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FIFTH W.D.M. PATON MEMORIAL LECTURE

Waterton and Wouralia†

*,[1]A.T. Birmingham

[1]Department of Physiology and Pharmacology, Medical School, University of Nottingham NG7 2UH, England

It is for me a neat coincidence that this Winter meeting of the British Pharmacological Society is being held in Harrogate, Yorkshire because the story I wish to tell you involves a Yorkshire Squire; it also involves Nottingham, where I come from and it leads on to some pharmacological contributions from Bill Paton.

I am especially pleased and honoured to be giving a W.D.M. Paton Memorial Lecture because apart from admiring him for his scientific contributions I also had the privilege of working with him on some Society matters. I prefer this photo of Bill (Figure 1) to the more formal portraits because it shows him as we remember him at meetings. Incidentally, he was always Bill, never William, until he became Sir William in 1978.

My story begins about 200 years ago, in the late 1790s, when a young boy was being brought up in a large country house just south of Wakefield, Yorkshire; in fact about 25 miles south of where we are in Harrogate. The house, Walton Hall, was the local manor and his father was the Squire, who was a pioneer canal builder and parkland improver. With his brothers, the Squire had also invested in some sugar plantations in Demerara, South America. The house was built (1767–1768) on an island in a large lake and was connected to the mainland by a cast iron bridge (Figure 2). The rest of the estate covered over 900 acres of woodland and parkland and the young boy early developed an interest in natural history and spent many hours studying the birds and animals around his home. At the age of 10 he was sent away to school and in 1796 when he was 14 he went on to Stoneyhurst, a Catholic boarding school which had been founded 2 years before. Apparently by then he was already a bit of a daredevil. He was often absent on bird-nesting expeditions and was appointed rat-catcher and fox-taker to the school. The headmaster caught him climbing the face of a tower in search of a jackdaw and ordered him down just before a large chunk of masonry fell. Then in later years as a young man when (as a devout Catholic) he was on a visit to Rome, he climbed to the top of a lightning conductor of St Peter's and climbed a tower in the Vatican and hung his gloves up there as proof. The Pope asked him to remove them so he climbed the tower again. The man I am talking about was Charles Waterton, the first-born son of the Squire of Walton Hall (Figure 3).

Now, whilst he had been a schoolboy, an event occurred which was to have a profound effect on him. He was bitten by a cat a few days after a young man in a neighbouring village had died from hydrophobia (what we nowadays call rabies) having also been bitten by a cat. Rabies was of course endemic in England at that time and our young boy, although he kept his fears to himself, was for many months afterwards convinced he was going to die raving mad. This experience

Figure 1 Professor Sir William Paton, FRS (1917–1993). (By courtesy of the Wellcome Institute Library, London).

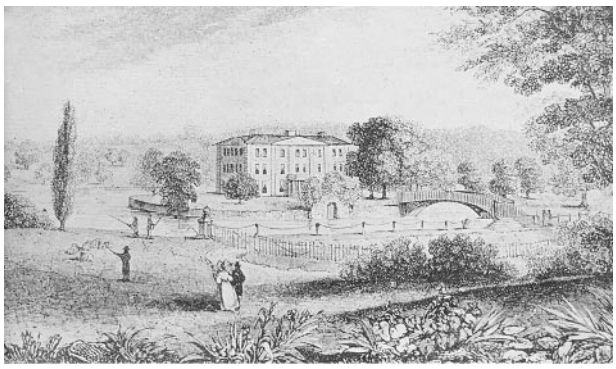

Figure 2 Walton Hall, Walton, Near Wakefield, Yorkshire, England. (Reproduced from Waterton's "Wanderings in South America" 1906 Edition).

*Author for correspondence.
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sowed the seed for a preoccupation with hydrophobia he had for the rest of his life, as we shall see.

After he left school, he stayed briefly with some uncles in Spain and then set off in 1804 to visit and help to manage the family sugar estates in South America. He sailed from Portsmouth at the end of November. The crossing took 6 weeks and he landed at Stabroek in what was then Dutch-owned Surinam, but became Georgetown in British Guiana in 1814 (now independent as Guyana).

