The first reversal of curare

RWD Nickalls * and EA Nickalls

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Abstract

This paper describes an experiment performed by J. Pal of Vienna in 1900, which showed that physostigmine reverses the neuromuscular blocking properties of curare. Pal's original article is translated from the German.

It has been known for over 150 years that animals recover completely from the effects of curare, providing that ventilation is adequately maintained. Indeed, as early as 1816 a donkey, later named Wouralia, made a full recovery following 4 hours of artificial ventilation, after being given the South American arrow poison 'wourali' (curare) into a shoulder wound.[1] As curare gradually became more available, scientists increasingly used it to facilitate physiological experiments. Using this new technique for immobilisation, animals were now subjected to all sorts of new drugs and experimental conditions. Unfortunately for anaesthesia suxamethonium was first tested in this way. Hunt and Taveau[2] injected it into curarised animals as early as 1906, and not surprisingly they failed to notice its relaxant property.

In the 19th century there was no known antidote to curare, and experimenters therefore had to wait patiently for its effects to wear off if the animal was to survive. However a chance finding by Pal[3] in Vienna in 1900 heralded the foundation of modern relaxant practice nearly half a century before curare was introduced into general clinical use. Pal, who was interested in gut physiology, was persuaded to inject physostigmine into a curarised dog in order to see its effects on the bowel. There was a marked increase in peristalsis; but surprisingly, the dog started breathing spontaneously. Further experiments confirmed that physostigmine antagonised curare. Such are the inner workings of serendipity.

At the time, however, it was somewhat paradoxical to find that physostigmine should antagonise curare at all, since it had been known for many years that physostigmine itself caused profound muscle weakness, and even frank paralysis when given in sufficient doses.[4-6] Furthermore, this antagonism of curare seemed all the more surprising as physostigmine was already known to be a specific antagonist of atropine,[7-8] there being no clear mechanism of action linking atropine with curare.

Pal's findings were written up within a week of his confirmatory experiment in an article entitled 'Physostigmine, an antidote to curare', which was published in the journal 'Zentralblatt für Physiologie' the same year.[3] In view of the significance of Pal's discovery, our translation of his little known paper is given below. Regarding the 'Pravaz syringe' referred to by Pal, there is an excellent discussion on G. C. Pravaz and his syringe in a recent article by Boulton.[9]

*Department of Anaesthesia, Nottingham University Hospitals, City Hospital Campus, Nottingham, UK. email: dick@nickalls.org [www.nickalls.org/dick/]

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Physostigmine: an antidote to curare[1]

by

J. Pal (Vienna)

sent to the editor 22 July 1900

(*Zentralblatt für physiology* 1900; 14: 255–8)

A survey of the literature up to now shows that the resuscitation of curarised animals is only possible using continuous artificial ventilation. The subject, as the title indicates, seemed important enough for me to briefly describe my findings, particularly as this is not my present field of work and I am unable to follow it up. Dr J. Rothberger,

[1] Pal J (1900). Physostigmin ein Gegengift des Curare. *Zentralblatt für Physiologie* 1900; 14: 255–8.

Demonstrator at the Institute for General and Experimental Pathology has taken it over for further investigation.

During the course of my work, which was directed towards elucidating the innervation of the gut,[1] I was persuaded to investigate the action of physostigmine on the bowel. I experimented on artificially ventilated curarised animals. On one occasion, when I injected physostigmine intravenously, strong muscle twitching occurred, and I noticed that the animal was breathing spontaneously. I was able to stop the ventilation and continue my observations without it. All my experiments using physostigmine were carried out in a similar way, and I always had to let the animals bleed to death afterwards.

In order to establish the reversal of curare objectively, I decided to carry out the following experiment. On the 14th July 1900, at 10.45 am, in the presence of Professor Biedl, I curarised a ¾ kg dog with an intravenous injection of a 2% solution of curare using a Pravaz syringe, and began artificial ventilation. The curare completely paralysed the voluntary muscles, and no respiratory movements were seen. At 10.48 am I injected 2·5 mg of physostigmine salicylate intravenously. At 10.52 am, 4 minutes later, there was strong twitching, spontaneous respiration, and a considerable flow of saliva. At the same time one could see, through the abdominal wall, typical waves of peristalsis moving small quantities of matter along.

At first these spasms—one could say pseudo-respiratory movements—were completely irregular. The respiratory tracing (while temporarily stopping the ventilation) is shown in Fig. 1.

These spasms gradually increased in depth, progressing to adequate respirations. By 11.04 am these were of normal depth, although there was still some twitching. It was only necessary to ventilate occasionally, and then only as a matter of caution. At 11.15 am I injected another dose of physostigmine (1·25 mg) and discontinued the ventilation at 11.16 am. The trace of respiration is shown in Fig. 2. In order to counter some epileptiform spasms which had appeared on the tracing, two doses of morphine hydrochloride were given (10 mg each), whereupon these greatly diminished (see Fig. 3.). An indwelling cannula was inserted at 12.15. I returned to see the animal at 5 pm. The dog was conscious and trembling, reflexes were present, and it made attempts to move. The animal received no treatment and died the following day.

