

## SCIENTIFIC SECTION

### ADDITIONAL STUDIES ON MIRÉ.\*

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In 1923, Dr. Rusby reported before this section, under my name, preliminary pharmacodynamic studies on a plant brought back by the Mulford Biological Exploration of the Amazon Basin under his direction. The plant is a shrub which grows sparsely in the mountains of Bolivia and which is known to the natives by the name of Miré.

As reported by Rusby, the wood of the stem or root is extracted with boiling water and the decoction drunk. It produces paralysis of voluntary muscles, resembling that of alcoholic intoxication, but without disturbance of sensation or intellect. After a time, there is a profuse perspiration, which apparently leads to destruction of cutaneous animal parasites.—My own experiments on animals, reported by Dr. Rusby at the 1923 meeting of this section, confirmed these actions.

Extracts of the root or stem injected into frogs or mammals, produce a peculiar train of symptoms. In frogs, doses of an aqueous or alcoholic extract corresponding to 0.03 mgm. of drug per Gm. cause extreme weakness of all voluntary muscles accompanied by more or less violent jerking and twitching. These symptoms come on a few minutes after the injection and last for many hours, the frog lying flat on the floor of the cage with the legs and the trunk muscles jerking spasmodically and more or less continuously. The heart is somewhat slowed, or not affected and there is excessive secretion of mucus by the skin, but no other symptoms. This condition lasts for several hours and is followed by extreme muscular weakness, the animal finally recovering. Doses 2 to 3 times as large produce similar symptoms, but the twitching lasts several days, the heart beating almost normally, but finally becoming very slow and eventually ceasing in diastole.

The tremors are not influenced by decapitation nor by section of the cord. If the sciatic nerve is cut before the injection is given, the twitching occurs, but less actively than in the intact leg. Section of the nerve after twitching has begun, may cause it to cease entirely. When the leg is ligated at the hip, leaving the nerve free, no twitching occurs in that leg, although there is loss of voluntary motion. There is no curare action.

In mice, doses of 0.3 mgm. per Gm. cause a similar twitching of the leg muscles followed by paralysis; respiration becomes jerky and irregular and eventually ceases.

In rabbits, intravenous injection of 2 cc. of a 10 per cent infusion (0.2 Gm. per kilo) is followed by slowing of the pulse with slight rise of blood pressure, increase of knee jerks, salivation and, in some animals, increased peristaltic movements.

These results indicate that Miré causes motor paralysis by action on the spinal cord, associated with stimulation of some part of the peripheral motor apparatus. There is stimulation of secretions, especially of the saliva and the sweat.

No report was given at this meeting, on the preliminary chemical studies which were made at the same time as the pharmacodynamic work.

I found that the drug contained, both in the root and stem, three principles.

1. A strongly fluorescent body, soluble in chloroform, ether and alcohol but

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\* Read before Scientific Section, A. Ph. A., Philadelphia meeting, 1926.

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less soluble or perhaps when pure, insoluble, in water. This substance when injected into mice or frogs in a dose representing about 20 mgm. of drug per Gm. of animal or about 3 mgm. of solids to an average 20 Gm. frog or mouse, causes paralysis without twitching. Even much larger doses do not cause death in frogs or markedly influence the heart's action.

2. A body of alkaloidal character soluble in alcohol but precipitated from alcoholic solution by ether. The root yielded 3 Gm. per kilo of this body not perfectly purified. Freshly prepared solutions are pale yellow and not opalescent, but on standing they deepen in color, changing from yellow to a reddish wine color, and showing opalescence. It is very active physiologically, an amount corresponding to 10 mgm. per Gm. of drug and containing less than  $\frac{1}{2}$  mgm. of solids for a 20-Gm. frog killing a frog within an hour or two.

3. A body of alkaloidal character soluble in alcohol and not precipitated by addition of ether. The root yielded 5 Gm. per kilo of a relatively impure body which gave a pale yellow, permanent solution in water. It is about equally active with the other alkaloid, an amount corresponding to 5 mgm. per Gm. and containing even less than  $\frac{1}{2}$  mgm. of total solids, producing similar symptoms in frogs.

In addition to these principles, the drug contains a small amount of starch, but no tannin and but little soluble coloring matter. The constituents of the root and stem resemble one another.

In March 1925, Prof. Youngken reported in the JOURNAL OF THE A. PH. A., that Miré appeared to belong to a genus of South American shrubs, *Brunfelsia* of the *N. O. Apocynaceæ*. He identified it as *B. hydrangæformis*, which had been described by Pohl in 1827.

Another species of the same genus, *B. hopeana* or *Manaca*, has long been known to medical and pharmaceutical science. Material from this plant brought back from South America by Dr. Rusby about 1880 was studied carefully by Brandl, who published details of the chemistry and pharmacology in 1895. He found three principles, corresponding closely to those which I found in Miré. The first of these, which was fluorescent in alkaline solution, he believed to be identical with esculetin; the second, precipitated from alcoholic solution by ether was termed manacin; and the third, soluble in hot alcohol but less in cold and also precipitated by ether, manacein.

The symptoms produced in animals by Manaca and its alkaloids were almost identical with those produced by Miré. Frogs showed violent twitching, largely of spinal origin, accompanied by weakness and followed by paralysis. In mammals there was rise of blood pressure, followed by slowing of the heart, with fall. The cardiac slowing was not prevented by section of the vagus nerves. Stimulation of secretions, especially cutaneous, urinary and gastroenteric was also noted.

We may conclude that Miré is very similar to Manaca in its composition and action. It will never be a commercial rival, as Manaca is very abundant and cheap, while Miré is relatively rare and would be expensive to market.

**Bibliography.**—Rusby (Miré) JOUR. A. PH. A., 13, 2 (1924). Githens (Preliminary Report on Miré) JOUR. A. PH. A., 13, 2 (1924). Youngken (Botanical Position of Miré) JOUR. A. PH. A., 14, 195 (1925). Brandl, *Apoth. Ztg.*, 10, 622 (1895). Brandl, *Z. Biol.*, 31, 253 (1895). Brewer, *Ther. Gas.*, 3, 326 (1882).