

## THE USE OF CURARE IN ANÆSTHESIA AND FOR OTHER CLINICAL PURPOSES\*

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**I**F 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 laugh, 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 administration to 90 patients under general anæsthesia, and others have used it hundreds of times in various conditions.

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<sup>1</sup> 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 this 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<sup>2</sup> 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 pharmacopœia. Its secrets have been for centuries carefully guarded by the witch doctors who

make it, and for this reason any accurate 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 detailed history of its manufacture, and with botanical samples of over forty plants which the Indians use in making various kinds of crude curare. Through the co-operation of the Research Laboratories of E. R. Squibb & Sons, and Professor A. R. McIntyre, of the University 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 was obtained which seemed safe for human trial. This substance was offered to the medical profession for experimental study under the name of "Intocostrin", (Extract of Curare, Squibb).

Professor A. E. Bennett, of the University of Nebraska, began using intocostrin in order to minimize the traumatic effects of the violent muscular contraction in patients undergoing metrazol shock therapy for various psychiatric disorders. He<sup>3</sup> and others<sup>4</sup> 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. A recent report by Dr. J. A. Cummins<sup>5</sup> tells of his experience with curare at the Ontario Hospital, Hamilton; and at the Verdun Protestant Hospital, Montreal, curare is being used to modify the effects of electric shock convulsions.

In June, 1940, Dr. L. H. Wright, of E. R. Squibb & Sons of 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 anæsthesia to relax the muscles of our patients when they got a little too tense. I agreed that such an effect is often to be desired but was too horrified at the old poisonous reputation of curare to be seriously interested. I met Dr. Wright again in October, 1941, and asked him how he was getting on with curare in anæsthesia. He said he still thought the idea was sound, but that so far as he knew no one had tried it. I thought I had 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 operat-

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ing room of the Homœopathic Hospital of Montreal. We administered the drug intravenously to patients under general anæsthesia, and found that it acts quickly, producing in less than a minute a dramatic and complete relaxation of the skeletal muscles. Even under the most favourable circumstances, and with every general anæsthetic 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 complete relaxation, uniformly, quickly and harmlessly, has seemed to us a blessing to both surgeon and anæsthetist.

#### ACTION OF CURARE

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 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 affected. 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 effect is 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 anæsthesia present.

Curare affects only the neuro-muscular junction and it is in no sense an anæsthetic agent. Therefore, we do not recommend its use to prolong the effect of spinal anæsthesia unless the patient is heavily sedated or a general anæsthetic is used in combination with the spinal. In two patients we repeated the injection during the same operation and obtained relaxation after each injection without harmful effect. There is some evidence, however, from animal experimentation that the drug may have some cumulative action, so we feel that in anæsthesia it should not be repeated indiscriminately but should be used only to overcome some critical

situation, and subsequent muscular relaxation should be maintained by the use of the anæsthetic agent itself.

#### USE DURING ANÆSTHESIA

Intocostrin is marketed in 5 c.c. vials of a sterile aqueous solution which contains 20 mgm. of the pure curare substance to each c.c. We have found that 5 c.c. (or 100 mgm. 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 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 anæsthetist, 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 the pulse or blood pressure. Respiratory depression and even cessation of respiration occurred in a few cases, but we are so accustomed to artificial control of the respiration in patients under modern anæsthesia technique that such an effect does not worry us at all, and there has never been any harmful postoperative disturbance. Almost all our patients have been under cyclopropane anæsthesia, but a few received nitrous oxide and ether. One young man undergoing cholecystostomy for a very severe acute hæmorrhagic pancreatitis was given open ether with most unsatisfactory abdominal relaxation. He was given 5 c.c. of intocostrin and immediate relaxation ensued but there was also cessation of respiration. An endotracheal tube was introduced and anæsthesia continued with controlled respiration and cyclopropane and oxygen. I am glad to say that in spite of the ether, the curare and the pancreatitis, he subsequently recovered.

The drug prostigmin, which is allied chemically to physostigmine, apparently bears the closest resemblance to a true physiological antidote of curare. In patients with myasthenia gravis it acts to inhibit the choline esterase and to restore the acetylcholine preponderance at the myoneural junction.<sup>6</sup> Since curare action is very similar to the effect of myasthenia gravis, prostigmin should quickly counteract the curare effect. For this reason an ampoule of prostig-

min should always be available when curare is given, although in our cases we have not had to use it.

After 25 cases we were so greatly impressed with the uniform results obtained when an adequate dose of curare was given that in July, 1942, Dr. Enid Johnson and I published a preliminary report on "The use of curare in general anaesthesia".<sup>7</sup> This has led to further clinical trial by anaesthetists in the United States and Canada, and many have written me that they believe this to be an important new approach to the problem of muscular relaxation in anaesthesia. Dr. S. C. Cullen, of the University of Iowa, has recently published<sup>8</sup> a report on the use of curare in 250 patients under inhalation anaesthesia. It is gratifying to learn 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 as a routine 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 a satisfactory result 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 by manual compression of the breathing bag was all that was necessary to restore the patient to normal breathing.

During recent months we have not used curare very frequently, and our total series has grown only to 90 cases simply because we were satisfied with its efficacy and wished to keep it for cases in which it was really needed. Inadequate relaxation is not a frequent complication with modern anaesthesia technique and the good anaesthetist should not need curare every day or even every week. It is still a potentially dangerous drug, and I would not like to see it used indiscriminately by unskilled anaesthetists simply because they were too inefficient to obtain muscular relaxation by ordinary anaesthetic procedures. Also, one should not expect too much of the drug. According to our present knowledge, curare is simply a powerful but short acting adjuvant to anaesthetic agents, to be used in an unconscious patient to tide one over an emergency situation where complete relaxation

is demanded. We have found it to be required most frequently in strong, young adults who may be just as resistant to any anaesthetic agent as are some men to the effects of whisky. I do not recommend it as an aid during the excitement of a difficult induction, or for a short procedure such as the reduction of a dislocation, because in these cases such an agent as intravenous pentothal may do the work perfectly satisfactorily, and probably more safely.

