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 x 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."

It has seemed to us that the increased interest in curare, from both the experimental and the clinical points of view during the past decade, has made it desirable to collect in a single paper some of the more important steps which led up to present knowledge relating to this most interesting and active substance. Therefore, it is our purpose in this paper to trace the historical development of curare, from its use as an arrow poison by South American Indians down to the isolation of the active agent, d-tubocurarine chloride, a chemically pure crystalline compound, and the use of this substance in man. Likewise, in this review the development of erythroidine and quinine derivatives which have curare-like action will be discussed in relation to curare. The similarity of the effects of erythroidine and quinine derivatives in the laboratory animal and in man also will be set forth.

The word "curare" will be used when the agent was obtained as the crude dried extract from whatever source. "Curarine" will be employed to denote a relatively pure alkaloid from Strychnos toxifera. "Intocostrin" identifies a biologically standardized form of curare. "D-tubocurarine chloride" refers to the crystalline, chemically pure, active material obtained from the plant, pareira, or Chondrodendron tomentosum.

CURARE

Sources of Curare.—The main geographic sources of crude curare are the northern and northwestern basins of the Amazon River, the
upper part of the Orinoco basin, British Guiana and eastern Ecuador (1, 2).

The botanic sources of curare are variable. Considerable confusion characterized the earlier literature because of lack of exact data in the correlation of crude curare with definite botanic sources. Then, too, the natives who supplied the curare mixed material obtained from many plants and herbs in their stew. Sollmann (3) stated that curare is obtained from various species of Strychnos such as (S. toxifera and S. castelnacii). The twelfth revision of the Pharmacopoeia of the United States (4) lists three species of Strychnos as sources. Folker's (5) reported that at least five species of Strychnos used by South American Indians in the preparation of curare contained quaternary ammonium alkaloids that have paralytic action. Gill (1, 6), McIntyre and King (7), Bennett (8), Wintersteiner and Duteher (9) stated that curare is obtainable from Chondrodendron tomentosum.

King (10), who first isolated and determined the chemical formula of d-tubocurarine chloride from tubucurare of an unknown plant source in 1935, pointed to members of the genus Chondrodendron as probable sources of the active ingredients of crude curare.

Gill (1, 11) collected and made curare in the field from vines identified as Chondrodendron tomentosum; this work represented the first time that the exact source of a form of curare was recorded. This "authenticated" type of curare formed the basis of McIntyre's studies as well as the source of material from which Wintersteiner and Duteher in 1943 prepared their crystalline d-tubocurarine chloride.

Chemical Aspects.—The early samples of curare were prepared by the making of a water extract of leaves, bark, stems and roots of many plants. The liquid was strained off and evaporated to a thick syrup or to dryness, and was brought out from the site of preparation in one of three types of containers: bamboo tubes, gourds or earthenware pots. The name of the container used was given to its contents; hence such appellations as tubucurare, calabash curare or pot curare.

Boehm (12) reported the isolation of different alkaloids from the three different types of crude curare; King (10) later made the same observation.

For many years it was thought that the curare exported in the three aforementioned types of containers had been obtained and prepared from different types of curare-containing plants, but Gill (1) recently discounted this idea, saying that regardless of the plants from which a given batch of curare had been prepared, the batch was simply placed in the most accessible container.

The preparation of "intocostrin" as described by the makers in the article of acceptance by the Council on Pharmacy and Chemistry of the American Medical Association (13) is given below:

"Intocostrin prepared from Chondrodendron tomentosum extract is made by first extracting with alcohol a desiccated curare obtained from a heavy syrup
of the bark and stems of Chondrodendron tomentosum. The alcoholic extract is evaporated to dryness; a sterile filtered solution having a pH of 4.6 – 4.8 is made and adjusted to a standard potency of 20 units per cubic centimeter. The final solution contains sodium chloride 0.45 per cent and triehlorobutanol 0.5 per cent; sterilized by filtration and its pH again adjusted to 4.6 – 4.8.

"In the preparation of intocostrin from pure d-tubocurarine chloride crystals, the crystals are obtained from the desiccated curare or from the crude syrup. . . .

"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."

Numerous chemical studies have been made on various samples of curare of unknown sources, and the lack of homogeneity and of adequacy of the size of the samples may account in part for the different results published in the literature.

