

The first use of physostigmine in the treatment of atropine poisoning¹

A translation of Kleinwächter's paper entitled 'Observations on the effect of Calabar bean extract as an antidote to atropine poisoning'

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<http://www.nickalls.org/dick/papers/anes/physostigmine1988.pdf>

Abstract

This paper describes a clinical experiment performed by Drs Kleinwächter and Niemetschek in Prague in 1864, which showed for the first time that oral Calabar bean extract (which contains physostigmine) reverses the toxic effects of atropine. Kleinwächter's original paper is translated from the German.

This paper relates the earliest known account of the use of physostigmine (as an extract of Calabar bean) in the treatment of systemic atropine poisoning, in Prague in 1864 [1]. It was a bold therapeutic step at the time, in view of the fact that the side effects of too large a dose were known to produce muscular weakness [2] and even paralysis and death [3].

It is significant that the two doctors involved (Dr Kleinwächter and Dr Niemetschek) were ophthalmologists [4], in view of various reports the previous year (1863) that the conjunctival application of an extract of Calabar bean counteracts the mydriatic action of atropine [3, 5–7].

Background

The surgeon and botanist William Freeman Daniell³ (1817–1865) witnessed while resident in Calabar, West Africa, the use of certain poisonous seeds by the natives for the purposes of Trial by Ordeal, a common practice in that part of Africa. Daniell relates the following in a lecture to the Ethnological Society in 1846.

'If found guilty, they are usually forced to swallow a deadly potion, made from the poisonous seeds of an aquatic leguminous plant, which rapidly destroys life. . . . If, however . . . the accused should be so fortunate as to throw the poison off the stomach, he is considered as innocent, and allowed to depart unmolested' [8].

¹For an earlier letter regarding this and the involvement of Argyll Robertson see <http://www.nickalls.org/dick/papers/anes/physostigmine1980.pdf>

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³For WF Daniell see: <http://www.nickalls.org/dick/papers/rwdnPapers.html#daniell>

A few years later a Scottish missionary by the name of Rev. Zerub Baillie was also resident in Calabar. Baillie had previously studied medicine in Edinburgh, and in a letter to his former teacher J. H. Balfour (Professor of Medicine and Botany, University of Edinburgh), he gives the following classic description of physostigmine poisoning [9].

‘I have several times been called upon to visit people under the influence of this poison. The symptoms, so far as I have observed them, are as follows: The patient, when fairly under the influence, presents a peculiarly stupid, drunken look, the face is flushed and swollen, the eyes protruding, the mouth externally has somewhat the appearance of a person under salivation. At first there is a considerable flow of saliva, which eventually becomes frothy; the pulse is moderately full; the limbs gradually become powerless; the person walks very like an individual under the influence of strong drink; the muscles of the tongue, as well as the other muscles of the body, soon appear to get into a state of paralysis; the breathing becomes laborious, and the patient gradually sinks.’

Baillie subsequently sent some of these so-called Calabar beans to Professor Christison (Professor of Materia Medica and Therapeutics, University of Edinburgh) for investigation. In 1855 Christison writes [2],

‘Meanwhile I have fallen in with another African ordeal-poison, of much greater energy and interest . . . The only notice of any kind that I have seen of it, is a short allusion to it by Dr Daniell, in an ethnological paper . . . From such trials as I have made, it seems one of the most singular and intense poisons yet known, and well worthy of a more complete investigation than I have been hitherto able to accomplish.’

Christison ate, by way of experiment, one quarter of a bean and became dangerously weak [2]. Significantly, this experiment made him realise that the weakness was because of a peripheral rather than a central effect. Christison describes this realisation [2].

‘. . . I tried to raise myself on my elbow to vomit, but failed. I made a second more vigorous effort, but scarcely moved. At once it struck me—this is not debility, but volition is inoperable.’

Somewhat later, Dr Richard Fraser (a student of Professor Christison), made an extensive study in animals of an extract of Calabar bean [3], and discovered its miotic action on the pupil. The ophthalmologist, Dr Argyll Robertson, also worked in Edinburgh at that time. He had been investigating a variety of vegetable extracts in order to find a substance with ‘actions exactly opposite to those well known to result from belladonna or atropine.’ Argyll Robertson goes on to say [5],

‘These investigations were, however, productive of no satisfactory results, until my friend Dr Fraser informed me that he had seen contraction of the pupil result from the local application of an extract of the ordeal bean of Calabar. I resolved to investigate this substance . . . to ascertain whether it exerted any influence on the accommodation of the eye.’

This work led Argyll Robertson to describe the first clinical uses of physostigmine [5], namely to reverse the prolonged and unpleasant mydriatic action of atropine,

and to constrict the pupil in cases of retinitis with photophobia, as well as ciliary muscle paralysis.

Argyll Robertson's paper which described the first clinical use of this new agent was published in March 1863 [5], and only 18 months later an extract of Calabar bean was used systemically by Drs Kleinwächter and Niemetschek in Prague to treat a case of atropine poisoning. A translation of their extraordinary paper is presented below. (In view of the historical nature of Kleinwächter's paper it is translated fairly literally, and follows the original German closely.)

