

Curare: the South American arrow poison

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ABSTRACT The history of curare is both curious and convoluted. A product of South American culture it emerged in the sixteenth century from the mists of antiquity at the same time as quinine, coca, and chocolate. Like quinine, at first came the extract but no plant, and later the plant but no chemical compound. It took more than 300 years and the efforts of many explorers and scientists to resolve the problem. These included Condamine, Humboldt, Brodie, Waterton, Bernard, Dale, Walker, and King. Finally, the pure compound d-tubocurarine was isolated from the liana *Chondrodendron* and synthesised. Its specific physiological action was blockade of the effect of acetylcholine at the neuro-muscular junction. Such a paralytic poison could be used to kill oneself or others. The bizarre plot to kill the Prime Minister, Lloyd George, during the First World War is described. Fortunately this nefarious plan was thwarted by the Secret Service!

KEYWORDS Anaesthesia, chondrodendron, curare, South America, strychnos, tubocurarine

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From the mists of antiquity Man has been fascinated by poisons. This fascination was even more compelling if the poison came from exotic lands. The possibilities of their employment in warfare and hunting, or their surreptitious use in homicide or suicide, conveyed a sense of power to the poisoner and a sense of loathing in the observer. Even now the production of chemical weapons of destruction is a matter of international concern as exemplified by the threat of ricin and botulinum toxin. It is not surprising therefore that, during the time when the Spaniards and Portuguese were vying for the conquest of South America, the travellers' tales of a powerful paralytic poison, used by the natives in hunting, should exert a magnetic hold over the hearts and minds of the explorers and colonisers.

As will be seen, the word curare is a generic term which (with many others) was applied indiscriminately to these arrow poisons. Initially the explorers had the extract but no plant and later the plants but no pure compound. The story is in this way reminiscent of that of quinine which I have described in a previous article in my series on the poisonous and medicinal plants.¹

In this short account I can only paint a broadbrush outline of the 400-year history of curare. For a more detailed treatment the reader is referred to the excellent monographs by McIntyre² and Bryn Thomas.³

THE SPANISH EMPIRE

As the Conquistadores penetrated South America in the sixteenth century travellers' tales came back that the natives were using arrows tipped by a deadly poison.

One important chronicler was Pietro Martyre d'Anghera who, although born in Italy, lived for many years in Spain. He collected stories from the many travellers who returned from the Americas to Spain and eventually they were published in his celebrated volume *De orbe novo* (Concerning the New World).⁴ He was also known for his claim that syphilis was imported from the same continent. He describes the natives making several attacks on the invading Spanish and during these assaults using poisoned arrows. A number of men and horses were killed, and their deaths were preceded by a profound paralytic state.

He also tells that the 'poison' which coated the arrows was produced from plants and that 'criminal old women' were locked up in a confined space and forced to produce the toxin! When the fumes of the poison overwhelmed them it was deemed to be ready and the natives then opened the secret place to recover the poison and coat their arrows. As we shall see later, this account is apocryphal. In fact, as Waterton would testify later, women were regarded as being totally unclean and as such were excluded from the sacred rite of the preparation of the poison. Exposure to the female of the species could diminish the magical powers both of the toxin and the medicine man!

Over the next 200 years, 1500–1700, many explorers, clerics and writers then discussed and described the arrow poison. They included Bartolome de las Casas (the Apostle of the Indians), Oviedo, D'acuna, Gumilla, Herra, and Gomora. Incidentally this last individual was the first person to describe the tropical disease yaws (framboesia).^{2,3}

A consensus view developed, derived from these accounts. There definitely was an arrow poison and it was extracted from a herb known only to the Indians. This was formed into a paste by boiling off the excess liquid of extraction and adding other herbs. The black paste was then smeared carefully on the points of the arrows. The slightest wound produced by the arrow could prove fatal and there appeared to be no effective remedy against the poison (see below). The person preparing the extract must take great care, as if it got into an open wound this also could prove fatal.

In this period the source of the poison was hotly disputed. As we shall see later, this is not surprising as several different genera of plants would prove to be involved. Initially some authorities suggested that it came from 'venomous apples' which resembled the 'muscadel pears' of the Island of Sicily, Italy. These apples grew on certain trees which were covered with many branches and leaves. It is possible here that these writers were describing *Strychnos toxifera* (see Schomburgk below and Figure 1). The fruit of *Strychnos* does indeed look like an apple although the plant is a rain jungle (forest) liana. The British explorer John Hawkins also mentions 'apples' which are 'fair and red' as a possible source of the poison.⁵

In order to understand the geographical origin of the arrow poison, we must now take a brief diversion into the complex topography of the river basins of the Amazon; the Orinoco and the Essequibo (see Figure 2). The Amazon is considered to have its origins 2,300 miles from the sea at the junction of two major rivers in Peru: the Marañon and the Ucayali. One thousand miles downstream it is joined by another major river on its northern bank, the Rio Negro.

