HISTORICAL BACKGROUND, EARLY USE AND DEVELOPMENT OF MUSCLE RELAXANTS

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The first account of poisoned weapons used in the Western Hemisphere was written by Peter Martyr d'Anghera.[1] Martyr, as he is frequently known, began to collect material for his *De Orbo Novo* soon after the first voyage of Columbus. He was an attentive listener to tales brought home by adventurers returning from the New World, and he wove their stories into a long and detailed chronical. Written in Latin and first published in its entirety in 1516, this celebrated book contains many references to deadly weapons and the venoms used to poison them. Inevitably some of the stories, faithfully recorded by Peter Martyr, were exaggerated by frequent repetition. Indeed, the reputation for lethality of some of the poisons, like the virulence of certain micro-organisms, appears to have been enhanced by rapid and repeated passage from mouth to mouth. For example, Hartsink wrote in all seriousness that a woman carrying her infant was slightly wounded by an arrow which, being poisoned, caused her death within a few minutes, whereupon the infant, though unwounded, "straight away died by reason of his proximity to the poisoned mother." Another story, the fable of the old women, first related by Peter Martyr, became firmly established very early and survived nearly two and a half centuries. It was repeated by almost all who wrote about South America including the highly imaginative Gomara who never ventured across the sea and probably never left Spain. The story first appears in the eighth decade of *De Orbo Novo,* it says:

> They like to use bows and poisoned arrows. They poison their arrows with the stings of scorpions, the heads of certain ants, poisons which they manufacture and those little plums I have mentioned, as well also as the juice they distil from certain trees in which they dip their arrows. But everybody is not permitted to make this mixture. There are certain old women skilled in the art, who are shut in at certain times and furnished with the necessary materials; during two days these women watch and distil the ointment. As soon as it is finished the house is opened, and if the women are well and not found lying on the ground half dead from the fumes of the poison, they are severely punished, and the ointment is thrown away as being valueless; for the strength of the poison is such, that the mere odor of it, while compounding almost kills its makers.

Doubtless the account written by Herissant, who in 1751 had heard the story of the old women from Condamine, is true. He describes how a young boy was overcome in a small closet where a curare preparation was being prepared over a slow fire. It seems altogether probable that this boy was simply overcome by the then unknown gas, carbon monoxide. Fontana, whose work on poisons is an eighteenth century classic, dispelled the belief that curare poisoning could occur by inhalation. He exposed pigeons to the fumes from heated "ticunas" (another name for curare) and reported that they all survived without ill effects.

The interesting and romantic but unscientific period abounds in fantastic tales, but a careful reading of these early histories makes it clear that several entirely different types of powerful poisons were used. Some, for example, "surely killed the victim three or four days after the wound."[2] Among the symptoms described were "diabolical facial contortions," these could have been the result of tetanus. Other symptoms such as "weakness so great the victim can barely breath and after a day or two dieth" possibly indicates botulism. Many early writers assert that the poisons contained parts of dead animals and it is possible that the growth of putrifactive organisms produced various toxins, but it is impossible to decide to what extent deaths were the direct result of the presence of these toxins in the poisons smeared on the weapons. In any case these delayed deaths cannot have been caused by curare in the modern sense. Indeed the term "curare" is not

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found in these early writings but was first used by Margraaf in 1648, and Barrere writing in 1741 says ". . . les Indiens, enduisent leurs flêches avec le suc de cururu qui est une liane."

Three types of weapons poisoned with curare are still made by a few surviving primitive peoples. These are darts shot from blow guns, strikingly reminiscent of those found in Malaya (where another poison is used) and poisoned arrows and spears. They were vividly described by Waterton a century ago whose *Wanderings in South America* makes excellent reading. He says, "the bow is generally from six to seven feet long. . . . The arrows are from four to five feet in length. . . ." Specimens of poisoned weapons collected by the present author from the Amazon in 1957 tallied closely with Waterton's description. The arrows have slender tips shaped something like a large surgical cutting needle and containing curare in grooves along the broad sides. These slender points break off and the beautifully made, straight and nicely fletched arrow, falls to the ground. Retrieved, it is fitted with another point and is again ready for use. These hard arrow points are made of wood evidently corresponding to what Waterton called "Coucourite." The size and strength of the bows I found in the Altāmira region were surprising, because the Indian inhabitants in general were usually not more and often less than five and one-half feet in height and their build was rather slender. I learned that these long arrows are often shot from a sitting or lying position with the archer using both hands and feet.