Charles Waterton was to spend the next 20 years living within the region of the Amazonian rain forests which gave him a wonderful opportunity to indulge his interest in natural history and the collection of specimens of birds and animals. Over the years he made four expeditions up the rivers Demerara and Essequibo to collect specimens. He developed his own methods of taxidermy and preservation of specimens for display. Before he left England for South America in 1804 he had, on his way to Portsmouth, stopped off in London and dined with Sir Joseph Banks, the famous explorer and naturalist (who had been the leader of the scientific expedition on Captain Cook's barque 'Endeavour' during the exploration of the South Pacific 1768–1771, and was President of the Royal Society from 1778). During their meeting they had discussed the collection of specimens and Sir Joseph Banks knew Waterton would be interested in the stories of the special poison that the Amazonian tribes used to tip their arrows to immobilize and kill their prey for easier retrieval in the dense forest. Reports were reaching Europe from the 1770s to the early 1800s and samples of the poison were being studied. Sir Joseph encouraged Waterton to collect some samples during his stay in South America and to find out if it would work on larger animals as well as on small prey. As an experienced traveller in the tropics Banks also advised Waterton to return home to England at least every 3 years for rest and recuperation. Waterton certainly followed this advice, for by 1819 he was making his ninth crossing of the Atlantic! The significance of this is that Waterton would have been back in England around the time when Benjamin Brodie was reporting in February 1811 to the Royal Society that he had studied a sample of the South American arrow poison (which he called woorara) and had shown that if he regularly inflated the lungs of the poisoned animal (he used rabbits and cats) the heart would continue beating and the animal would recover. In view of the immobilizing effect of the poison he also later (1812) made the suggestion that it might be useful in the medical management of 'spasmodic convulsive disorders' such as tetanus and hydrophobia.

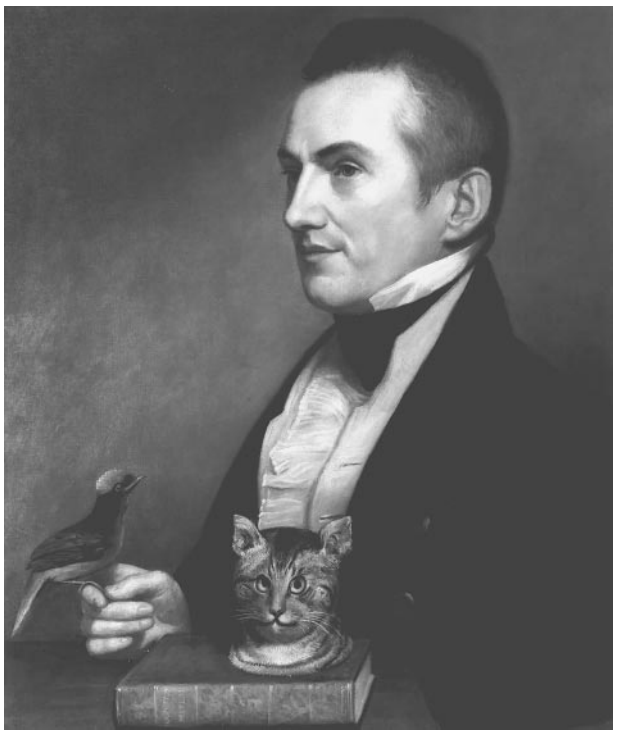

Figure 3 Charles Waterton (1782–1865) painted by C.W. Peale in Philadelphia, USA, in 1824. (By courtesy of the National Portrait Gallery, London).

It seems likely that Waterton knew of Brodie's work and would have been especially intrigued by the mention of hydrophobia and would have been reminded of Banks' query about the efficacy of the poison in large animals. So, when he was back in Demerara he set off in 1812 on an expedition into the rain forest, as he later wrote, 'the chief object of which was to collect a quantity of the strongest wourali poison'. You will notice that whereas Brodie had called the poison woorara, Waterton called it wourali; in fact there were at various times about 20 different but similar-sounding names which seem to have been European attempts to render the Amazonian native word *uirary* which in their languages meant *uira*, a bird, and *ary*, to kill. The version of the word which later became generally accepted in Europe was of course curare.