Boehm (12) obtained curarine (C_{19}H_{26}N_{2}O) from gourd curare, protocurarine (C_{19}H_{23}NO_{2}) from pot curare and tubocurarine (C_{13}H_{21}NO_{4}) from tubocurare. In addition to these quaternary ammonium bases, he obtained some tertiary ammonium bases. Later, King (10) obtained crystalline d-tubocurarine chloride (C_{38}H_{44}O_{6}N_{2}Cl_{2}) from a sample of tubocurare, and as a result of studies of degradation products, proposed the structure for this substance that appears in figure 1.

![Representation of the structure of d-tubocurarine chloride as proposed by King (10).](image)

Wintersteiner and Dutcher (9) reported the isolation and chemical characterization of d-tubocurarine chloride from curare known to be prepared from Chondrodendron tomentosum. Their empiric formula (C_{38}H_{44}O_{6}N_{2}Cl_{2}) is the same as that of King, and their structural formula is the same except for the location of one methoxy group. They stated that their substance is identical to that of King. Wintersteiner and Dutcher prepared what proved to be identical to the dimethylether iodide of d-tubocurarine, and it is interesting to note that this new substance is about nine times as active physiologically as the parent compound.

Wieland, Konz and Sonderhoff (14) have isolated from gourd curare a crystalline compound, toxiferine (C_{27}H_{27}O_{2}N_{3}·HCl), which contains no methoxy groups or phenolic hydroxyl radicals. This substance is a very active curarizing agent.
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Experimental Studies in the Laboratory and Other Studies.—Brodie (15), as early as 1811, observed that curare poisoned warm-blooded animals by depression of respiration, although the site of action of curare in producing this decrease in respiration was not localized until the studies of Pelouze and Bernard (16) and Bernard (17) showed the action to be peripheral. At about the same time, Kölliker (18) published his studies on the site of action of curare.

During the intervening years a great number of studies have been reported on the action of curare on various animals and on patients suffering from various diseases. In most of the earlier experimental studies the curare employed was very impure; because of this impurity determinations of the secondary effects, other than the effect on the skeletal nerve-muscle system, are not consistent from curare to curare or from investigator to investigator.

The studies of Boehm (12), from both the chemical and pharmacologic points of view, extending from 1894 to 1920 with his extensive review, cover very well the earlier observations on curare.

Skeletal Nerve-Muscle Studies.—Studies on the effect of curare or its derivatives on the nerve-muscle system vary from those of Bernard (17), who used curare in the whole frog, to those of Steiman (19), who studied the effect of curare on an efferent nerve fiber to a single muscle fiber. Bernard found that when curare was injected into the lymph sac of a frog, the muscle (gastrocnemius) did not contract when the nerve to the muscle was stimulated, but that direct stimulation of the muscle produced a contraction. Steiman, using a nerve-single muscle fiber preparation, found that the addition of curare to the bath soon caused a cessation of contraction on stimulation of the nerve, but that direct stimulation of the muscle fiber resulted in contraction.

The mechanism by which curare blocks the transmission of nerve impulses to the muscle fiber is thought to be due to an increase in the stimulus threshold of the muscle to acetylcholine.

Brinkman and Ruiter (20) perfused the indirectly stimulated muscles of the hind leg of a frog and obtained a substance in the perfusate that was similar in action to acetylcholine. The perfusate obtained on nerve stimulation after complete curarization likewise contained an acetylcholine-like substance.

Dale, Feldberg and Vogt (21) showed that the stimulation of pure motor nerve fibers to voluntary muscles in the dog and cat causes a release of acetylcholine in the venous perfusion fluid. Likewise, they have shown that this acetylcholine is released on stimulation of the nerve after complete curarization by curarine, so that it appears that curarine does not produce its effect by preventing the formation and liberation of acetylcholine, which is thought at present to be the chemical mediator of the transmission of impulses from the nerves to the skeletal muscle.

Brown, Dale and Feldberg (22) compared the effects of the close
intra-arterial injection of minute amounts of acetylcholine to those produced by maximal nerve stimulation in the cat. They found that the contraction produced by acetylcholine was very similar in speed and amplitude to that produced by nerve stimulation. They found also that curarization produced by the intravenous injection of 0.7 mg. of curarine per kilogram of body weight decreased markedly the contraction on nerve stimulation and abolished the contraction on the injection of acetylcholine.

From the results of much work carried out between the original studies of Pal (23) in 1900, who first showed the mutual antagonistic action of physostigmine and curare, and those of Briscoe (24) in 1936, in her investigations of curarine and physostigmine in myasthenia gravis, considerable data have been obtained which show that curare acts by increasing the threshold of the muscle to acetylcholine, and that the administration of physostigmine and, more recently, neostigmine (prostigmine), permits the accumulation of acetylcholine to such an amount as to be active even when the threshold of the muscle is increased.

