The Clinical Use of Curare

By Harold R. Griffith, M.D.

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If anyone had suggested a few years ago that I should present a paper on the clinical use of Curare I would have been inclined to call him crazy. For to most of us Curare has always been a fabulous poison vaguely connected with South American Indians and detective novels, useful in the physiological laboratory but far removed from the realm of practical therapeutics. Nevertheless I have now to report its intravenous administration to fifty patients under anesthesia, and others have used it many hundred times in various conditions. The modern history of Curare is briefly as follows:

Curare has long been known to science — in fact the earliest reference to its use is in Hakluyt's description of Sir Walter Raleigh's voyage up the Orinoco in 1595, when even then the Indians were using it as an arrow poison. In 1814 Watterton and Brodie observed that asphyxia from respiratory paralysis was the cause of death in Curare poisoning, and in 1840 Claude Bernard confirmed this observation in a series of physiological experiments which have become famous. But the modern history of Curare, or what one might call the "civilization" of the drug, dates only from 1938 when Richard C. Gill, an American who had lived for many years on the edge of the upper Amazonian jungle of Ecuador, and who had himself just recovered from an attack of spastic paralysis, led an expedition into the South American wilderness in the hope that he might obtain a sufficient quantity of Curare and knowledge of its manufacture to make possible its use in scientific medicine as a treatment for spastic disease.

In his book "White Water and Black Magic", Gill tells most interestingly of the difficulties dangers and final success of his quest. Curare, which among the Indians is known as "the flying death" is the most sacred and mystifying of all the ~~strange~~ drugs in the primitive pharmacopoeia. Its secrets have been ~~for centuries~~ carefully guarded by the witch doctors who make it, and for this reason any accurate ~~knowledge~~ information about its origin and its ingredients has been most difficult to obtain. Nevertheless Gill returned to civilization with a large supply of the crude drug, a complete detailed history of its manufacture and ~~with~~ with botanical samples of over sixty-five plants which are used in making various kinds of Curare. Through the cooperation of the Research Laboratories of E. R. Squibb and Sons, and Professor A. R. McIntire of the Univ. of Nebraska this crude Curare was subjected to its first really thorough pharmacological study. The so-called true Curare substance" was separated from various other toxic ingredients which are present in the Indians arrow poison, and after extensive Animal experimentation a product

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was obtained which ~~to they felt was~~ seemed safe for human trial. ~~and ready for~~ ~~They presented~~ This substance was offered to the medical profession for experimental study under the name of "Intocostrin." (Extract of Unauthenticated Curare, Squibb.)

Prof A. E. Bennett of the University of Nebraska began using this "Intocostrin" in order to minimize the traumatic effects of the violent muscular contractions in ~~patients under psychiatric~~ patients undergoing Metrazol shock therapy for various psychiatric disorders. He and others have reported after many hundred injections that this preparation of Curare is harmless to the patient, and extremely valuable in preventing the fractures which formerly resulted rather frequently from shock therapy. ~~This new~~

A recent report in the CMA Journal by Dr. J.A. Cummins tells of his experience with Curare at the Ontario Hospital, Hamilton, and at our own Verdun Protestant Hospital Curare is being used to modify the effects of electric shock convulsions.

In June 1940, Dr L.H. Wright, of ~~the~~ New York, told me of this new work with Curare and remarked how nice it would be if we could use some of it in anesthesia to relax the muscles of our patients any time ~~at all~~ they got a little too tense. I ~~must~~ agreed that such an effect is often to be desired but was too horrified at the old poisoners reputation

Curare to be seriously interested. I met Dr. Wright again in October 1941 and asked him how he was getting on with Curare in anesthesia. He said he still thought the idea was alright but that so far as he knew no one had tried it. I thought I'd better not pass up a good thing any longer, so Dr. Wright kindly sent me some ampoules of "Intocostrin" and in January 1942 we began using it in the Operating Room. The drug is administered intravenously to patients under general anesthesia, it acts quickly and in less than a minute there is a dramatic and complete relaxation of the skeletal muscles. Even under the most favorable circumstances, and with every general anesthetic agent, occasions do arise when it seems impossible to get the patient sufficiently relaxed to make an upper abdominal exploration or to close a friable peritoneum. To have a drug at hand which will give the patient at these critical moments this complete relaxation, uniformly quickly and harmlessly has seemed to us a blessing to both surgeon and anesthetist

The typical curare action consists essentially of an interruption of nervous impulses to muscle, this interruption taking place at the termination of the nerve fibres at the muscle cells, and probably consists in a neutralization of the acetylcholine reaction which is the fundamental neuro-muscular stimulation mechanism. When ~~Curare~~ a drug having a pure curare action is introduced intravenously it very rapidly produces a paralysis involving skeletal muscles of which in practice the diaphragm and intercostals are the last to be effected. In moderate doses there is apparently no effect on cardiac or involuntary muscle. The drug is excreted almost as rapidly as it acts. So that the duration of action is transient. In our experience the effects usually observed within a few seconds attains its maximum in about five minutes and does not last longer than fifteen or twenty minutes. There is a good deal of individual variation in patients as to the duration of effect, and this depends also to some extent on the depth of anesthesia present. Curare affects only the neuro muscular junction

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and it is in no sense an anesthetic agent. Therefore we do not recommend its use to prolong the effect of Spinal anesthesia unless the patient is heavily sedated or a general anesthetic is used in combination with the Spinal. In two patients we repeated the injection during the same operation, obtained relaxation after each injection without harmful effect. ~~or evidence of Cumulative action~~. There is some evidence, however, from animal-experimentation that the drug may have some cumulative action, so we feel that in anesthesia it should not be repeated ~~cautiously~~ indiscriminately, but should be used only to overcome some critical situation, and subsequent muscular relaxation should be maintained by the use of the anesthetic agent itself.