Acknowledgements

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*Translation***Observations on the effect of Calabar bean extract
as an antidote to atropine poisoning**

by

Dr Kleinwächter

(Second ophthalmologist at the Kaiser Hospital, Prague)

Berliner Klinische Wochenschrift, 1864; p. 369–71

A number of single rooms in the Kaiser hospital in Prague were being given their annual thorough 'cleaning-out' by some of the inmates of the local prison on 20 August last year. However, while this was going on, some of the prisoners broke into a locked box which they had found in one of the rooms. They found inside the box three small bottles containing a clear liquid which they assumed to be alcoholic spirits. Four of the men then broke the seals and drank some of the contents.

At about 9 am the following morning, whilst making my rounds, I was called to go urgently to one of the rooms that the prisoners had been working in, since four of the men had apparently poisoned themselves by drinking something they had found. I hurried along to the room straight away and found that the prisoners had broken into a medical box. I found that three bottles, each of which contained four drachmas [14.2 ml] of an atropine solution, made up of one grain [64.8 mg] of atropine sulphate per drachma of distilled water [18.25 mg/ml] had had their seals broken. One bottle was more than half empty, another almost half empty, while the third appeared to be full.

The four men, who were aged between 24 and 30 years old, were affected to varying degrees. One of the prisoners, however, showed no signs or symptoms of atropine poisoning; he had indeed tasted the atropine solution assuming it to be spirits, but once he discovered his mistake he immediately spat it out. One of the other men had been more daring, and had actually swallowed a mouthful. It was not until several minutes later, according to him, that he began to notice any ill-effects. I found nothing abnormal when I examined him, other than that he had slightly dilated pupils. His temperature and pulse were both normal, and in fact his only symptom was of an uncomfortable rawness along the roof of his mouth.

The third prisoner must have swallowed considerably more of the atropine solution, because I found him in a state akin to extreme drunkenness. He was leaning against the wall, his knees sagged, his head lolled about and he was supported by one of the other prisoners. He was laughing loudly and seemed to be in excellent spirits, although he was quite delirious and unable to speak coherently. There was a cyanosed tinge to his face; his sclera were injected, and his pupils markedly dilated. His temperature was increased to 31 °R [38.7 °C]; his pulse was weak, but was somewhat slower than one would have expected under the circumstances, scarcely 70 beats per minute. He also continuously moved his arms and legs in a curious way, which has been described previously by Falck in association with atropine poisoning ('Important clinical signs of poisoning', by Dr C.Ph. Falck of Marburg, in *Virchow's Archives*). These movements were similar to a sort of swimming action; the prisoner continually groped about on the floor, alternately reaching out and then retracting his arms, as if he were trying to pick up some small object. He continually made efforts to get up as long as he was on the floor, and when he did not succeed he would drag himself on to 'all-fours' and shuffle around in a circle. He appeared not to be in any pain, and was generally affable and chatty, albeit incoherently. His respiratory rate was increased, but not significantly so.

The fourth prisoner was clearly the most affected. Unable to stand, he lay outstretched on the floor, scarcely able to move his limbs. His whole body, and especially his face, had taken on a cyanosed hue. His temperature was alarmingly high, and his breathing was laboured and noisy. His pulse, which was about 60 beats per minute, could scarcely be felt. The heart sounds were faint, and urine was passed involuntarily. His pupils, which did not react to light, were so dilated that the iris appeared only as a narrow peripheral band. Furthermore, his nose had started to bleed rather heavily. He appeared to be unconscious for most of the time, but would occasionally shout out incoherently and move his arms and legs in a convulsive manner. He threw himself about so violently that four men could hardly restrain him during one particularly severe episode. Careful observation suggested that he was, in fact, not in any pain; indeed, no sign of discomfort showed in his face.

There was complete dryness of the mouth in the last two prisoners described; no spontaneous retching; and no sign that either of them felt at all unwell. Indeed, they both protested noisily whenever one attempted to do anything to them. I immediately wrote out a prescription for some ipecacuanah, namely an infusion of one and a half drachma of ipecacuanah root sufficient to produce six ounces, with half an ounce of simple syrup [an infusion of 5.8 g of ipecacuanah root made up to 190 ml, together with 15 ml of simple syrup; literally this is ‘... ein Infusum Rad. Ipecac. e Drachma et semis ad unc. sex, Syrup. simpl. unc. semis ... ’] and ordered some strong black coffee to be brought up from the kitchen. When the infusion of ipecacuanah arrived from the pharmacy, a measure was given to the fourth prisoner to drink while it was still warm. However, he only managed to swallow half the measure (about one tablespoonful). On trying some more, he spat it all out. This was followed by signs not unlike those of hydrophobia, namely convulsions of the whole body when given something to drink, and in spite of help from the medical attendants, we had to abandon the ipecacuanah treatment. However, after about 5 minutes he vomited approximately two tablespoonfuls of liquid, the colour of which resembled that of egg-yolk. This was followed by another episode of violent delirium, which was more severe than any before.