The upper waters of the Orinoco river divide at a watershed near its source; one part flows south to join the



FIGURE 1 *Strychnos toxifera*. Bentham

Negro, the other continuing as the main stream towards the Caribbean. The unusual link between the Amazon and the Orinoco is now called the Casiquiare Canal. However, its existence was denied for a considerable period of time. It was first reported by d'Acuna in 1641 and subsequently confirmed by de la Condamine (1742) and by von Humboldt (1800).^{2,3} The latter collected curare vines (or lianas) in this area (see Figure 2).

The Essequibo, 620 miles in length, runs through British Guiana (now Guiana) and also empties into the Caribbean. In the upper reaches of this river lived the Macusi, a tribe of Indians whose arrow poison came to be regarded as one of the most potent available. It was in this area that,

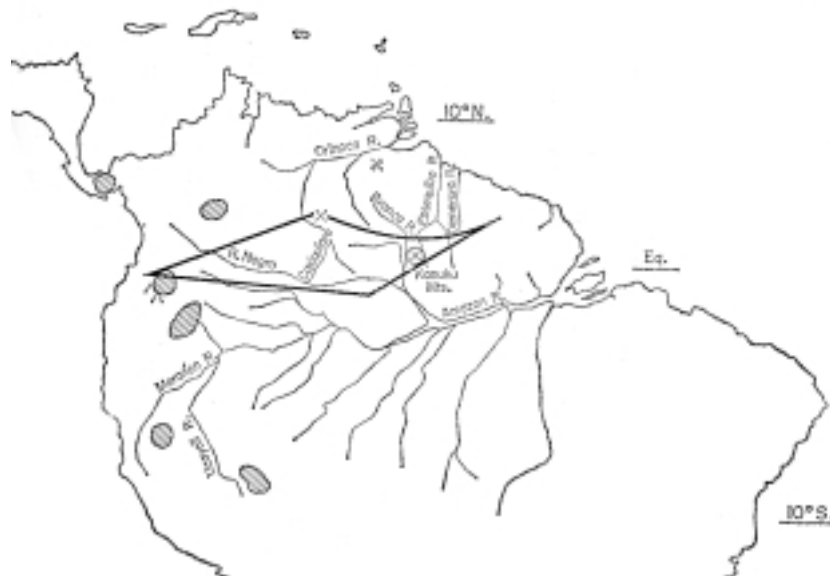


FIGURE 2 The river basins of the Amazon, Orinoco and Essequibo

as we shall see, the Yorkshire naturalist Waterton and the Schomburgk brothers would concentrate their efforts in the first part of the nineteenth century.^{6,7}

Returning to the sixteenth century, the next actor in the unfolding drama was Sir Walter Raleigh (1552–1618) who played, at various times, the role of merchant venturer, poet, and Queen Elizabeth's favourite (or scapegoat). As many were at the time, he was captivated by the idea of the City, or Land, of Gold (El Dorado) and he went with five successive expeditions to the Orinoco (and its tributaries) in his attempts to find the legendary treasure.⁸

The expeditions were generally unsuccessful but Raleigh wrote a book, to boost his prospects of fame and fortune, entitled the *Discovery of the Large Rich and Beautiful Empire of Guiana* (published in 1596). In it he describes El Dorado as being located between the upper reaches of the Amazon and Orinoco rivers on Lake Manoa. The whole thing was of course a total fiction!

In the same volume Raleigh also gives an account of the arrow toxin which also appears to be, in the main, a confabulation. He seems to have confused the effects of curare with those of a putrefying wound. He also claimed that garlic was an antidote. This assertion, together with those of others advocating the use of salt, seawater, sugar, and tobacco were all shown later to be completely erroneous, not to say dangerous!

Ultimately, Raleigh was to suffer both family and personal disaster. In 1617, on his last expedition to the area of the Orinoco, his son was killed by the Spaniards in an ambush (Figure 3). He returned to England a broken man and was subsequently condemned to death for treason and executed in 1618.