Now Waterton had heard that the strongest, most sought-after wourali was made by the Macushi tribe in the south of Guiana near the border of Brazil. He set off with a canoe and six natives and like them he travelled barefoot and they journeyed some 400 miles, at the start of the rainy season. They travelled up the Demerara and then the Essequibo rivers (Figure 4). He collected samples of wourali at three points, the last from the Macushi at the village of Pirara. While he was with the Macushi tribe he gradually persuaded them to show him how they collected the ingredients and how they made the poison. It was not easy to persuade them as they usually made the poison in secret and with mysterious ceremony. It became clear to Waterton that the main ingredient was a vine they called *urari*. They cut the bark of the vine into shavings and made an aqueous extract, then added various other ingredients and concentrated the mixture by evaporation over a fire in a hut in great secrecy and ceremony. There were over the years many attempts to discover the botanical constituents and to witness the preparation but probably only Waterton in 1812 and Robert Schomburgk between 1838 and 1841 were successful with the Macushi. Schomburgk was a trained botanist and identified the vine as one of the *Strychnos* species and gave it the now accepted name *Strychnos toxifera* (Figure 5). It is clear that *Strychnos toxifera* was quantitatively the main ingredient; the other, muramu, was there to thicken the concentrated liquor. The consistency was important because it had to stick and dry onto the tips of darts and arrows.

Waterton brought back some wourali and poison-tipped arrows from his 1812 sojourn with the Macushi (Figure 6). The arrows were made from palm leaf stems and a quiver would contain five to six hundred in a roll. The small arrow was shot from a blowpipe and the seal in the pipe was made with a plug of wild cotton around the stem of the arrow. A supply of cotton was kept in a small wicker basket. A larger poison-tipped arrow would be shot with a bow for large game. Because the hunting was in a dense forest and the game mostly high up in the branches above, the requirement was for the poison to take effect in less than 3 min to keep the prey within sight and retrieving distance. Given the need to know that a batch of poison was satisfactorily potent it is not surprising to

learn that the natives invented their own bioassay. As the evaporation and concentration proceeded they would from time to time dip an arrow into the juice and try it on live game. When it was sufficiently strong it was poured into a small earthen pot or into a gourd, the dried fruit case of a plant. When he had collected his own wourali samples Charles Waterton made his own trials of their effectiveness by inoculating several birds and small mammals with the poison and he noted that it 'manifests itself by an apparent unwillingness of the bird to move'. But true to his commitment to Sir Joseph Banks he tried it on large animals including a 560-pound ox which needed the poison from three arrows to kill it so he concluded that the dose needs to be adjusted to the size of the animal. He also remarked that his flesh was 'very sweet and savoury at dinner' thus confirming what the natives obviously knew already, that you could safely eat prey that had been killed by wourali.

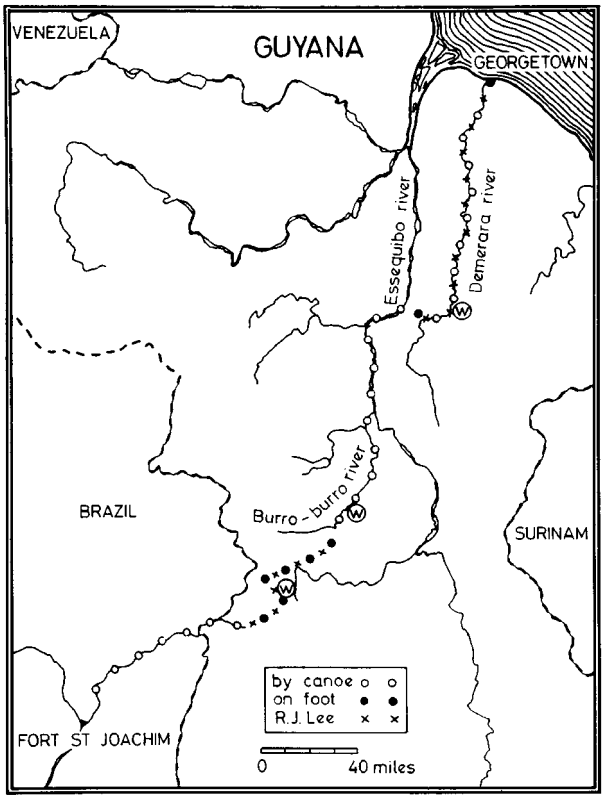

Figure 4 Charles Waterton's route from Georgetown to Fort St. Joachim in 1812. The three encircled W's indicate the approximate sources of his Wourali. (Reproduced from Smith, W.D.A., *Br. J. of Anaesth.*, (1983), **55,** 222, with permission from the BMJ Publishing Group).

