C_{16}H_{19}NO_{3} and it is a tertiary base. Dihydro-beta-erythroidine and beta-tetrahydro-beta-erythroidine, as well as beta erythroidine methiodide, have been prepared and examined for their curare-like activity.

Folkers and Koniuszy (103) have isolated erythramine, C_{18}H_{21}NO_{3}, from *E. sandwicensis* and *E. subumbrans*. 

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Experimental Studies in the Laboratory.—Skeletal Nerve-Muscle Studies.—Lehman (98) used an alcoholic extract of the seeds of *E. americana* and showed that the paralytic action was peripheral. He also showed that this extract was effective in reducing the convulsions in rats, pigeons, rabbits and dogs which were produced by strychnine, cocaine, camphor and picrotoxin. Folkers and Unna, (96, 97) in their extensive survey of fifty-one species of *Erythrina*, found by alcoholic extraction of the seeds that all extracts when injected into the frog produced peripheral paralysis. There was a great variation in the potency of the extracts from the different species. Expressed in the terms the authors evolved to designate potency of paralytic effects, the alcoholic extractive from 1 Gm. of seed of *E. eggersii* would paralyze 166,000 Gm. of frog, whereas the extractive from 1 Gm. of seed from one specimen of *E. variegata orientalis* would paralyze only 500 Gm. of frog.

Harvey and Masland (26) have shown that beta erythroidine in doses of 15 to 17 mg. per kilogram of body weight produced about the same degree of depression of nerve-muscle function as did 1 to 2 mg. of curare (intocostrin) per kilogram of body weight.

Unna, Kniazuk and Greslin (104), in their studies of muscle action potentials after electrical stimulation of the motor nerve, showed that beta erythroidine administered in a dose of 1.5 mg. per kilogram of body weight to the cat, inhibits muscular action, and that this depression produced by beta erythroidine and its derivatives could be abolished by the use of prostigmine.

Rosen, Ziegler and Cominole (105) showed that the administration of 3 to 4 mg. of beta erythroidine per kilogram of body weight reduced the incidence of metrazol-produced convulsions of dogs.

Studies on the Central Nervous System.—Pick and Unna (29) reported that dihydro-beta-erythroidine, administered in doses greater than the dose necessary to produce peripheral paralysis, would cause depression of the electrical activity of the brain in frogs as shown by results of electro-encephalographic studies. This central depression persisted longer than did the peripheral paralysis, and was not altered by the use of prostigmine.

Chase and Lehman (88) found that in order to observe a central respiratory effect of beta erythroidine and dihydro-beta-erythroidine it was necessary to give four to ten times the paralyzing dose.

Studies on the Autonomic Nervous System.—Picard and Luco (106) reported that the use of an alcoholic extract of the seeds of *E. crista galli* blocked preganglionic impulses at the ganglion, abolished the effect of acetylcholine injected at the ganglion and prevented the normal response to stimulation of postganglionic parasympathetic fibers. The quantity of the extract used had no inhibitory effect on the normal response to postganglionic sympathetic stimulation.
Studies on Absorption.—Erythroidine and its derivatives are effective when taken by mouth. Uma, Kniazuk and Greslin (104) determined the lethal doses for mice, rats, rabbits and cats, by both oral and subcutaneous administration. As a rule the fatal dose administered subcutaneously was less than the fatal dose administered orally. The lethal dose of dihydro-beta-erythroidine in the cat was 2 to 3 mg. per kilogram of body weight, administered by either route.

Use in Clinical Medicine.—Burman (49-51) was the first to administer erythroidine to patients. He found that a dose of 300 mg. or more injected intravenously produced a reduction of the muscle spasm in patients. The order in which depression of various muscle groups occurred was the same as that noted after the injection of curare. There was no effect on the pulse or blood pressure.

Rosen, Cameron, Ziegler and Borenstein (107, 108) reported the use of beta erythroidine in conjunction with metrazol in metrazol shock therapy for thirty-seven patients. The dose used was about 25 mg. per kilogram of body weight; this was sufficient to produce bulbar paralysis. Fractures did not occur in these cases (156 treatments), and the therapeutic results were as good when beta erythroidine was used in association with metrazol as when metrazol was employed alone.

Williams (109) used smaller doses of beta erythroidine in his studies. Although he observed four compression fractures among the fifteen patients who received an average of ten treatments each, he believed that the severity of the convulsions was reduced.

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For the information of anesthesiologists who are contemplating application for certification by the American Board of Anesthesiology, Inc., or who are training physicians for the specialty, the following questions have been employed for Part I (written) examination in the past in Physiology:

1. Describe inhalation therapy that is indicated in the presence of pulmonary edema.

2. Discuss the important points to be thought of in connection with cyanosis in the anesthetized patient. (Cover all ordinary methods of anesthetizing patients.)

3. What are the approximate normal values for oxygen and for carbon dioxide, expressed in either millimeters, or tension, or percentage, in:
   (a) Inspired air  (c) Arterial blood  (e) Venous blood
   (b) Pulmonary  (d) Tissue spaces
                 alveoli

4. What physiological functions of the liver are of particular interest to the anesthetist and why?

5. (a) Assuming that they are available, under what circumstances during anesthesia would you recommend the intravenous use of whole citrated blood, plasma, solutions of glucose, physiologic saline solution, or solutions of acacia, gelatin, pectin or isinglass (agar agar)?
       (b) Under what circumstances would you use vasopressor substances with these substances and with which substances and in what dose?

6. Concerning the article, "Absorption, Distribution and Elimination of Ethyl Ether"; who wrote it, where and when was it published, and what important contributions to knowledge of the clinical use of ether did it contain?