When the black coffee arrived, I gave some to the third mentioned prisoner, who, in spite of considerable resistance and continuous chatter and laughter, eventually drank it. The fourth prisoner had swallowed hardly any of the ipecacuanah infusion, so I decided to write out another prescription for him: Tannic acid, 1 scruple, [1.3 g]; distilled water and cinnamon water, one ounce [28.4 ml] of each. (℞ Acid tannici Scrup. 1; Aq. dest.; Aq. Cinnam. ana Unc. 1). Unfortunately, however, neither the third nor the fourth prisoner could be persuaded to take any of it. Meanwhile, the condition of these two prisoners continued to deteriorate; delirium alternated with stupor. It was necessary, therefore, as a matter of some urgency now, to induce vomiting; and a colleague of mine suggested that we should have some beer brought up from the kitchen and add some tartar emetic to it [tartarus emeticus; antimony potassium tartarate]. I therefore obtained six grains [389 mg] of tartar emetic from the pharmacy and put half the powder in each of two glasses, which were then filled up with beer. However, while the less severely affected prisoner drank the beer and subsequently vomited a small amount, the other prisoner could not be made to drink any.

For safety reasons, the hospital regulations prevented me from admitting inmates of a prison, and I therefore had to return the men to the prison. The third prisoner was not a problem in this respect, but the fourth prisoner, owing to his worsening delirium, had to be restrained in a straight-jacket before he could be taken back to the prison. On the way I met a colleague (Dr Niemetschek; a former assistant in the sight-testing clinic, and now a lecturer in ophthalmic optics), and invited him to come and see these two

interesting cases. We handed the men over to the care of the prison Medical Officer when we arrived at the prison, and explained what had happened. Meanwhile, the third and fourth prisoners were put into bed with cold compresses applied to their heads. Dr Niemetschek thought that while we were discussing these two cases it might be a suitable occasion to experiment with the Calabar bean extract, and to try it orally [instead of topically on the conjunctiva], in view of its property of reversing the [mydriatic] action of atropine.

I did have a solution of Calabar bean extract, as chance would have it, which I had had prepared only a few days earlier by a reliable firm in Prague (the Golden Crown apothecary), so that we could experiment with it in our department. The concentration of the solution was six grains of Calabar bean extract per drachma of pure glycerine. This corresponds almost exactly to one drachma of Calabar bean [3.9 g] per drachma of glycerine [3.6 ml] as 3 drachma of bean yield 19 grains of extract. I went immediately and fetched the Calabar bean solution, and with the agreement of the prison Medical Officer, gave 10 drops on some sugar to the most severely poisoned man [since the physostigmine yield of Calabar bean is approximately 0.13% by weight, and the volume of 10 drops of glycerine BP using a standard eye dropper is approximately 0.7 ml, the dose of physostigmine was about 1 mg]. In addition, I attempted to put some drops of the solution into the conjunctival sac of the third prisoner, but did not succeed.

The fourth prisoner suddenly started to vomit about 15 minutes later, and brought up large quantities of liquid and food. His pulse now felt stronger, and had increased in rate to 75 beats per minute. His temperature decreased, and he passed a large quantity of urine. Furthermore, his delirium lessened, and he reported a raw sensation in his throat. The other prisoner, however, continued to show no improvement.

Later in the day, at about 2.30 pm, I returned to the prison to see how the two men had progressed, and found the [formerly] most affected prisoner sitting on his bed. He was now quite able to answer questions. His pulse was now both stronger and faster (80 beats per minute), and he complained of headache, and of feeling a bit disorientated. He also complained of poor vision, and indeed, his pupils were still quite dilated, although less so than before. By now he had recovered to such an extent that he was able to tell me how he had broken open the medical box and taken two mouthfuls from what he thought was a bottle of spirits. In contrast, the condition of the other prisoner remained unchanged despite the cold compress and the emetic which, admittedly, he had not taken. By the following day, the fourth prisoner (the one who had been affected most severely) had almost fully recovered. The third prisoner, however, was still showing signs of atropine poisoning, and his pupils were considerably more dilated than those of the man who had been treated with the Calabar bean extract.

These events are quite remarkable since only yesterday, when the two men were transferred from the hospital back to the prison, the condition of the fourth prisoner was so poor that I had seriously wondered whether he would even survive the journey. I do not believe that the effects described here can be attributed to chance alone, since the results followed so quickly and unmistakably for anyone to fail to recognise the cause. It is of the utmost importance, therefore, for the nature of this antagonism between atropine and the Calabar bean extract to be determined objectively by careful experimentation. Meanwhile, however, such a new and experimental treatment for atropine poisoning using the extract of Calabar beans, must of course be undertaken cautiously.

Should the effectiveness of the Calabar bean treatment be proven, then the previously used methods for the treatment of Belladonna poisoning, all more or less arbitrary and unreliable, will be unnecessary. We will then have a safe and effective antidote for this common form of poisoning (at least, it is frequently seen in our hospital), based on a

sound scientific hypothesis, rather than on a chance discovery.

The two prisoners I have described are now very much better. Indeed, the one treated with Calabar bean extract has now fully recovered.