Identification of the Plants and Their Curare Alkaloids

During the eighteenth century more exact and scientific observations gradually replaced the casual and often inaccurate descriptions of curare weapons made during the two previous centuries. Efforts were made to obtain botanical specimens used in the preparation of the poison. These were described in the works of Martius, the Schomburgks, Cervaux, Planchon and, in our century, by Krukoff, Moldenken, Sandwith and others. My previous description [3] can be summarized as follows: Two species of poisonous plants are used in curare making. In general curares from the forest regions of Equador and Peru contain ingredients derived from several varieties of *Chondodendron*, whereas those from the more easterly curare producing regions in the Guianas and lower Orinoco contain material from species of *Strychnos*. Other curares may contain both. Much of the black sticky mass of crude curare consists of gums, resins and other relatively inert materials. These are necessary to provide adhesive properties to the concoction to enable the poison to stay on the arrows and darts. Most of the fresh curares examined by the author have a characteristic but not unpleasant peaty or smoky odor. None of the many curares I have seen has given evidence of containing substances undergoing putrifaction.

Among the most potent curares are those obtained from *Strychnos toxifera* formerly found in calabash containers. "Pot" and "tube" curare are similarly designated according to the containers in which the preparations are carried. These were so named by Boehme [4] whose important contributions on curare appeared in 1895–1897. Calabash curare often contains the alkaloid Toxiferin I. It is reported as lethal to the average sized frog in amounts of approximately 0.3×10^{-6} grams; thus it is several hundred times more potent than the familiar *d*-tubocurarine, first isolated with difficulty from a sample of tube curare by King in 1935. In 1943 Wintersteiner and Dutcher obtained King's *d*-tubocurarine from an authenticated specimen of *Chondodendron tomentosum*, and subsequently this alkaloid became available in sufficient quantities for extensive clinical use. The isolation of the *Strychnos* curare alkaloids was accomplished by Wieland and his co-workers who made important investigations upon the pharmacological properties of the *Strychnos* curares. Their work was followed by the experiments of Marsh up to his untimely death. According to Marsh the *Strychnos* curare alkaloids produce a blockade of the transmitter acetylcholine at the neuromuscular junction in a similar manner to that produced by *d*-tubocurarine. He found no evidence of the depolarizing effect of decamethonum and related agents. These very potent alkaloids deserve to be examined more completely. There is no record of their large scale clinical usage.

The expense and difficulty of obtaining pure alkaloids from natural sources stimulated efforts

at synthesis and now several curariform substances are available and widely used clinically. This is not the place to present a detailed picture of the difficulties overcome by the numerous botanists and chemists occupied for years in unravelling the mysteries of the "curares." Suffice it to say that although brillant results have been obtained, the subject is far from exhausted and perhaps there are many potent and useful alkaloids yet to be discovered. Those interested in this phase of the curare story will be rewarded by consulting the sources cited below.

Early Pharmacological Studies and Practical Uses of Curare

The first attempts to investigate the mechanisms of curare poisoning were made in what is now French Guiana by Condamine. They were of little pharmacological significance. However, it is interesting to note that many of the earliest recorded demonstrations of curare, including those of Condamine, were made on fowls. They were killed by the curare and subsequently eaten. The meat of animals so killed was described not only as harmless but as being uncommonly tender and especially "sweet and of very good flavor." The glycogen content of muscle would in all probability, be higher than in animals killed after excitement and struggling had occurred. In 1811 Brodie reported to the Royal Society that artificial respiration could save the life of animals from otherwise fatal doses of curare. The widespread use of artificial respiration, though described earlier by Vesalius, can be said to date from Brodie's discovery.

Claude Bernard's interest in curare stems from his association with Magendie, who was familiar with the previous work of Fontana.[5] Magendie received samples of "ticunas" from Humboldt on the latter's return to Europe. Magendie often used curare in his acute mammalian experiments as a means of immobilizing his animals. It will be recalled that he worked before the discovery of the anesthetic actions of chloroform and ether; thus immobilization by anesthetization was unknown. Consequently it was natural for Bernard to be curious about this poison and to seek an explanation for the mechanism of its actions. His experiments on the frog in which he traced the site of action to the myoneural junction are among the classics of pharmacological investigation.