Intocostrin is marketed in 5 c.c. vials of a sterile aqueous solution which contains 20 mg. of the pure curare substance to each c.c. We have found that 5 c.c. (or 100 mg. of curare substance) is an adequate dose for the average adult. We make the injection intravenously, and quite rapidly, and have had no case of thrombosis or other local reaction. This dose is rather larger than that usually used by psychiatrists, but we feel that the conditions under which we work with Curare in

~~the Operating Room~~ surgery are much safer than those of most psychiatric institutions. In the Operating Room we have the patient already asleep, under the care of an experienced anesthetist and with adequate oxygenation, a free airway and ~~every~~ facility at hand for the proper control of respiration. In none of our patients have we observed any appreciable effect on pulse or blood pressure, ~~and in a few of them~~ Respiratory depression and even cessation of respiration occurred in a few cases, but we are so accustomed to ~~controlling~~ ~~the action~~ artificial control of the respiration in patients under modern anesthesia technique that such an effect doesn't worry us at all, and there has never been any harmful post-operative disturbance. Almost all our patients have been under cyclopropane anesthesia, but a few received nitrous oxide and ether. One ~~person~~ man undergoing cholecystostomy for a very severe acute hemorrhagic pancreatitis was given open ether with most unsatisfactory abdominal relaxation. He was given 5 cc Intocostrin with immediate relaxation but also cessation of respiration. An endotracheal tube was introduced and anesthesia continued with controlled respiration and cyclopropane and Oxygen. ~~In spite of the ether, the Curare, and~~

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The ~~prostigmine~~ drug "Prostigmine", which is allied chemically to physostigmine, ~~is~~ apparently ~~the closest~~ bears the closest resemblance to a true physiological antidote of curare. In patients with myasthenia gravis ~~its action~~ it acts to ~~restore the~~ inhibit the choline esterase and to restore the acetylcholine preponderance at the myo-neural junction. Since curare action is very similar to myasthenia gravis, prostigmin will quickly counteract its effect. For this reason an ampoule of prostigmin should always be available when curare is ~~used~~ given, although in our cases we have not had to use it.

~~the pancreatitis~~ I'm glad to say that in spite of the ether, the curare and the pancreatitis, ~~the~~ he subsequently recovered. ~~Prostigmin~~ ?

→ 7A ~~In our first twenty-five cases we often purposely lightened the anesthesia in order to assess the effect of curare in a variety of operations.~~

After twenty-five cases ~~we~~ ~~we were~~ greatly impressed with the uniform results obtained when an adequate dose was given, ~~that~~ ~~and~~ in July 1942, Dr Enid Johnson and I published a ~~sh~~ preliminary report in "Anesthesiology." ~~which~~ This has led to further clinical trial by anesthetists ~~throughout the Un in various~~ in the United States and Canada. Dr. Wesley Bourne has been good enough to tell me that he feels ~~that in a cases~~ there is a real place for ~~the~~ curare as part of the equipment of every well qualified ~~experienced~~ anesthetist. Air Commodore Macintosh, Nuffield Professor of Anesthesia at Oxford, writes me that he thinks this to be an important new approach to the problem of muscular relaxation in anesthesia.

~~Dr. Cullen of Iowa~~

~~Rovenstine~~

~~Macintosh~~

7B. → During recent months we have not used curare very frequently and our total series has grown only to 50 cases simply because we were satisfied with its efficacy and wished to keep it for cases in which it was really needed. Inadequate relaxation

Dr. S. C. Cullen, of the University of Iowa, has ~~[illegible]~~ recently ~~Completed a study~~ of ~~250 patients~~ sent me a report on the use of curare injections in 250 patients under inhalation anesthesia. He writes me that his work has confirmed our findings, and he says that surgeons with whom he works are enthusiastic about the results obtained. His technique of administration has been somewhat similar to ours except that he gives the curare now more or less routinely ~~to~~ before the peritoneum is opened in patients with whom he expects to have difficulty in securing relaxation. He has administered the drug in fractionally repeated doses to a number of patients with satisfactory result ~~[illegible]~~ in prolonging the period of complete muscular relaxation. He feels that curare is much more depressing to the respiration in patients under ether than under cyclopropane, but in every case artificial respiration ~~with intermittent inflation of the~~ by manual compression of the breathing bag was all that was necessary to restore ~~normal~~ the patient to normal breathing.

is not a frequent complication with modern anesthesia ~~methods~~ technique and the good anesthetist should not need curare every day or even every week. It is still a potentially dangerous drug, and I wouldn't like to see it used indiscriminately by unskilled anesthetists simply because they were too inept to ~~obtain~~ muscular relaxation by ordinary anesthetic procedures. ~~Also one should not expect curare to be more than a powerful but short acting~~ Also one should not expect too much of the drug. ~~It is not~~ According to our present knowledge, curare is simply a powerful but short acting adjuvant to ~~general~~ anesthetic agents to be used in ~~certain cases~~ an unconscious patient to tide one over an emergency situation where complete relaxation is demanded. We have found it ~~rare~~ to be required most frequently in strong young adults who may be just as resistant to any anesthetic agent as are some men to the effects of whisky. I don't recommend it as an aid during the excitement of a difficult induction or for a short procedure such as the reduction of a dislocation, simply because in these cases such an agent as intravenous pentothal may do the work perfectly satisfactorily and probably more safely.

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So much for Curare in anesthesia and in psychiatry. One might speculate upon other possible fields for ~~such a~~ clinical use. Perhaps we may find it of value in the treatment of any conditions where there is too violent muscular contraction or too persistent muscular spasm.