Koppanyi and Vivino (25), in their studies on the prevention and treatment of poisoning with d-tubocurarine chloride, showed that small doses of physostigmine or neostigmine would prevent paralysis and death in rabbits after a usually lethal dose of d-tubocurarine.

Harvey and Masland (26), investigating the action of curarizing preparations in man by recording the action potentials of the abductor digiti quinti muscle of the hand on stimulation of the ulnar nerve, found that a decrease occurred, after the intravenous injection of curare, in the action potentials when the subject showed signs of generalized weakness.

Studies on the Central Nervous System.—There have been numerous reports of the use of curare in various spastic diseases, and it was suggested that the beneficial results obtained in some cases might be explained on the basis of a central effect exerted by curare. In the studies by Hartridge and West (27) on dogs attacked by tetany which followed removal of the parathyroid glands, the authors observed that curare relieved the tetany without producing paralysis, and that this relief was not caused by a change in the irritability of the nerve-muscle unit as measured by the current needed for electrical stimulation of the nerve-muscle unit.

The most detailed studies of the effect of curare on the central nervous system are those of Feitelberg and Pick (28) and Pick and Unna (29) on the frog. Their procedure was to observe the effect of curare or d-tubocurarine chloride on the electro-encephalograms of both the normal and the pithed frog. Pick and his associates found that curare or d-tubocurarine chloride, when given in subparalytic or just paralytic doses, produced no changes from the control electro-encephalogram, but that if the dose of the curare preparation was in-
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creased 50 to 100 per cent above that which would produce paralysis of the skeletal muscles, abolition of electrical potentials in the brain occurred, and that this central effect persisted considerably longer than the peripheral action. They also noted that the administration of prostigmine, which hastened the recovery of the skeletal nerve-muscle function, had no effect in restoring normal electrical activity in the brain. Thus, in frogs at least, curare and d-tubocurarine chloride exert both peripheral and central effects which are independent of each other.

Whitacre and Fisher (30) reported the use of solution of curare (intocostrin) among five patients in certain surgical procedures without the use of any general anesthetic agent. Two of the patients received a local anesthetic agent at the site of incision; curare was administered in a single dose or divided doses until complete muscular paralysis was produced and consciousness was lost; the operative procedure was completed while the patients received additional doses of curare and were maintained on artificial respiration. The third patient received an initial dose of 125 mg. of curare; this immediately caused complete muscular paralysis and loss of consciousness. Artificial respiration was maintained throughout the operation while additional doses of curare were necessary to keep the patient paralyzed. A total of 405 mg. of curare (intocostrin) was given during an hour and forty-five minutes. In two of the above cases normal respiratory activity was regained ten and forty-five minutes, respectively, before consciousness returned. In the final two cases curare was administered until all muscles except the diaphragm were paralyzed and the operation started. Later, these patients received cyclopropane to complete the operation, and after awakening from the cyclopropane anesthesia, they were able to tell of the pain they had experienced while they were under the influence of curare alone before the administration of cyclopropane was started.

These reports of cases by Whitacre and Fisher seem to parallel the work of Pick and his associates—that is, in neither instance did subparalytic doses of curare affect the central nervous system, and in both instances activity of skeletal muscles returned before activity returned in the central nervous system.

Harris, Pacella and Horwitz (31) made electro-encephalograms of patients who received curare before a preparation of pentamethylene tetrAzol (metrazol). They found no significant changes that could be attributed to curare.

Studies on the Autonomic Nervous System.—There are two sites in the autonomic nervous system where curare may exert its effect on the transmission of impulses; that is, (1) at the ganglia and (2) at the effector cells. There is general agreement among various investigators that curare produces a depression of conduction through the autonomic ganglia, both the parasympathetic and sympathetic. Langley (32) in
1918 showed that the application of curare to autonomic ganglia abolished the conduction of electrical impulses from the preganglionic to the postganglionic fibers. In the autonomic ganglia, as in the voluntary nerve-muscle unit, curare blocks the transfer of electrical impulses at these cholinergic endings, but does not prevent the production and liberation of acetylcholine on stimulation of the preganglionic nerve fiber (33). The postganglionic nerve cells in a ganglion to which curare has been applied may be stimulated by other agents, such as potassium salts.