Urari, bark (*Strychnos toxifera*)	2 lb
Arimaru, bark (*Strychnos cogens*)	$^1/_4$ lb
Tarireng (not identified)	$^1/_4$ lb
Yakki (*Strychnos bredemeyeri* (*S. pedunculata*))	$^1/_4$ lb
Wakarimo (unidentified)	$^1/_4$ lb
Tararemu, from the root of the *tarireng* vine	$^1/_2$ oz
Muramu, bulbous root soaked in the half-cooked poison and the mucilage squeezed from it to thicken the poison (*Cissus* sp.?)	$1^1/_4$ lb
Manuca, very bitter bark of a large tree (*Zanthoxylum* sp.?)	4 small pieces

Figure 5 Robert Schomburgk's list of the main ingredients of Macushi Wourali. (Reproduced from Bisset, N.G., *J. Ethnopharmacol.* (1992), **36,** 20, with permission from Elsevier Science Ireland).

In 1813, the year following his expedition to collect the most potent Macushi wourali, Waterton was back in England on one of his many return visits and duly reported to Sir Joseph his findings on large animals. Now, Sir Joseph Banks and Benjamin Brodie were both associated with the Royal Veterinary College which at that time concentrated on horses and large farm animals and its director was Professor William Sewell. One day in 1814 these three invited Waterton to bring some wourali to the Veterinary College so that they could all take their interests further. Brodie had already shown 3 years earlier that you could revive small mammals from woorara poisoning by artificial respiration, Banks and Sewell were interested in its effect in large mammals and they all thought it might have a place in the management of the convulsive disorders, tetanus and hydrophobia. Three asses were procured and they did three rather well-planned experiments. One ass was innoculated in the shoulder and it died within 12 min. On the second ass a tourniquet was applied around the upper part of a foreleg and wourali was inoculated below it. The donkey walked about as usual and ate his food, then after an hour the tourniquet was released and the donkey died within 10 min. That showed that the poison needed to gain access to the general circulation to be effective. The third ass, bought from a sweep, was a female and here is Waterton's own account of her fate:

> 'A she-ass received the wourali poison in the shoulder and died apparently in ten minutes. An incision was made in its windpipe, and through it the lungs were regularly inflated for two hours with a pair of bellows. Suspended animation returned. The ass held up her head and looked around; but the inflating being discontinued, she sunk once more in apparent death. The artificial breathing was immediately recommenced and continued without intermission for two hours more. This saved the ass from final dissolution; she rose up, and walked about; she seemed neither in agitation nor in pain. The wound, through which the poison entered, was healed without difficulty. Her constitution, however, was so severely affected, that it was long a doubt if ever she would be well again. She looked lean and sickly for above a year, but began to mend the spring after, and by Midsummer became fat and frisky . . . the kind hearted reader will rejoice on learning that Earl Percy, pitying her misfortunes, sent her down from London to Walton Hall, near Wakefield. There she goes by the name of Wouralia. Wouralia shall be sheltered from the wintry storm; and when the summer comes she shall feed in the finest pasture. No burden shall be placed on her and she shall end her days in peace.'

In fact she lived another 25 years and breathed her last on 15th February 1839. She even had her obituary published in the St James's Chronicle, a paper local to Leeds and Wakefield.