The poison remained mysterious for another 300 years and this is reflected in the many names it went by, for example: ourari (Keynes 1596); wourara (Brodie 1811); wouralia (Waterton 1812); and urari (Schomburgk 1841).^{2,3}

FROM CONDAMINE TO WATERTON

From the death of Raleigh in 1618, to the 1750s, the Spaniards and Portuguese maintained their dominance over South America and largely kept out the British, Dutch and French. Then in the mid eighteenth century their hegemony began to break down; it would be smashed finally by Simon Bolivar (and others) in the late part of the eighteenth and the early nineteenth century.

One of the first men to penetrate the secret empires was the Frenchman Charles Marie de la Condamine.⁹ Born in Paris in 1701, he was to die in that city in 1774 after a lifetime spent in energetic scientific pursuit and travel. He journeyed to South America in 1735 where he stayed for ten years. Ostensibly he was to survey an arc



FIGURE 3 Sir Walter Raleigh (1552–1618) and his son Walter who was killed by the Spaniards in Guiana in 1617. (© National Portrait Gallery, London. www.npg.org.uk)

of the earth's meridian but secretly he was seeking to identify the tree that was the source of quinine.¹ He also became involved in the discovery of the Caoutchouc (rubber), the identification of platinum ores and the recognition of the barbasco tree (a source of the poisonous alkaloid rotenone).

When he returned to Europe he also took with him the first good specimens of the 'black pitch', the concentrated extract of curare. It had been claimed by Walter Raleigh that he had brought back similar preparations at an earlier date, but this must now be regarded as extremely doubtful.

Condamine made contact with an Indian tribe called the Yameos, who lived near the confluence of the Manañon and Ucayali rivers and who were particularly skilful in their use of the poison. He described their use of 'blowpipes which would propel wooden arrows up to a distance of 30 to 40 paces to bring down small or large game. The points are covered with a poison so active that it can kill in less than a minute.' When he returned to Europe, he used the 'black pitch' to carry out a famous series of experiments at the University of Leyden in the presence of the distinguished triumvirate of the Professor of Medicine Boerhaave, his pupil van Swieten and the famous anatomist Albinus. Condamine had previously maintained that sugar was an antidote to the poison but he failed to confirm this in the Leyden experiments.

Two investigators now took Condamine's observations further; Brocklesby and Bancroft.^{10, 11} Brocklesby obtained samples of the poison from Condamine and

embarked on a series of experiments in the cat. He was able to show that the heart went on beating for up to two hours following the apparent death of the animal. It was such observations that would lead Brodie and Waterton to consider later the possibility of artificial respiration (see below).

Bancroft on the other hand was to travel in Guiana for a number of years and there he extended Condamine's observations in the field. He considered that the poison produced by the Ticuna tribe was the most potent. Perhaps most important, he described the source of the poison as what he called 'nibbees' or what we would term lianas. They were ligneous cordage of great length and width. In diameter they could range from half an inch to 18 inches.

Bancroft also watched the natives producing the Woorara poison from the bark of the 'nibbee' and recorded the recipe as follows:

Bark of Woorara	6 parts
Bark of Warracouba Coura	2 parts
Bark of Couranabi	1 part
Bark of Baketi	1 part
Bark of Hatchy Baly	1 part.

This mixture was slowly heated and the fluid boiled off until the residue resembled pitch. Then slivers of the Cokarito palm were dipped into the gum and from there smeared onto the arrows.

Slowly, the knowledge was building up by experiment and observation. We now come to three of the great figures in the compelling saga of curare; von Humboldt, Brodie and Waterton. The combined efforts of these three men were to carry knowledge of the arrow poison forward towards the modern scientific era.

Alexander von Humboldt (1769–1859) was the scion of a noble and wealthy house in Germany.¹² He travelled to Paris in 1799 in the hope of joining Napoleon's expedition to Egypt. Unfortunately, he was prevented from doing so by the activities of Nelson and the British Navy. Instead he joined with Aimee Bonpland (1773–1858), a French gentleman of means, and they set off on an epic expedition to Venezuela, Columbia, Ecuador, and Peru. Finally, they returned via Mexico and America to receive high acclaim in Europe.

The two explorers were able to achieve many important tasks together. Their first success was the definite identification of the Casiquiare connection between the Orinoco and the Amazon waterways (see above). They also collected a magnificent total of 6,000 plants and sent regular shipments of these specimens back to Paris.

In Esmeralda, in May 1800, they were allowed to witness the preparation of the arrow poison. Humboldt notes in

his account, entitled a *Personal Narrative*, that this area was the most celebrated location for the fabrication of the active principle. He also describes how the natives used it for 'war, the chase and gastric obstruction'. However, his vital contribution was to identify the plant which was the source of the poison. He became certain that the Ticunas of this area used a variety of *Strychnos*, related to *Strychnos nux vomica* (which had already been described). This plant became known as *Strychnos toxifera* (Figure 1). He also established that the poison was stable if transported in bamboo tubes (hence tube curare) or calabashes. It could be tasted without danger and was an excellent 'stomachic'!