So much for curare in anaesthesia and in psychiatry. One might speculate upon other possible fields for clinical use. Perhaps we may find it of value in the treatment of conditions in which there is too violent muscular contraction or too persistent muscular spasm. Gill had hoped that it would prove an effective treatment for the various forms of spastic paralysis. This dream has come true to a certain degree, and Burman<sup>9</sup> and others are now advocating the use of curare and erythroidine hydrochloride for spastic and dystonic states. An obstacle to the effective use of curare in the treatment of these conditions is that its action is fleeting and cannot be long maintained. However, since the treatment of spastic paralysis is concerned largely with the re-education of muscles and nerves, a drug such as curare, which will give even temporary relaxation to those who are in a state of constant spasm, has proved to be a great help in bolstering the patients' morale and giving them confidence and hope. Cullen<sup>10</sup> reports a case of tetanus successfully controlled by repeated curare injections; and it might be used for the control of eclamptic and other forms of convulsions in unconscious patients, providing that oxygen and means of artificial respiration were always at hand.

This, then, is the story of the transformation of a drug from the kettles and gourds of Indian witch doctors to the biological standardization and sterile ampoules of modern medicine. What chapters of the story remain to be told only time will show, but I think that enough has already been revealed to assure for curare a definitely useful place in our pharmacopœia.

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### RÉSUMÉ

Le curare du commerce s'appelle "intocostrin" (Squibb). Il fut d'abord utilisé pour diminuer la violence des convulsions thérapeutiques produites par le métrazol, puis par l'électro-choc, puis, depuis janvier 1942, comme adjuvant de l'anesthésie générale, pour favoriser le relâchement des muscles abdominaux. Son mode d'action, on le sait, est son effet inhibant au niveau de la jonction myo-neurale, par neutralisation de l'acétylcholine. Son antidote est la prostigmine. Le curare ne doit pas être employé de façon routinière, mais dans les seuls cas où le relâchement musculaire ne peut s'obtenir autrement. Les états spasmodiques et les dystonies en profiteront peut-être. JEAN SAUCIER

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## ANO-RECTAL SUPPURATIVE DISEASE AND ANO-RECTAL FISTULA

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IT is a recognized truth that the surgeon time and again encounters patients suffering from ano-rectal fistulæ who return seeking a cure for this ailment, having previously been operated on without success. It is my opinion that no other surgical lesion so frequently fails of cure following operative interference as that of ano-rectal suppurative disease. This fact has become notorious amongst medical and lay people. The fear of a resultant incontinence in effecting a successful outcome for this lesion is ever present in the minds of many operators. Much confusion exists concerning the whole problem of peri-rectal suppurative disease and fistula-in-ano. The anatomy of the anus and rectum as now described by the English school,<sup>1</sup> completely and thoroughly demonstrates that the accepted anatomy of the anus and rectum upon which has been based the treatment of suppurative disease and ano-rectal fistula hitherto, must be completely revised. The principles and practice of rectal surgery are fundamentally dif-

ferent from the principles carried out in general surgery.

In the period between 1934 and 1940 we have had under our care slightly over 400 patients suffering from either acute or chronic peri-rectal suppurative disease. Of these, 205 cases were of the acute variety. In this presentation the phrase chronic peri-rectal suppurative disease applies to and will be synonymous with what is known as fistula-in-ano, and ano-rectal fistula. These patients presented themselves in private practice and in the public wards of our department. Acute peri-ano-rectal suppurative disease may be defined as an infective process of the peri-anal or peri-rectal tissues by one of the pus-forming organisms, with a strong tendency to become chronic after spontaneous drainage, or after surgical incision. It is strangely interesting, and often discouraging, that a peri-rectal suppurative lesion will so often persist in a chronic form following what appears to have been adequate surgical drainage. Infection by any one of the pus-forming organisms of the peri-rectal tissues presents itself as a stubborn refractory pathological condition, resisting cure under the simple surgical principle of drainage by adequate incision.

A dubious prognostic attitude is taken by some surgeons in cases of chronic and long-standing fistulæ, because on the one hand these are often regarded and labelled as tuberculous with a so-called doubtful prognosis; and, on the other hand, the fear of an incontinent ano-rectum militates against a complete and thorough operative procedure. In this series of cases under review the writer happily reports an ultimate cure in practically every case in which surgical measures were undertaken. In this reasonably large number of operative cases only one patient had anything resembling an inadequate ano-rectum.

### ANATOMY OF THE ANO-RECTUM IN RELATION TO ANO-RECTAL SUPPURATIVE DISEASE

In order to deal adequately with acute and chronic peri-ano-rectal suppurative disease one must possess a thorough knowledge of the anatomy of the ano-rectum, particularly of the muscles and fascia of the lower part of the rectum and anal canal. An infective suppurative lesion may occur anywhere in the peri-ano-rectal region as follows: directly beneath the mucous membrane or squamous epithelium of the lower rectum and anal canal; between the various components and subdivisions of the ano-rectal sphincters and their fascia; far above the levator apron, or so far below this as to present itself under the peri-anal skin in the ischio-rectal fossæ. The term ischio-rectal abscess as commonly applied to many types of

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