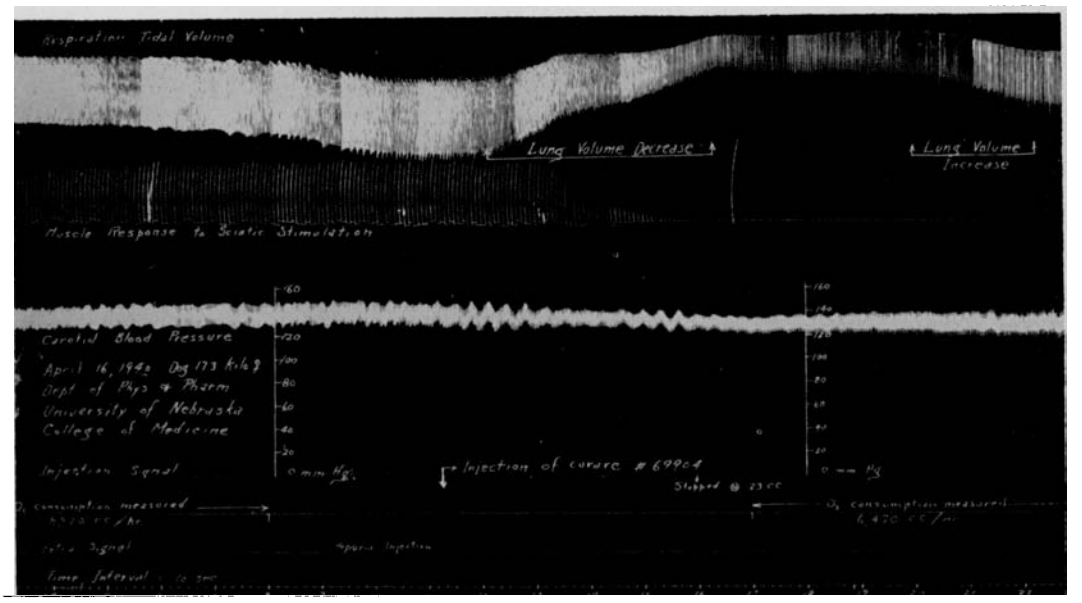

Fig. 1. Record of assay on the dog of solution used clinically in shock therapy. Assay of solution of partially purified tube curare. The material was relatively free of tertiary amines and contained chiefly *d*-tubocurarine and *Chondocurine dimethochloride*. Note that the blood pressure remains virtually unchanged. The lung volume and tidal volume are somewhat decreased. The single contraction of the leg muscle is the result of *direct* stimulation.

In a sense they mark the beginning of modern physiological concepts concerning motor innervations of skeletal muscles. It will be recalled that Bernard demonstrated that there was no failure of conduction along the motor nerves in curarized frogs; neither was there failure of the ability of muscles to respond to *direct* stimulation. Consequently the paralysis resulting in inability of the muscles to respond to *indirect* stimulation localized the action of curare at some point between nerve and muscle.[6] This finding led to the discovery of the motor end-plates and sole-plates in muscles which in turn paved the way for today's knowledge of chemical transmission at the nerve-muscle junction. Without curare, the discovery of the role played by acetylcholine in nerve-muscle transmission would undoubtedly have been delayed.

While the conclusions of Bernard are universally recognized and accepted, it must not be forgotten that there remains a large number of unanswered questions relative to the detailed mechanisms of action of curariform drugs. This is particularly true regarding the actions of curare drugs upon abnormal muscles as, for example, in myasthenia gravis, some of the dystrophies and following denervation.[7, 8] A partial answer to some of these questions may be forthcoming in the near future. Experiments by the author and his associates indicate that certain types of muscle dystrophy,[9] like denervated muscle, appear to suffer impairment of cholinesterase activity at the neuromyal junction, and consequently react to curariform agents differently from normal muscles.

Clinical Use

The first attempted use in the United States of curare as a therapeutic agent in man was made almost 100 years ago when a case of tetanus was treated by Sayres in New York