Importantly, Humboldt also recognised that, in different areas of South America, distinct poisons were obtained from diverse plant sources. He concluded his account by stating that he hoped that an alkaloid could be isolated from *Strychnos* one day, in a manner analogous to the work that was proceeding at that time on morphine (from the opium poppy) and strychnine (from *nux vomica*). Little did he know that the instability of tubocurarine would lead to a delay in this essential step which would last for more than 100 years.

The next person to take up the challenge of curare was Benjamin Collins Brodie (1783–1862), a leading English surgeon.¹³ In a series of experiments on poisons he investigated curare, alcohol, almond oil, aconite, and tobacco. He concluded that curare paralysed the muscles of respiration but that the heart continued to beat for some time (thus rediscovering what Brocklesby had noted earlier) and stated also that the brain died because it was perfused with 'dark coloured blood'. He reasoned therefore that if ventilation could be maintained by a tracheostomy together with pumping in air, life could be maintained, and in 1811 he succeeded in doing this in a cat.

Later, he claimed that it was he (and Sewell) who resuscitated the famous donkey, Wouralia (although Waterton disputed it). Certainly it is clear that both Brodie and Waterton had grasped very clearly the concept of artificial respiration in treating poisoning with curare. Wouralia the donkey would live for another 25 years at Waterton's home after her near encounter with death!

We must now turn to Charles Waterton (1783–1865) perhaps the most colourful character to be associated with the long history of curare, and a genuine English eccentric.⁶ A devout Roman Catholic, he was the Squire of Walton Hall near Wakefield in South Yorkshire, England (Figure 4). Debarred from public office on the grounds of his religious affiliation, he nevertheless contributed a great deal to our knowledge of the natural history and the geography of South America. At Walton Hall he set up the first bird sanctuary in England and also, in his private laboratory there, developed greatly the techniques of taxidermy which have proved useful even up to the present day.

His family owned estates in British Guiana and initially he went out to manage these. Following this period he made journeys of exploration between 1804–12. Working particularly in the areas enclosed by the rivers Demerara, Essequibo and Branco he made detailed studies of the flora and fauna. He had wrestling matches with both a boa constrictor and a cayman (crocodile) and survived these and various other dangerous encounters with both natives and animals! These episodes are described in what proved to be a very popular account entitled, *Wanderings in South America* which was to act as a great stimulus to the travellers and scientists who followed.¹⁴

Waterton observed the rituals of the Macusi Indians in the preparation of curare (Wouralia) and obtained samples of the poison in a potent form which he shipped back to Wakefield. Over 100 years later Mogeley obtained some of these from the Leeds University Medical School and showed that they were still active! In fact they had about 10% of the potency of pure tubocurarine chloride. This is a testimony to the acumen of Waterton and the long-lasting stability of the compound when in the form of pitch.¹⁵

The Wouralia poison contained not only the ground up vine (or liana) but also other roots, venomous ants, and the pounded up fangs of the fer-de-lance and bushmaster snakes! Waterton deduced, correctly, that the paralysing poison was the vine (or liana) and that the dose required to kill was proportional to the body weight of the animal. He also described the woods used to manufacture both the arrows and the blowpipe, and how this process was carried out. He derided the



FIGURE 4 Charles Waterton (1782–1865). Portrait by CW Peale. Note the stuffed animals.
(© National Portrait Gallery, London. www.npg.org.uk)

possible use of antidotes, including salt and garlic, and maintained that the only way to combat the poison that had any chance of success was to excise the wound and, if possible, to apply a tight ligature above the area to block the venous return.

When Waterton returned to Yorkshire he continued his interest in Wouralia and proposed that the preparation might be of value in the treatment of hydrophobia (rabies) and lockjaw (tetanus). Unfortunately he was never able to put these ideas into practice. The nearest he got to it was when he rushed to Nottingham to try and save a police sergeant who had been bitten by a rabid dog. He was too late - the policeman died the day before he reached the city. As we shall see, 100 years later, he would prove to be right about tetanus but wrong about rabies. The pathology would show that rabies was a disease of the central nervous system and as such not amenable to a peripheral paralytant.

THE BOTANICAL PROBLEM

After the definitive observations of Humboldt and Waterton in the early 1800s several matters had now become clear:

- 1 There was indeed a powerful paralytic poison used by various different tribes of South American Indians such as the Ticunas and the Macusi.
- 2 The poison seemed to originate in lianas (vines) and possibly vine apples.
- 3 Humboldt had identified *Strychnos toxifera* as one source of the poison but the work of Waterton suggested that there might be others.

