THE ALKALOIDS OF THE AMARYLLIS "BELLADONNA."*

BY DR. FRED B. KILMER.

At the outset of the European War, the belligerent nations placed an embargo upon the exportation of certain drugs, including belladonna. This induced a correspondent in a neutral country to send us a substance which he termed "belladonna root," and which substance he said grew in abundance and could be furnished in quantities if a market could be found for the same.

The substance was a bulb, which, upon investigation, proved to be the *Amaryllis belladonna,* or the so-called "belladonna lily." The statements of our correspondent, coupled with a natural curiosity, induced us to make a further examination.

As to the plant itself, the following statement is made by a horticulturist of repute:

Formerly there was included in the genus *Amaryllis* a large number of species, several of which have been separated and now have distinct genera. All that were classed as *Amaryllis* a few years ago are now classed as *Hippeastrum,* and there remains in the genus

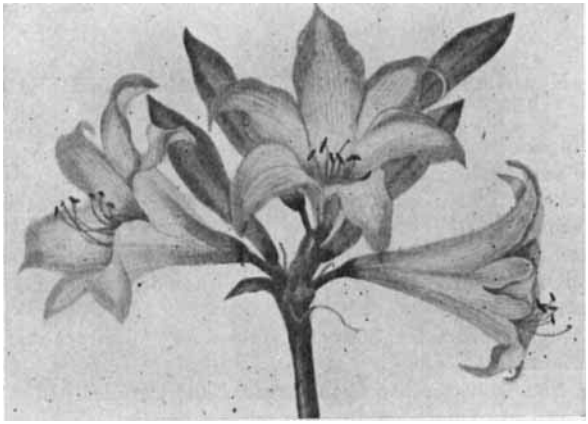

FIG. 1.—*Amaryllis belladonna,* flowering tops.

Amaryllis only one species, viz.: *Amaryllis belladonna,* of which there are several varieties. (*Amaryllis Johnsoni, Aulica, Regina,* etc., are now properly *Hippeastrum Johnsoni, Aulica, Regina,* etc.)

All these plants are cultivated to a considerable extent in green-houses and gardens, and in recent times have attracted considerable attention at flower exhibitions. The "belladonna" lily is the most showy and the most beautiful of any of the varieties found in the genus.

How this plant received the designation "belladonna" cannot be explained. It bears no relation to the solanaceous plants, and is certainly far removed from the atropa belladonna.

The part of the plant used in our experiments was the bulb. By the usual method of assay a solid extract made with alcohol showed upon assay 3.37 percent alkaloid (approximating 0.3 percent alkaloid for the dried drug). The alkaloid was obtained in crystalline form by extracting the drug with chloroform

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and ether under the methods ordinarily used for extraction in assaying, the solvents evaporated, the resultant extract washed with acidulated water made alkaline with ammonia; the resultant liquid was again washed with chloroform, followed by a second washing with chloroform and acidulated water, neutralized with ammonia, then washed with ether and from the ether washing crystals were obtained by the aid of a few drops of alcohol.

In the few attempts made, however, the crystals were not considered as absolutely pure; they were somewhat stained, and there adhered to them a certain amount of non-crystallizable matter.

We may here note that in submitting the facts as to the presence of the crystallizable alkaloid in the *Amaryllis belladonna* to Prof. John Uri Lloyd, he stated:

I have changed my mind concerning the importance of crystals in alkaloidal compounds. I am of the opinion that with few exceptions all alkaloidal compounds are colloidal or amorphous. I believe this will be irrefutably established, and that eventually a re-study will have to be made of alkaloids in which the natural structure of the alkaloid will be found to be colloidal and not crystalline. The method of individuality will then have to be based upon solubility and insolubility factors, together with physical and physiological actions. In other words, the natural plant alkaloid as obtained will be of the nature of tannin, and in my opinion they will all be found to be naturally colored, somewhat after the intrinsic colors of tannin.

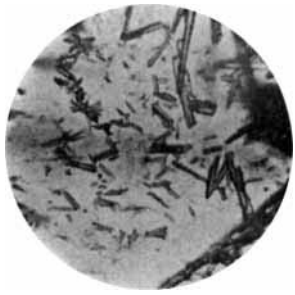

FIG. 2.—Crystals of the alkaloid of *Amaryllis belladonna*.