Luco and Mesa (34) reported their results of a study of the action of curare on the autonomic neuro-effector system in cats, as observed by the stimulation of preganglionic and postganglionic fibers innervating the muscles of the iris and nictitating membrane. The dose of curare used was that necessary to abolish respiratory activity in a cat anesthetized with 5-5-diallylbarbituric acid (dial). They found that curare abolished the pupillary response on stimulation of the preganglionic parasympathetic fibers to the eye. Likewise, curare prevented the contraction of the nictitating membrane on stimulation of the sympathetic preganglionic fibers. By the use of a dose of curare three to five times that necessary to produce paralysis of the skeletal muscles, they observed a partial reduction in effect when the postganglionic fibers to the iris were stimulated. However, when doses fourteen times that necessary to cause respiratory arrest were employed, there was no depression of effect on sympathetic postganglionic stimulation. Results of these studies support the original observations of Langley that curare blocks the transmission of impulses through the autonomic ganglia, and they go further to show than when curare is used in large doses the transmission of impulses from the parasympathetic postganglionic fiber to the effector cell is depressed.

In another report Luco and Altamirano (35) found that curare stopped the secretion from the submaxillary gland that routinely follows injection of acetylcholine.

Mautner and Luisada (36) investigated the effect of electrical stimulation of the vagus nerve on the heart of the dog, as reflected in the electrocardiogram, after curare had been administered. When a dose which was just below the full paralytic amount was used, the effect of vagal stimulation was greatly reduced; if the dose was sufficiently large to produce full curarization, then stimulation of the vagus nerve produced no changes in the heart as shown by electrocardiograms.

Gross and Cullen (37) have shown in their studies on dogs in which Thirty-Vella fistulas have been created that intocostrin or d-tubocurarine chloride, employed in a dose which will produce intercostal paralysis, routinely caused a reduction in tone and peristalsis of the intestine.

Ruskin, Ewalt and Deecherd (38) reported an extensive study on the effect of curare (intocostrin) on the hearts of twenty-one human beings, as reflected in the electrocardiograms. Their procedure was
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To make control records from five leads. Then, intocostrin in doses of from 1 unit to 1.6 units per kilogram of body weight was injected intravenously over a period of sixty seconds. Immediately afterward, and at frequent intervals thereafter, electrocardiograms, lead II, were made. At two to seven minutes after the injection, records were made in which all five leads were used. They were unable to detect any change in heart action caused by the curare used.

Harris, Pacella and Horwitz (31), Woolley (39) and Cleckley, Hamilton, Woodbury and Volpitto (40) have reported that the amount of curare that is ordinarily used in man has no depressing effect on the blood pressure.

Absorption and Excretion of Curare.—For the typical effect of curare to be observed, it is necessary that it be administered by the subcutaneous, intramuscular or intravenous route, through which effective concentrations can be reached. The rates of destruction and excretion of curare in the normal human being are such that the drug is noneffective when it is administered orally; however, if the renal vessels are ligated an effective concentration can be obtained by means of oral administration. Boehm (12) stated that the drug was eliminated by the kidney as shown by the curarizing properties of urine collected from a curarized animal.

Curare in Clinical Medicine.—The application of curare to problems in clinical medicine varies from that of relief from excessive contraction of skeletal muscles, as in tetanus or spastic disease, to the production of increased relaxation of abdominal muscles under light surgical anesthesia, to potentiating for diagnostic purposes the diminished ability of muscles for sustained repeated contractions in patients who have myasthenia gravis. Regardless of the end result desired in the use of curare in man, the mechanism by which these results are obtained is the same in all instances; that is, diminution of the effect of nerve stimuli on the voluntary or skeletal muscles, which diminution is thought to be brought about by the increase in threshold of the muscle for acetylcholine.

When curare is administered parenterally to man in a single large dose or in smaller repeated doses, there is a regular sequence in which the signs of complete curarization occur. First, the muscles of the eyelids and eyeballs are involved, resulting in a sensation of heaviness, ptosis, nystagmus and diplopia. Next, the facial muscles lose activity. Then the muscles of the neck and throat are affected, with resulting head drop and difficulty in speaking. Function of the muscles of the trunk and extremities is next depressed, and finally, the muscles of the diaphragm are paralyzed.

A generalization in relation to the use of curare in man should be made before a review is undertaken of the special conditions in which curare may be of benefit; that is, the effect of an overdose of curare can be corrected by the administration of physostigmine and also neostig-
mine (prostigmine), which, since the studies of Pal (23) in 1900, has been known to be a pharmacologic antidote for curare. Furthermore, by artificial maintenance of the patient’s respiration for a few minutes, recovery usually will result from the rapid elimination of curare.