These events led us to conclude that physostigmine is an antidote to curare. It was possible with the first dose of physostigmine to rapidly reverse a paralysing dose of curare. It only remained to treat the side-effects of the physostigmine. Although atropine is particularly recommended for this, I think the addition of morphine is very useful.

I would particularly like to emphasise that in curarised animals the diaphragm is one of the first muscles to respond to physostigmine. Although I have not found any reference in the literature to our findings described here, Harnack and Witowski,[2] in a thorough investigation into physostigmine and calabarine, also studied the opposing action of curare. While they did find that curare paralysed the muscle effects of physostigmine, they did not appreciate that physostigmine could completely reverse the effects of curare.

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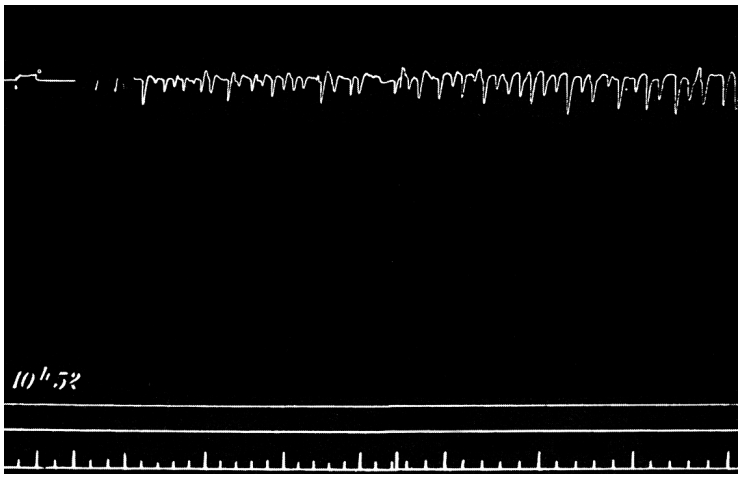

Figure 1:
The onset of diaphragmatic movements at 10.52 am (4 min after the injection of 2·5 mg of physostigmine

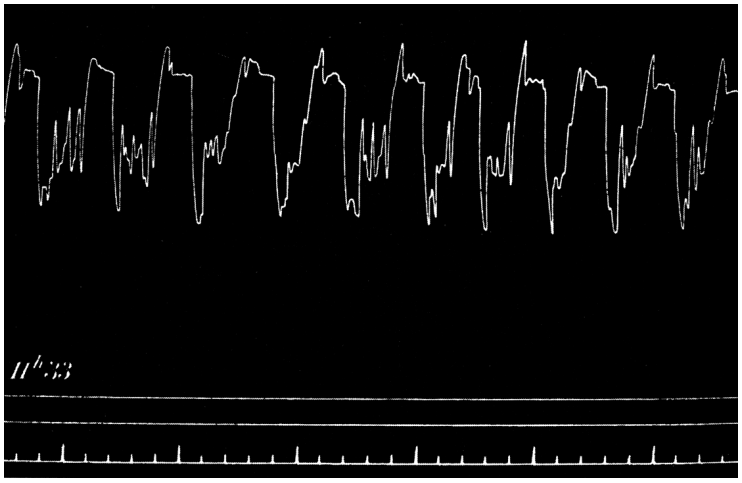

Figure 2:
Respiration at 11.33 am. Some twitching of the diaphragm still present.

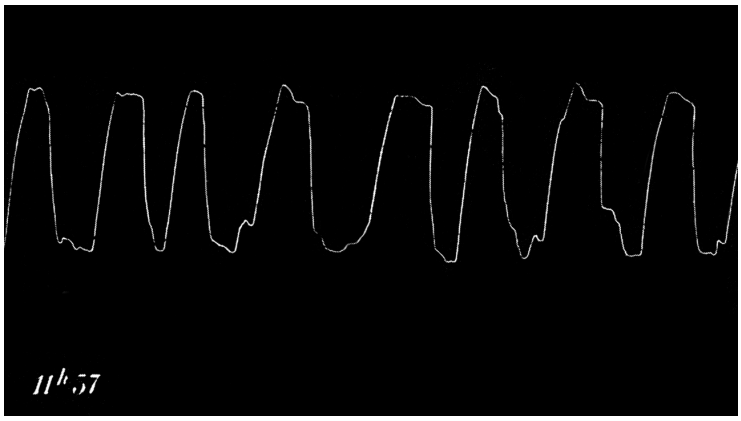

Figure 3:
11.57 am. After two 10 mg doses of morphine hydrochloride. The twitching has temporarily subsided. (Time markers are not given, but drum speed is the same as in Fig. 2.)