Physostigmine for anticholinergic poisoning[1]

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http://www.nickalls.org/dick/papers/anes/physostigmine1980.pdf

Sir, — Dr Cleghorn and Dr Bourke state [Aug. 16, p. 368] that physostigmine was used in the treatment of anticholinergic toxicity for the first time in 1968. Ten years earlier Forrer and Miller (1958) published a paper on the atropine antagonist properties of pilocarpine and physostigmine. Coma was induced with very large doses of atropine (212 mg) and was readily reversed by 4 mg of physostigmine: "... by 20 mins there was a complete restoration of the patient's pre-treatment psychophysiological status".

A less pure form of physostigmine was used to treat a case of atropine poisoning in 1864 by Dr Kleinwächter , an ophthalmologist in Prague (Gaddum 1954). Kleinwächter (1864) examined four prisoners who, while cleaning out the sick-bay, had drunk a solution of atropine sulphate, thinking it was liquor. Two patients were very ill, delirium alternating with stupor. He happened to meet a former colleague Dr Niemetschek, who remarked that this would be an opportunity to experiment with an extract of Calabar bean, an antagonist of atropine. Kleinwächter continues:

> "As it happened I had a solution of Calabar bean extract in glycerin with me, which had been made up by a chemist a few days ago for us to experiment with in our department. The strength of the solution was: six grains of Extract of Calabar in one drachm of pure glycerin. This corresponds almost exactly with 1 drachm of Calabar bean [3·9 g] per drachm of glycerin [3·6 ml] as 3 drachms of bean yield 19 grains of extract. I immediately took the solution, and gave about 10 drops on some sugar to the most intoxicated prisoner ..."

The physostigmine yield of Calabar bean is $0{\cdot}1 - 0{\cdot}15\%$ by weight, so the dose of physostigmine was about 1 mg. The result was dramatic:

> "After we had waited a quarter of an hour, the patient started to vomit violently ... the body temperature fell, the delirium lessened and the patient became quieter ... and then he passed a considerable amount of urine. Later that day Kleinwächter "found the prisoner who had been most intoxicated, sitting on the bed and when I questioned him he answered rationally ... He complained of not being able to see very well, and the pupils were considerably dilated (although already less than before) ... The other prisoner still lay on his bed and seemed to be in no better condition ..."

[1] For a more comprehensive article, together with a translation of Dr Kleinwächter's original paper, see http://www.nickalls.org/dick/papers/anes/physostigmine1988.pdf

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Both Kleinwächter and Niemetschek were ophthalmologists and would have been familiar with the work of Argyll Robertson (Robertson 1863a) and Ogle (1863), who had shown that extracts of Calabar bean antagonised the action of atropine on the pupil. In 1864 sixty children in Liverpool were affected in an outbreak of Calabar bean poisoning (Anon 1864a, 1864b; Cameron 1864, Holmstedt 1972) but the general physicians attending them did not try atropine as an antidote—surprisingly, in view of the articles which had appeared in the general medical Press during the previous year (Ogle 1863, Harley 1863, Anon 1863). The miotic property of an alcoholic extract of Calabar bean had been demonstrated at a meeting of the Liverpool Medical Institution on April 16, 1863, Argyll Robertson having sent three beans (Anon 1863).

Dr Thomas R. Fraser is well remembered today as the one who suggested to Argyll Robertson the idea of using the extract of Calabar bean clinically (Robertson 1863a), but at the time he felt that his contribution was not appreciated. In a sour letter in 1863 he wrote to say that in informing Argyll Robertson of his discovery he had forgotten "that by so doing I incurred the risk of losing the advantage of being the first to announce what was my proper discovery" (Fraser 1863). Fraser ended by saying:

> "A young writer will be excused, in the meantime, for expressing his chagrin to find paper after paper written on the ophthalmic application of the ordeal bean, in only the first of which allusion is made to the discoverer . . . "

Argyll Robertson felt obliged to respond:

> ". . . I desire to state that I do not claim, and have never, either directly or indirectly, claimed the credit of having discovered the property possessed by the Calabar bean of contracting the Pupil: on the contrary, I have from the first acknowledged that the discovery was Dr Fraser's" (Robertson 1863b).

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