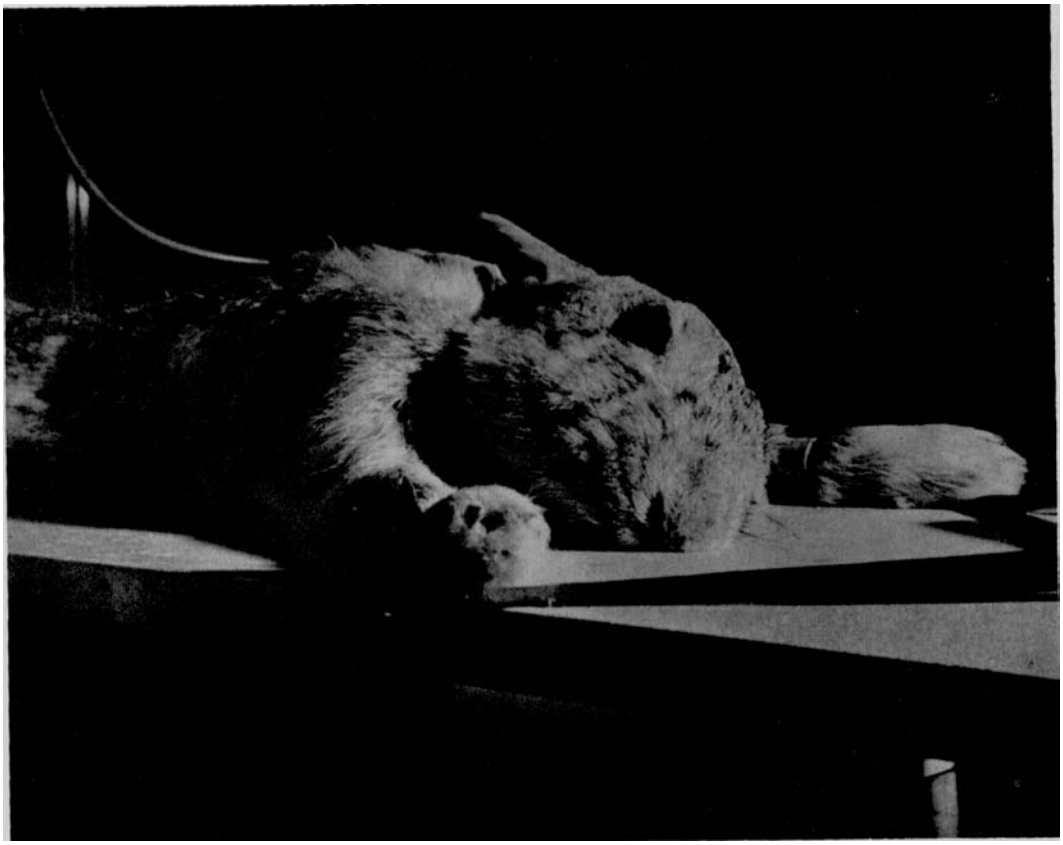

Fig. 2. Rabbit head drop assay. Normal rabbit at beginning of intravenous injection for "head drop" assay of aqueous curare solution. The solution is run into the vein in doses of 0.1 ml. every 15 seconds until the end point is reached.