This botanical problem would be largely solved by the Schomburgk brothers; Robert and his younger sibling Richard.⁷ They spent many years in the Caribbean and northern part of South America between 1830–50. Robert became perhaps the more famous, as he made a number of important contributions to widely different areas of knowledge.

First of all, he surveyed the boundary between Venezuela and British Guiana which was to become known later as the Schomburgk line. The two brothers also surveyed the upper reaches of the Essequibo in the same area where Waterton had been active 20 years previously. Working with the Urari tribe, Schomburgk was able to confirm the previous account of Humboldt that their poisonous plant was of the genus *Strychnos* from the family Loganiaceae and he named it *Strychnos toxifera* (Figure 1). He also made extracts of *Strychnos toxifera* and satisfied himself that these contained the active poison. Since that time other species of *Strychnos* have been identified including *cogens*, *mitscherlichii*, and *pedunculata*. All these contain curare together with other alkaloids such as calebassine.



FIGURE 5 *Chondrodendron tomentosum*. Ruiz et Pavon 1794.

In comparison with the genus *Strychnos*, the family Menispermaceae has a more restricted geographical distribution, being confined to the Guianas and the Amazon basin. Nine species of the genus *Chondrodendron* have been identified and they produce varying amounts of different sorts of the paralyzing alkaloids.

The first identification of *Chondrodendron tomentosum* was by Hippolyto Ruiz and Joseph Pavon.¹⁶ After their South American expedition of 1793 they brought back several thousand plants for identification and classification. Amongst them was *Chondrodendron tomentosum* (Figure 5). Later on in the twentieth century, King would extract d-tubocurarine from this species of the liana.¹⁷

Other *Chondrodendrons* yield different alkaloids: platyphyllum gives chondrocurare and l-beeberine; microphyllum yields d-beeberine.

THE NINETEENTH CENTURY PHYSIOLOGISTS

From about 1850 onwards, physiology became a discipline in its own right, largely in the German and French medical schools. The early studies of Orfila in Paris also stimulated the science of toxicology.

A major influence on both physiology (and curare) was the work of Claude Bernard (1813–78) (Figure 6). His work included important studies on gastric secretion (1844), the glycogenic properties of the liver (1849) and the effects of the sympathetic nervous system on vascular control (1851). He was also the first to realise the importance of the 'milieu intérieur' or, as



FIGURE 6 Claude Bernard (1813–78). Performed defining experiments on the action of curare.

we would say now, the internal environment of the mammalian body. This idea presaged the idea of homeostasis, perhaps one of the central concepts of animal physiology.

In 1855, Bernard succeeded to the Chair of Physiology at the College de France. Having obtained samples of curare from Goudot he embarked on a long series of experiments.¹⁸ The results can be summarised as follows:

- 1 Entry to the blood stream is necessary for the action of the poison.
- 2 Absorption of curare by the stomach and intestine is poor and variable.
- 3 Curare is a crystalloid and will pass through a semipermeable membrane by dialysis.
- 4 Death is caused by respiratory failure without convulsions and without pain. The heart continues to beat long after respiration ceases. Revival will occur if artificial respiration is maintained for a long period.
- 5 The essential action of the poison is on the motor nerves while the sensory nerves remain unaffected.
- 6 The voluntary nerves of the extremities are the most sensitive to the poison; followed by those of the thoracic muscles; and then by the phrenic nerves to the diaphragm.
- 7 Curare and strychnine have their actions at different sites: curare peripherally, strychnine centrally.
- 8 Both the sciatic nerve and the gastrocnemius muscle retain their ability to function after the poison is applied. Therefore the site of action must lie in the junctional area between the two.¹⁸

This is a marvellous summary of the properties of curare, but Bernard was at a loss to explain and understand the structure and function of the junctional area. It would take the work of Del Castillo and Katz³⁴ to demonstrate that there were packets of a transmitter substance present in the motor nerve end plate and that these were jumped across the gap to activate the myofibrils beyond. As we shall see below, the chemical transmitter would prove to be acetylcholine, and curare would be shown to block the effect of this messenger compound. We must now divert to a bizarre political episode during the First World War.

KILL THE PRIME MINISTER: WE'LL HANG LLOYD GEORGE ON A SOUR APPLE TREE!