In any condition in which curare is to be used, the physician should have either physostigmine or neostigmine available for immediate intravenous injection. An efficient method for the maintenance of artificial respiration likewise should be at hand for instantaneous application. The only death which followed the use of curare to be reported in the literature occurred in a patient whose heart kept beating for six to seven minutes after paralysis of the skeletal muscles; this patient had had the benefit of artificial respiration but not that of neostigmine administered intravenously (41).

Curare in Tetanus, Rabies and Strychnine Poisoning.—In the earlier literature (2) there are reports of the use of curare to relieve the convulsions caused by tetanus, rabies and strychnine poisoning. Busch (42) wrote that Demme had treated twenty-two tetanic patients with curare, and that eight of these patients had survived.

Bremer (43) reported that experimental tetanus, produced by the intramuscular or subcutaneous injection of tetanus toxin, could be relieved readily by the injection of curare. Cole (44) obtained recovery of one of three tetanic patients to whom he administered curare. He administered four doses, each 32 mg., intravenously in a period of twenty-four hours, and the patient in question was free of symptoms for thirty-six hours. Subsequently, three more doses of 32 mg. each were administered over a period of twelve hours and the patient concerned made an uneventful recovery.

West (45) described in detail the procedure he used in the treatment of ten tetanic patients with curarine. He said he prefers the continuous intravenous drip method of administration of curarine. Although death was the ultimate outcome for nine of his ten patients, West did show that the frequency and severity of the convulsions could be reduced by the use of curarine. Bennett (46) was able to abolish the continuous tetanic convulsions of two patients by the use of curare. Cullen and Quinn (47) reported the use of curare in four cases of tetanus, with recovery in one case.

Curare in Spastic Diseases.—Bremer (43), in his discussion of tonus and contraction of skeletal muscles, stated that curare, administered in a dose of 0.25 mg. per kilogram of body weight, abolished the rigidity in decerebrate cats. He suggested that curare is effective in spastic diseases because it interrupts the continuous “involuntary” stimuli without abolition of the stimuli that occur in attempts at purposeful movements.

West (48), on the basis of previous results obtained by Hartridge and himself in the use of curare for relief of the spasticity of dogs which had parathyroid tetany (27), administered curare to thirty patients.
who had rigidity of pyramidal tract and extrapyramidal tract origin. Although his results in the majority of these cases were unsatisfactory, there was in certain cases a selective removal of spasticity, as opposed to depression of voluntary activity, sufficient to make it desirable that further studies on this subject be carried out. West reported that 16 to 20 mg. of d-tubocurarine chloride, when administered subcutaneously to a patient who had disseminated sclerosis with spastic paraplegia, produced diminution of the spasticity without weakness, but that when doses of 50 mg. were employed, relaxation was produced in association with signs of generalized curarization.

Burman (49–51) presented extensive reports of his use of curare and erythroidine hydrochloride in spastic and dystonic states. The curare he used was prepared in a sterile, biologically standardized solution for intramuscular and intravenous use. The concentration was 5 mg. per cubic centimeter of solution (of such potency that 4.4 mg. per kilogram of body weight was fatal to 50 per cent of the frogs used for standardization). Since Pick and Unna (29) found that all frogs recovered from a dose of d-tubocurarine chloride of 3 mg. per kilogram of body weight, the curare used by Burman was very active.

Because of the uniform potency of the solution of curare, Burman was able to individualize the dose for his patients by starting to administer small doses and gradually increasing the dose until the desired effect was produced. Usually, a dose of 25 mg. administered intravenously produced satisfactory effects; if the solution was administered intramuscularly, the amount needed was about 50 mg. The dose in such cases, he thought, need not be greater than that required for paralysis of the muscles of the eyes and face. The maximal effect was noted immediately after intravenous injection, whereas after intramuscular injection the desired effect was obtained in twenty to thirty minutes, and signs of curarization persisted for three to four hours. From a clinical point of view, the spasticity was relieved for two to three days. Burman therefore repeated his injections at intervals of two to three days. Electromyographic studies of these patients showed the effects of curarization twenty-four hours after curare had been injected. There was no change in the blood pressure or pulse rate after curare had been administered to these patients.