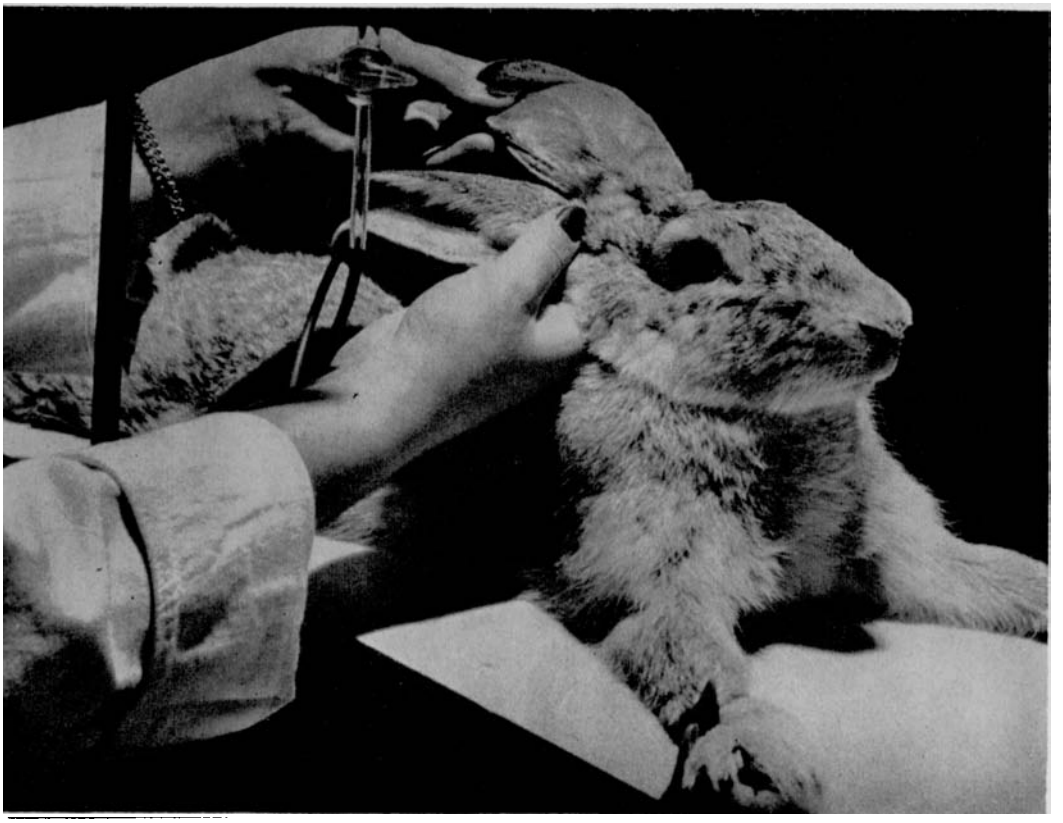

FIG. 3. Rabbit head-drop assay. End point of assay. The rabbit is unable to raise its head. The "head-drop" method was devised by H. A. Holaday of the E. R. Squibb Institute for Medical Research who supplied these photographs.

City. Sayres applied the curare preparation locally and this of course resulted in failure.

Attempts to use curare in tetanus continued throughout the second half of the nineteenth century. The use of crude, unstandardized preparations of curare with their many side-reactions caused by a variety of impurities, resulted in disappointment and clinical interest in the drug dwindled. It was not until 1935 that interest in the therapeutic application of curare was revived when King's isolation of the pure curare alkaloid *d*-tubocurarine made the extensive clinical investigations by West possible.

The amounts of *d*-tubocurarine isolated from a single sample of crude curare in a bamboo container were understandably too small for large scale clinical use. Consequently the first modern extensive clinical trials of curare were performed with the standardized preparation "Intocostrin," the prototype of which was prepared and standardized on dogs in the author's laboratory (fig. 1). Today's widespread acceptance of curariform drugs in medicine stems from the use of this early standardized preparation in shock therapy by A. E. Bennett in 1938 at this Institution and to the work of Griffith and Johnson, who in 1942 introduced the use of Intocostrin into anesthesia. In 1945 the latter authors reported on 300 cases. The large scale production of Intocostrin was undertaken by E. R. Squibb & Sons, and H. A. Holaday of that organization devised the convenient and reliable "rabbit head-drop" method of standardization (figs. 2 and 3). The same method is also used for the standardization of *d*-tubocurarine. "Pure" alkaloidal curariform preparations must be controlled for potency by biolog-