Political assassination in the UK is a rare occurrence indeed. The most notable exceptions were when the Duke of Buckingham was killed by a disaffected soldier in 1628 and when, in 1812, Spencer Perceval was killed by Bellingham in the House of Commons.

During the First World War, a bizarre plot emerged to kill both Lloyd George (the Prime Minister) (Figure 7) and Arthur Henderson (the Paymaster General). The plot revolved around a Mrs Wheeldon, her two daughters, and a son-in-law called Mason who owned a chemist's shop in Southampton. One daughter lived with Mrs Wheeldon in Derby and acted as a go-between, the other daughter was married to Mason and lived on the south coast.

The group as a whole were typical Adullamites – conscientious objectors, disgruntled with the war and annoyed with the political system as a whole. Unfortunately they allowed their dissident group to be infiltrated by one 'Gordon' and he became aware that they were hatching a plot to murder the two prominent politicians.



FIGURE 7 David Lloyd George (1863–1945). Prime Minister during the First World War. A target for assassination!

'Gordon' informed the Head of Intelligence, Major Melville Lee, who promptly sent a second secret agent, Herbert Booth, to Derby in the hope of gaining further information. He was able to ingratiate himself with the plotters and was rapidly taken into the group as a co-conspirator. He was given an airgun together with pellets and darts that had been dipped in curare. Armed with this potentially lethal weapon, he was instructed to hide on Walton Heath Golf Course in Surrey, and there to ambush the Prime Minister!

Mr Mason also sent a parcel to Booth in Derby which contained two tubes of strychnine and two of curare. All this material was handed over by the Secret Service to Bernard Spilsbury, the famous pathologist.¹⁹ He identified both the poisons and gave his opinion that there was enough curare to kill several individuals. Interestingly he refers in his notes to Waterton's *Wanderings in South America*.

As a result of all this evidence, the four conspirators were brought to trial. The plotters' defence was that they intended to use the curare to kill (or disable) guard dogs. The Attorney General, FE Smith (later Lord Birkenhead) disposed of this argument with relish and the jury decided that three of the accused were guilty. Mrs Wheeldon received a sentence of ten years, Mr Mason, seven, and Mrs Mason, five. The go-between (Mrs Wheeldon's other daughter) was acquitted.

Was the plot feasible? Perhaps. However strychnine would seem in some ways a more powerful threat than curare if Lloyd George's domestic servants could have been suborned. Certainly the chances of hitting Lloyd George with a poison dart would seem somewhat unlikely whether at Walton Heath or elsewhere.

As a footnote to this bizarre plot we should mention that doctors have been accused of having used curare to murder patients. Of course physicians can obtain the poison relatively easily and their actions can be difficult to detect.

THE END OF THE BEGINNING

In 1918, at the end of the war, curare was still regarded as a mysterious, devilish substance. Progress would now be relatively rapid over the next 20 years, and would in that time identify the chemical nature of the poison and how it worked on the natural transmitter at the myoneural junction.

Help at first came at a tangent, as is often the case! It was known that if the Vagus (or 12th cranial) nerve was stimulated, then the heart would slow. It was postulated that a substance was being released at the cardiac nerve endings by such stimulation and this came to be known as the Vagus substance. Otto Loewi was to largely solve this problem.²⁰

Previously, in 1914, Sir Henry Dale²¹ had suggested that the transmitter substance for the parasympathetic nervous system could be an ester of choline, perhaps acetylcholine. This choline ester might have the so called muscarinic actions on the heart and nicotinic actions on skeletal muscle.

Loewi now set up his famous two heart preparation and showed that when the first heart was slowed by stimulation of the vagus nerve, a substance was released which, if it were passed into the perfusion fluid of the second heart, proceeded to slow its rate. This effect could be antagonised by atropine, a recognised blocker of the muscarinic effect. After a long series of experiments, he concluded that the Vagus substance was likely to be a choline ester, probably acetylcholine, as Dale had suggested ten years earlier, because its breakdown could be prevented by the alkaloid physostigmine, the natural poison derived from the Calabar bean (*Physostigma venenosum*).²⁰

Moreover, in high dose, acetylcholine could produce a block of skeletal muscle activity (transmission) similar to that produced by curare. The stage was set by Loewi's experiments. Was the natural nicotinic transmitter at the myoneural junction acetylcholine and could its effect be blocked by curare? Help was to come from an unexpected direction – namely a less well known hospital in London; St Alfege's, Greenwich. Dr Mary Walker worked at this hospital as a physician, and had developed a particular interest in the rare neurological illness myasthenia gravis.²² She became convinced that the ptosis, double vision, and muscular weakness, manifest in this disorder, reflected the fact that there was an endogenous curare-like substance circulating in the blood of these patients. She was also aware of two other pointers. First, that patients with myasthenia were exquisitely sensitive to minute doses of impure curare and also, that Pal had shown at the turn of the century that, in animals, physostigmine could antagonise (or reverse) the effects of the alkaloid.²³ She determined, therefore, to see if physostigmine would improve the condition of patients with myasthenia.