Bennett (46) has used curare in a wide variety of cases of neurologic diseases. For seven children who had severe spastic paralysis the use of curare provided immediate relief of the spasticity; this relief persisted for a short time after the injection. The use of curare in some of the cases increased the favorable results that were expected from the orthopedic procedures and physiotherapy. The convulsions of a patient who had status epilepticus were prevented by the continuous intravenous administration of curare. The incoordinate movements of patients who had Huntington’s chorea ceased and did not return for a few hours after the injection of curare.
Denhoff and Bradley (52) reported a detailed study of the use of curare in the form of intocostrin in the treatment of six children who had cerebral palsy. They found that the intramuscular route of administration gave the most satisfactory results in these cases. By careful preliminary observations a maintenance dose was established for each patient. This dose varied from 0.9 to 3.3 mg. per kilogram of body weight. The larger dose was necessary in the most severe generalized spastic condition, and as a rule the desired effects persisted for three to four days. The particular advantage in the use of curare in the spastic child was that it permitted an acceleration in the response to the muscle-training and educational program which are the basic factors in management of these patients.

Repeated studies of electrocardiograms, pulse rates and blood pressures of these subjects during their treatment with curare showed that curare in the amounts used produced no changes demonstrably different from those in the control observations.

Schlesinger (53) reported the administration of curare (intocostrin) to a patient who had transverse myelitis. He found that after curare had been injected intramuscularly the patient was able to carry out active exercise procedures. He also used a suspension of d-tubocurarine in peanut oil and myricin, and found that a single dose of this suspension given intramuscularly produced good relief of spasticity for three days without weakness of the muscles.

James and Braden (54) reported the use of curare for the treatment of spasms of the lower extremities of twelve patients who had paraplegia which followed transverse myelitis caused by wounds. They obtained best results when the curare was given intramuscularly in doses of 50 to 70 mg. four times daily. One of their patients received 156 injections (varying from 70 to 160 mg.) in a period of six weeks, and marked reduction in spasticity followed each dose. There was no reduction in the effect of an individual dose when administration of curare was repeated over a long period.

Curare in Metrazol and Electric Shock Therapy.—During the past eleven years the use of shock therapy and convulsions produced by the intravenous injection of metrazol or by an electric current for schizophrenia, involutional melancholia and other forms of psychosis has gained wide acceptance as a valuable procedure in these conditions. One of the most undesirable sequelae of this treatment is the relatively high frequency of occurrence of fracture of bones of the spinal column and extremities.

Bennett (55) reported that the incidence of fractures of the humerus or femur which accompany this form of treatment has been between 1.5 and 2 per cent, and that the incidence of dislocations has been as high as 17 per cent. The incidence of compression fractures of the vertebrae has ranged between 40 and 50 per cent. Easton and Som-
mers (56) reported that the incidence of fracture was 26 per cent in a series of 800 patients who received metrazol therapy.

Because of the high frequency of occurrence of fractures during convulsive treatment Bennett, who was using curare in the management of children who had spastic paralysis, tried curare as an agent to reduce the incidence of fractures during metrazol-induced convulsions. The dose which he employed was sufficient to produce paralysis of the extremities, and the calculated convolution-producing dose of metrazol was given intravenously soon after the action of curare had become fully developed. The severity of the convolution was greatly reduced by the administration of curare, but the therapeutic effect of the metrazol-induced shock was in no way reduced by the use of curare. By the time the patient recovered consciousness after the convolution, the paralyzing effect of the curare had worn off.

In a more extensive paper, Bennett (8) reported the use of curare (intocostrin) in association with metrazol among 101 patients who received an average of 6.2 treatments each. In only one patient was there evidence of a fracture (a compression fracture of the seventh thoracic vertebra). The dose of intocostrin employed (containing 10 mg. per cubic centimeter) was about 5 cc. per 100 pounds (45.4 Kg.) Electroencephalographic records of patients receiving curare and metrazol did not differ from those of patients receiving metrazol alone.

Harvey and Masland (26) investigated the actions of curare, beta erythroidine and quinine methochloride and found that the severity of convulsions produced by metrazol was less after the administration of curare than after use of the other two agents.

Easton and Sommers (56) reduced the incidence of occurrence of fracture in shock therapy from 26.1 per cent, when metrazol was administered alone, to 5.8 per cent, when the use of metrazol was preceded by the administration of curare.

Goldman and Baber (57), Woolley, Jarvis and Ingalls (58), Cash and Hoekstra (59), Ebaugh (60), Bennett (61) and Heldt, Hurst and Dallis (62) reported on the administration of curare to patients immediately before the production of convulsions by electric shock. Curare was given about two minutes before the electric shock was produced. Curare reduced the severity of the convulsions and the danger of fracture.

(To be concluded in July issue)

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