In the first experimental work with this drug, we were not able to obtain the alkaloid in crystalline form. For the purpose of making a physiological test a syrupy extract was prepared by extracting the dried drug with a mixture of chloroform one part, ether four parts; the percolate was shaken out with acid water, the acidulated water was made alkaline, shaken out with chloroform; the resultant chloroform solution containing the alkaloid was evaporated to a syrupy extract.

This alkaloid containing syrup was submitted to Prof. Robert A. Hatcher, of the Department of Pharmacology and Materia Medica, in the Cornell University Medical College of New York, for physiological test. At first no intimation was given to Prof. Hatcher as to the drug from which the extract was obtained. He reported as follows:

I am inclined to believe that this extract is a mixture consisting very largely of hydrastin, or similarly acting substances.

Doses of approximately 100 milligrammes of the original extract per kilogramme of body weight of cat or dog, injected intramuscularly, cause a peculiar muscular stiffness and incoördination, with respiratory stimulation and subsequent depression. A dose of approximately 200 milligrammes of the extract per kilogramme of cat, injected intramuscularly, proved fatal in four hours and twenty minutes, causing respiratory paralysis.

The effects are not identical with those of any pure principle with which I am acquainted,

but partake largely of the nature of hydrastin (muscular stiffness, convulsive twitching, respiratory distress, and incoördination, but fail to produce typical strychnin-like convulsions).

The extract is an almost pure alkaloid, that is, a very high percentage of alkaloid is present, for it dissolves in dilute acid, and a 1:50,000 solution with an excess of sulphuric acid, which gives a copious precipitate with Mayer's reagent. The dilute sulphuric acid solution of the extract has the typical greenish fluorescence of a solution of hydrastin.

An extract of the extract, made by treating it with $\frac{N}{100}$ sulphuric acid, was without mydriatic action on the cat's eye, and the residue presented the typical actions of the original extract. An extract made by treating the extract with dilute sulphuric acid and normal saline caused feeble mydriasis in the cat (much as hydrastinin does).

Very large doses are not emetic for cats and dogs (hydrastin sometimes causes emesis) and this circumstance excluded the presence of any of many groups, such as: The picrotoxin group; the digitalis group; aconite group, and many others. Gelseminin is far more active than this extract; coniine presents certain muscular symptoms like this extract, but it is emetic.

I think it most probable that this extract contains a large percentage of hydrastin contaminated with decomposition products formed during the manipulation, or else that we have to do with a little known alkaloid that resembles hydrastin in certain respects.

Subsequent statements by Prof. Hatcher were to the effect that the physiological action of the extract did not coincide exactly with that of hydrastin, but that the resemblance was so close that one is forced to conclude that there is either a high percentage of that alkaloid, or a closely associated one—that the manipulation has resulted in the formation of hydrastin, or a closely related alkaloid. Certainly the action elicited proved the presence of these two alkaloids, or other constituents that have closely related action.

After the experiments above stated had been performed, a search of the literature revealed the fact that B. Fragner had, in 1891, announced the occurrence of alkaloids in the *Amaryllis belladonna* which he named "Bellamarine." Fragner had isolated from the *Amaryllis belladonna* four substances which seemed to be distinct from each other, so far as shown by the colors given in contact with acids of certain salts. Fragner states that the alkaloid is excessively abundant on the scales of the bulb of the *Amaryllis belladonna,* also in the roots and in the epidermis cells of the leaves. In the *Amaryllis formosissima,* alkaloids were found in the bulb, the root, the leaves and the flower.

It seems to the writer that it is unfortunate that the name "Belladonna" should have been attached to the Amaryllis, as it bears no relation to the well known *Atropa belladonna.* It is likewise unfortunate that the first investigator should have given the name "Bellamarine" to the alkaloid. This designation "Bellamarine" would indicate an association with the alkaloids of belladonna, to which by its chemical and physiological actions it bears no relation. Indeed, as stated by Prof. Hatcher, it is more closely associated with the alkaloids of hydrastin, with little or no relation to those of belladonna.

I might suggest that a more appropriate name for the alkaloid of the *Amaryllis belladonna* would be "Amarylline," and the alkaloids of the other species of related plants to be given a name following the particular plant in which they may be found, as, for example, "Reginin."

In any event, it is worth while recording the not generally known fact that the *Amaryllis* and, similarly, the *Hippeastrum* all contain highly active poisonous alkaloids. The question as to whether these alkaloids could be made available in medicine would need further study and elucidation.

JOHNSON & JOHNSON LABORATORIES, NEW BRUNSWICK, N. J.