The effects were nothing short of dramatic and came to be known as the 'miracle at St Alfege's!' Patients responded to doses of physostigmine of the order of 1–2 mg with sustained improvement in both their vision and their muscular power. Control injections of water, pilocarpine, strychnine, ephedrine, and acetylcholine had no effect. Physostigmine given by mouth was much less effective than that given by injection.²² Walker argued that physostigmine acted as an anticholinesterase at the myoneural junction as it had been shown to do at the cardiac nerve endings (see Loewi above). This pioneer work had two main consequences. First, it paved the way for the use of anticholinesterases in the treatment and diagnosis of myasthenia gravis (neostigmine and edrophonium respectively). Second, neostigmine would prove very

useful as the agent used to reverse the effect of tubocurarine in surgical procedures (see below).

Walker's hypothesis that there was an excess of a circulating curariform substance in myasthenia gravis we now know to be wrong. In fact autoantibodies are produced which attack the acetylcholine receptor. These antibodies can either be removed by plasmapheresis or their production by the T lymphocytes inhibited by glucocorticoids. Nevertheless her serendipitous observations in 1934 were soon backed up by other developments in the next few years.

In 1936, Dale, Feldberg and Vogt²⁴ showed in their important and decisive paper that stimulation of the motor nerve fibres of voluntary muscle releases acetylcholine at the myoneural junction and that when transmission is prevented by 'curarine' stimulation of the nerve causes the release of the usual amount of acetylcholine. So the impasse had been overcome – acetylcholine was indeed the 'nicotinic' transmitter at the myoneural junction.²⁵

Within short order the chemical problem of the nature of 'curarine' would also be solved. Throughout the 1930s, King had been working on a form of curare known in Europe as the *Radix pareirae bravae* (literally, the effective root) which had been used by mouth for 70 years in rheumatic diseases and urinary tract complaints. This was largely made up of *Chondrodendron tomentosum* although it almost certainly contained other species of *Chondrodendron*.

King showed first that *Radix* contained an alkaloid bebeerine and, on methylation, this compound yielded an isomer of d-tubocurarine.¹⁷ However, different preparations of *Radix* gave rise to distinct alkaloids for example *Chondrodendron platyphyllum* yielded l-bebeerine whereas *Chondrodendron microphyllum* gave rise to the dextroisomer d-bebeerine.

King's major success was when, in 1935, he isolated pure d-tubocurarine from a curare specimen (Figure 8).¹⁷ He concluded that some preparations of *Radix* did contain

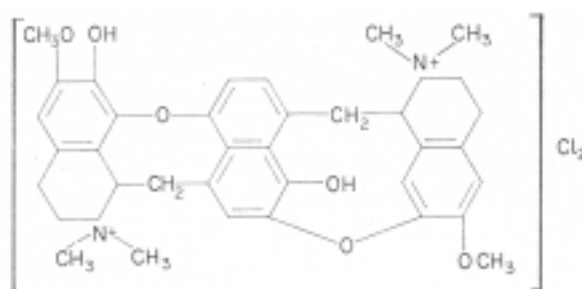


FIGURE 8 The chemical structure of d-tubocurarine chloride (after King 1940).

this alkaloid derived from *Chondrodendron tomentosum*. The final achievement was by Wintersteiner and Dutcher in 1943 at Harvard University; they were able to extract pure d-tubocurarine from a known specimen of *Chondrodendron tomentosum*.²⁵ The work of the Harvard group was the finishing post in the long path from the Indian tribes to the ultimate scientific goal!

It subsequently transpired that the d-isomer of tubocurarine has a marked effect on transmission in the rat phrenic nerve diaphragm preparation, whereas the laevo-isomer is only weakly active – yet another example of stereospecific selectivity.

In the 1930s, Richard Gill had brought back to North America 26 different species of liana from Ecuador which he had collected from the Jivaros and Quechia tribes.²⁶ One of his specimens of tomentosum provided the first curare extract to be produced commercially for use in the clinical sphere. This became known as Intocostrin and was marketed by Squibb Inc. of New Jersey as an Unauthenticated Extract of Curare!