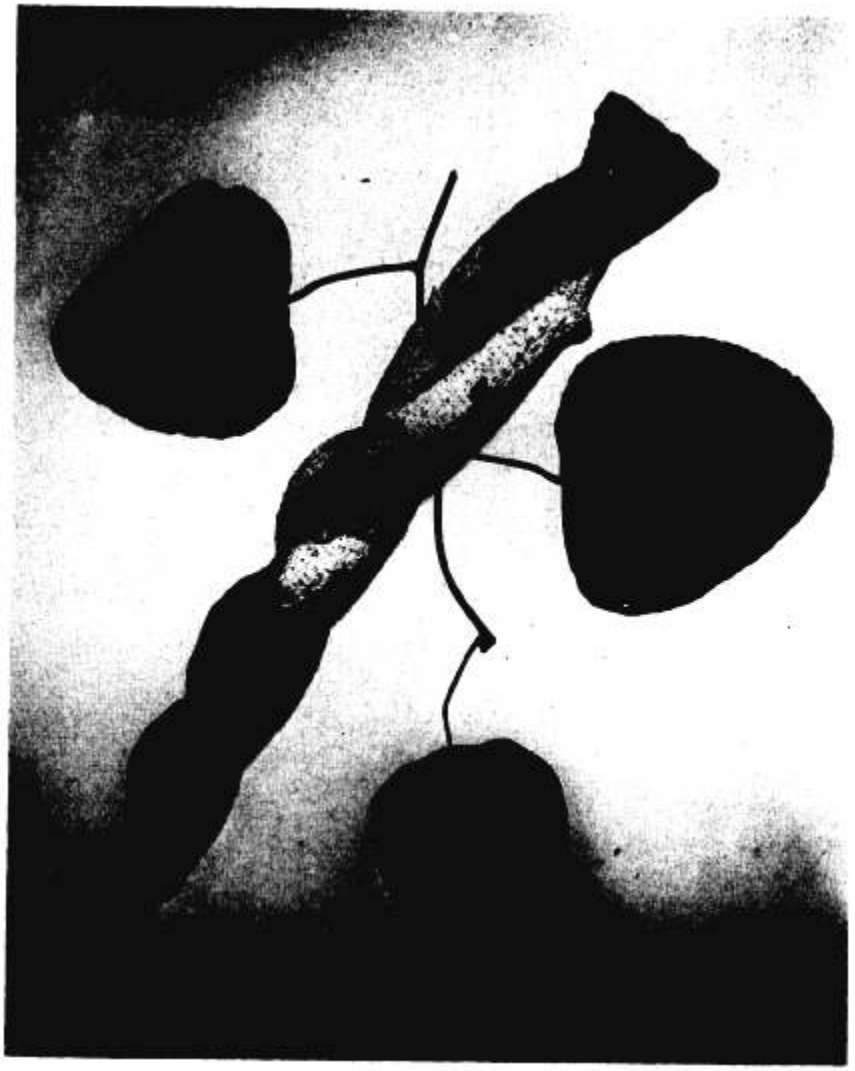

FIG. 4. Source of *d*-tubocurarine. The twisted bush-rope or stem of *Chondrodendron tomentosum* and leaves. The leaves are approximately 10 cm. across their maximum dimension. Courtesy Dr. W. A. Lott of the E. R. Squibb Institute for Medical Research.

ical methods. This is evident when it is recalled that "pure" crystallin *d*-tubocurarine was found by Wintersteiner and Dutcher to contain various quantities of *d*-chondocurine dimethochloride. These two alkaloids of identical molecular weights are indistinguishable one from the other by ordinary methods, but the isomers differ markedly in potency hence the necessity for biometric standardization. These careful chemical studies by Wintersteiner and Dutcher [10] were facilitated by the availability of ample supplies of botanically authenticated *Chondrodendron tomentosum* vines (fig. 4), and by the availability of large quantities of crude curare from Ecuador brought to this country through the energy and enterprise of Richard Gill. Cullen and Gross confirmed the favorable results obtained by Griffith and Johnson and also made the important discovery that ether anesthesia markedly decreased the amount of curare needed for muscle paralysis. These two groups of pioneer investigators established the usefulness of curariform drugs as adjuvants in anesthesia.[11]

The many clinical trials of curare in a wide variety of conditions ranging from spasticities to hiccough have been described elsewhere.[12] But mention should be made here of the important pioneer work of Burman who experimented with the Erythroidin alkaloids in spastic conditions. Erythrina plants do not appear to have been utilized as materials for the preparations of crude curare. Nevertheless their alkaloids possess a curariform action. The successful treatment of spastic states with curariform preparations awaits the development of long lasting, relatively mild agents. Today, anesthesia is the field in which nearly all the curariform preparations are used. As frequently happens synthetic compounds have been discovered having advantages over the naturally occurring drugs, and possibly some yet to be discovered synthetic substance may replace the natural alkaloids entirely. Preparation of the synthetic substances arose from the work of Ing, and Zamis and Paton [13] on the so-called onium compounds, and of these perhaps the most successful is succinylcholine. It was Paton's careful and ingenious experiments that revealed the depolarizing actions of this group of compounds. Succinylcholine by virtue of its usually short period of action lends itself particularly well for use in anesthesia. Indeed, modern anesthetic equipment is almost a necessity when this agent is used because it not infrequently produces abrupt cessation of respiration. Other synthetic compounds of interest are Flaxedil and Mytolon. However, the former compound may produce tachycardia and the latter bradycardia, a property shared by succinylcholine. Flaxedil is known in Europe as Gallamine and was synthetized by Bovet whose brillant work in chemosynthesis earned him the Nobel prize.[14]

Conclusion

The long historical background of the curare drugs and their slow establishment as useful clinical agents illustrates the importance of toxicology as the stimulus responsible for much of physiology and pharmacology. Just as a study of curare aroused interest in nerve-muscle physiology, the study of other arrow poisons, notably ouabain, increased our knowledge of the pharmacology of glycosides. There are many other examples of this sort including Magendie's work on strychnine, Barger and Dale's work on the "ptomaines" and the muscarinic substances.

Indeed, the realm of anesthesiology can be said with justification to have developed as a consequence of studies of intoxication. It should be emphasized that the unwanted side-reactions of presently available curariform compounds offer a promising field for further investigation.

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