The successful outcome of artificial respiration on wourali poisoning confirmed the beliefs of the experimenters that wourali should be considered for the management of hydrophobia and tetanus. Indeed, Professor Sewell said that if he were ever to suffer hydrophobia he hoped his physicians

would consider the use of wourali. Waterton was also impressed and later wrote that

> 'Several . . . scientific gentlemen . . . are of the opinion that wourali . . . would prove useful in cases of hydrophobia and locked jaw' and that he 'would perform the operation . . . providing the attending medical gentlemen . . . consider the case . . . hopeless. Under the circumstances Mr Waterton could do the needful with a steady hand; should his attempt prove ineffectual, he would not feel daunted were he called upon to take his trial at York for a cool and deliberate act of manslaughter.'

Little did he realise that one day he would be taken at his word.

Our story now moves to Nottingham and to the Nottingham General Hospital which had been opened in 1782, the year of Waterton's birth, with 44 beds serving a population of 25,000. By its 50th anniversary in 1832, it had expanded to 70 beds (Jacob, 1951).

On 5th February 1839, just before midnight, Mr Isaac Phelps, a police inspector, was on duty near the city centre of Nottingham when he heard a dog whining. He found the dog to be at the bottom of a hole in the road which had been dug for a large weighing machine. He obtained a ladder and brought the dog to the surface, whereupon the dog bit him on the nose and ran off. The bite was cauterized by a surgeon, the wound healed quickly and he remained in good health until 22nd March some 7 weeks later. He then began to experience some spasmodic twitchings around the nose and mouth and became increasingly unwell over the next 3 days, including attacks of giddiness and difficulty in swallowing fluids. He was admitted to the General Hospital where hydrophobia was diagnosed. One of the doctors had read of Waterton and the suggestion of the use of wourali and it was proposed that he be sent for. Now Walton Hall, where Charles Waterton was the Squire, and where he had lived since his final return to England in 1824, was about 50 miles, as the crow flies, north of the centre of Nottingham and the General Hospital. So in 1839 it would have taken many hours for the urgent message to reach Waterton and for him to reach the hospital. He arrived only to learn that the patient had died 6 h earlier.

Figure 6 Waterton's label for his collection 'Quiver with poisoned arrows for the blow pipe from Guiana 1812' (Photograph reproduced with permission from Wakefield M.D.C. Museums & Arts).

Although he arrived too late to help Phelps, it was arranged that Waterton should stay on and demonstrate the action of wourali to the Nottingham doctors. To meet the requirements of the Apothecaries Act of 1815, there was an Apothecaries' Medical School within the General Hospital and the resident Surgeon-Apothecary from 1825 was Mr Francis Sibson. Waterton and Sibson used a dog and two asses to demonstrate the effects of wourali and the effectiveness of artificial respiration. The two asses each received the poison in a shoulder. Sibson with four assistants applied artificial respiration 16–18 times a minute through bellows inserted into the trachea, for 7.50 h in one ass and 2 h in the other. Both recovered. It was said that 'Between the hours of 4 and 5 in the afternoon the second ass was so much recovered as to be able to carry Mr Waterton around the room'. The doctors were convinced of the possibility of the use of wourali in hydrophobia and lockjaw. More than a century after these events one of the wards at Nottingham General Hospital was named Waterton Ward; it commemorated Nottingham's brief association with a remarkable man, a true nineteenth century eccentric. After his first expedition in 1812 he went on further expeditions and travels to indulge his chief interest which was wildlife and he became a celebrated natural historian of his day, especially good at preserving his own specimens by his own method of taxidermy. He wrote of his travels and experiences in a book entitled 'Wanderings in South America' (1825) which went to many editions and reprints, the last as recent as 1973 by Oxford University Press. He also wrote 'Essays on Natural History' (1838) which included an autobiography. The last edition was dated 1857.

Charles Waterton died in 1865 at the age of 83 but interest in the potential use of wourali (curare) in the management of rabies continued for years. For example, an Annotation in 'The Lancet' of 30th March 1878 referred to some 'late outbreaks of hydrophobia . . . [and] . . . a recent occurrence at Windlesham near Bagshot where a rabid dog succeeded in biting five persons'. The author believed that 'It is most desirable that, if any cases occur, a thorough trial of curara should be made . . . this supposed remedy does not seem to have been tried in any case in this country since its alleged effects became known. No doubt this is in part due to the difficulties which attend its efficient use'. The reason doctors had been reluctant to use curare in the management of convulsive disorders, in addition to the problem of lack of standardisation between samples, was that artificial ventilation was not an established procedure. But a drug company eventually produced a product, presumably standardised by bioassay, probably on frogs. From 1887 the Burroughs Wellcome catalogue listed under its 'Tabloids' brand name, tablets of curare at 1/12 grain (price 8 shillings) for use in preparing a solution for hypodermic injection. It is unlikely that it was ever used in man.