THE CLINICAL USES OF CURARE

Intocostrin (Squibb) became available for the first time in the late 1930s. The questions arose immediately; how could it be employed in clinical medicine, and would it prove to be safe? After all it was a mixed extract of quaternary alkaloids, although the main constituent was thought to be King's newly recognised d-tubocurarine. Each batch had to be standardised by the biological assay of the rabbit head-drop test but different batches were later shown to vary widely in their content of tubocurarine.

Late in the 1930s, McIntyre suggested to Bennett, the psychiatrist, that he should try Intocostrin as an adjunct in electroconvulsive therapy.²⁷ At that time metrazol (also known as leptazole BP and Cardiazol) was used to produce convulsions in severely depressed or schizophrenic patients. The terrifying tetanic seizures produced by the drug could cause fractures (and dislocations) as undesirable side-effects.

It soon became apparent that the use of Intocostrin, prior to convulsion, reduced the fracture/dislocation rate substantially whereas the effects on the electroencephalogram and the clinical response to therapy were not affected. Only a minority of patients required either prostigmine (the anticholinesterase) for reversal or artificial respiration. Other relaxant drugs were also examined as modifiers of electroconvulsive therapy including Beta-erythroidin derived from the seeds of *Erythrina americana*. Mill.²⁸

By 1943, Cummins was able to report on more than 3,000 patients in whom Intocostrin had been used to modify drug-induced convulsions.²⁹ Eventually the drug method

would be replaced by electroshock which was easier to standardise and control. A short-acting barbiturate, pentothal, was also used to anaesthetise the patient for a brief period to reduce the adverse experience.

The next step heralded a revolution in surgical anaesthesia. In July 1942, Harold Griffith and Enid Johnson of Montreal, in a short paper in *Anaesthesiology*, barely three pages long, reported that they had used Intocostrin in a series of 25 patients. They had anaesthetised the subjects with cyclopropane and found that this combination was safe and effective.³⁰ At the same time, the work on the pure alkaloid by the Harvard Group allowed Burroughs Wellcome to produce a safer preparation than Intocostrin, and rapid progress was made. Indeed as one journal put it the 'fantastic idea' had come to fruition! In the UK, immediately after the war ended in 1945, Gray and his colleagues embraced the use of tubocurarine enthusiastically, and by 1947 they had used it in a large series of 8,500 patients with no attributable deaths.³¹

Generally, d-tubocurarine appeared to be very safe if combined with endotracheal intubation. Occasionally bronchospasm proved a problem, and this was thought to be due to histamine release. This complication appeared to be more common with Intocostrin as compared with d-tubocurarine. In the 1940s, tubocurarine use became a standard part of surgical anaesthesia and this would last until the 1980s when atracurium, pancuronium and vecuronium came upon the scene.

The final development for curare was its use in the management of tetanus and status epilepticus.^{32, 33} Waterton had forecast in the 1830s that it might prove useful in tetanus but it would take another 100 years to prove his point, and it had to be combined with barbiturate anaesthesia, endotracheal intubation and pharyngeal toilet. The use of tubocurarine in status epilepticus bears some analogy to the situation in the induced convulsions of electro-shock therapy.³⁴

FINAL THOUGHTS

Looking back at the story of curare, there are a number of striking questions. The first is how did the American Indians discover the arrow poison? Presumably this all happened by trial and error. The next intriguing phenomenon was that those who knew the arcane secret were given the power and status of medicine men. They obviously recognised the danger inherent in the preparation of the poison and for that reason women (and particularly menstruating women) were regarded as potentially unclean and had to be excluded from the process!

The Spanish Conquest was both brutal and oppressive, yet out of it came curare, quinine, tobacco, and the potato which were definite ameliorating features. However, progress was then held up for about 200 years until the

gentlemen explorers like de la Condamine, Humboldt, and Waterton had the funds and time to spend years in the rain forests. They also needed the expertise to recognise the plants, and the drive to bring back active preparations of curare to Europe.

Then came the scientific revolution in the nineteenth and twentieth centuries, led first by the physiologists under Bernard, and followed by the chemists spearheaded by King. The isolation, characterisation and synthesis of d-tubocurarine in the 1930s were of course the defining developments which set the modern scientific scene.

The plot to murder Lloyd George is an interesting and bizarre aside in the story of the arrow poison. Perhaps we should not laugh it off in these present days of national and international terrorism. In recent years biological

poisons, such as ricin and physostigmine, have been used to commit murder. With modern firearm systems, it would be much easier to deliver a lethal charge of curare or a similar paralysing poison, and by the time the nature of the wound had been realised it could be too late. If ricin can be used as a successful agent for murder, as with Georgi Markov, then curare surely can!

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