When Waterton ceased his 'Wanderings' he devoted his energies to establishing and cataloguing his collection as a museum at Walton Hall. He had succeeded to the squiredom on the death of his father in 1805; he owned the estate for 60 years. He built a wall around the estate and allowed no guns to be fired within it. The Waterton family sold the estate in 1878 and after many changes of resident, including a period as a maternity hospital, it has since 1970 been much restored and opened as a country club. Waterton left his collection to his old school Stoneyhurst and it is now cared for and on display at Wakefield City Museum near Walton Hall.

1982 was of course the 200th anniversary of Charles Waterton's birth and the Yorkshire Society of Anaesthetists held a Symposium at Walton Hall to commemorate his

contributions to natural history and taxidermy and to the early history of curare. Part of the Symposium was organised by Dr W.D.A. Smith and Dr F.R. Ellis of the Department of Anaesthesia, Leeds University. One of the papers read at the meeting presented the results of a modern analysis and bioassay of samples of Waterton's 1812 wourali (from a small piece of resin and scrapings from the tips of three arrows) now kept at Wakefield City Museum. On the rat isolated phrenic nerve-diaphragm preparation, the extract was still a fully potent reversible neuromuscular blocking agent. Chemical analysis revealed that the activity was not due to the presence of d-tubocurarine. Tubocurarine was isolated in 1935 by Harold King from a sample of tube curare from the Pharmaceutical Society's museum. It was known that the vine used for curares, stored in bamboo tubes, was not *Strychnos toxifera* but a different species *Chondrodendron tomentosum* and tube curares came not from the eastern Amazon forests explored by Waterton but from the more western parts of Brazil and Peru. Harold King later turned his attention to the *Strychnos toxifera* vine and showed the active principle to be toxiferine, which had also been isolated from calabash curares by Wieland *et al*. (1937). Harold King was a celebrated analytical chemist working at the National Institute for Medical Research in London and when he needed some pharmacological testing of the 12 alkaloids he had isolated, he asked a young colleague working in a nearby laboratory, one Dr W.D.M. Paton. Using the frog ED_{50} and the rabbit head drop tests Paton showed toxiferine I chloride to be the most potent of the alkaloids (and this to be some 200 times more potent than d-tubocurarine chloride). Paton published a review article on the pharmacology of curarising substances in the same year (1949) and I suspect it was the chance request from King that stimulated Bill Paton's long term interest in and subsequent major contributions to the field of neuromuscular blockade. The definitive study on the pharmacology of the toxiferines was published in 1951 by Paton and another of his colleagues at the National Institute, Walter Perry.

By this time, the 1950s, tubocurarine was becoming established as an adjunct to surgical anaesthesia (McIntyre, 1947) and naturally the question arose as to the possible place of toxiferine in anaesthetic practice. Waser & Harbeck 1959 and Foldes *et al*., 1961 studied it in patients. It was found to be perfectly effective and many times more potent than tubocurarine but there was already an indication of what proved to be its major disadvantage, namely a much longer duration of effect, but like tubocurarine it was readily reversible with an anti-cholinesterase.

But wourali lived on! The chemists at Roche Laboratories reduced the duration of action of toxiferine I by producing the diallyl nor-derivative and it was introduced into clinical practice as alcuronium. (Lund & Stovner, 1962). The Squire of Walton Hall would have been pleased.

I record my indebtedness to Dr Denis Smith who encouraged my interest in Charles Waterton, by his own researches and by inviting me to attend the Symposium in 1982.

I thank Miss S.J.A. Flynn, Archivist (Historical Records) at Glaxo Wellcome for finding the reference to 'Tabloid' curare tablets in past Burroughs Wellcome catalogues.

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