

V. ON THE ACTION OF LOBELIN UPON THE CIRCULATORY ORGANS

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Introduction

Lobelia inflata is a native plant of North America, and has been used for a long time by the public against all kinds of respiratory disturbances. Its vulgar names are Emetic Weed, Emetic Herb, Wild Tobacco, Indian Tobacco. All investigators, except one, state that it was unknown to the Indians. The first report we have of it was given in 1875 by Cutler,⁷ who stated that he had cured himself with the tincture of *Lobelia inflata*, after having suffered from Asthma for ten years. In 1809, upon Cutler's recommendation, it was admitted into Medicine. The name *Lobelia inflata*, however, is most intimately connected with the name of Thomson,² Thomson, an empiric, had founded a sect in Massachusetts, which used *Lobelia* so frequently, that its members often were called "Lobelia Doctors."

Lobelia inflata contains several alkaloids three of which are isolated: Lobelin, Lobelitin and Base B. The action of the last two is similar to the action of Lobelin, but weaker. The most important agent is, of course, Lobelin, which was, until recently, only isolated in the form of amorphous salts, such as chlorides and sulphates. Wieland,²⁶ in 1916, however, succeeded in preparing a crystalline hydrochloric salt, which was an important achievement. The dosage of the amorphous preparations was uncertain. They were destroyed by heat and could never be obtained

chemically pure. The crystalline preparations are free from all these disadvantages. The most important difference, however, between the action of the amorphous and crystalline preparations is that the former causes vomiting, in fact this action was until recently emphasized as the principal action, while the crystalline preparations have no such effect.

There has been, and still is, an uncertainty as to what group of alkaloids Lobelin belongs to. Procter,⁹ in 1838, and Dreser,²³ in 1889, assigned it to the Nicotine group. Dreser,²³ however, also described properties according to which it could be classified just as well under the Atropine group. In his latest investigations Wieland²⁷ concludes that Lobelin belongs to the group of Coriamyrtin and the Querbacho alkaloids.

As to the action of Lobelin, I want to call attention only to its most remarkable property, that of a respiratory poison. As I have already mentioned, it has been introduced into Medicine as a remedy against Asthma and has been used as such for a century. The justification of this use was apparently established by Dreser²³, in 1889, who found a threefold action of Lobelin.

1. The terminations of the Vagus nerve were paralyzed, thus relieving the spasm of the bronchial muscular apparatus.

2. The center of vomiting was stimulated whereby the bronchial glands were excited and expectoration promoted.

3. The center of respiration was stimulated which was thought to relieve dyspnoea.

Wieland²⁷, on the other hand, working with crystalline Lobelin, was unable to find any relaxation of the bronchial musculature, nor did he find any emetic action. The two essential properties, which had made the amorphous Lobelin an ant-asthmaticum, were thus proved not to be due to Lobelin.

Though Lobelin thus was discarded as a remedy against Asthma a wider and perhaps more important field was opened for it by the investigations of Wieland²⁷, who found that Lobelin is a specific stimulant of the respiratory center.

In this connection I want to mention some of the clinical observations. Injections of Lobelin were used by Hellwig²⁹ and Hoechstebach³⁰ in respiratory paralysis during narcosis.

Eckstein and Romingen,²⁸ of the pediatrics clinic in the University of Freiburg, reported that in cases of Pneumonia and other infectious diseases as well as in grave acute and chronic alimentary disturbances—in which a central respiratory paralysis often causes death—Lobelin had been used with success and even as a life-saver.

There are two large fields which are very promising for Lobelin: poisonings of the respiratory center as caused by morphine, hypnotics, alcohol, and carbon-monoxide; and in urea of the respiratory center during labor, causing asphyxia of the newly born.

Heretofore, all authorities have observed an effect upon the circulation. Their results, however, are very unsatisfactory, partly due to lack of technique and partly due to the fact that they have limited themselves to studying the action of the drug upon the nervous apparatus, and neglected the effect upon the heart muscle and the blood vessels, in particular the capillaries.

Between the results of Ott,¹³ Edmunds,¹⁹ Ronnberg²⁷ and Dreser²³ a certain agreement exists. They have found that after the injection of small doses of Lobelin an increase of the blood pressure and a decrease of the pulse rate takes place. The application of large doses, however, produces a decrease in both the blood-pressure and pulse rate. The different observers explain these phenomena in different ways: as an action of the drug upon the terminations of the vagus nerve,—like the action of Atropine—as an action upon the ganglion of the vagus nerve—as with Nicotine—or as an effect of vomiting. Besides, all their results were obtained with unreasonably large doses.

In the present investigation it will be shown that Lobelin has properties, which, though not strong enough to justify its classification as a cardiac stimulant, nevertheless favorably support its principal action as a respiratory stimulant.

The effect of Lobelin upon the heart muscle and the capillaries was studied by experiments carried out after the following scheme: The toxic dose was first determined, then the threshold of activity, and finally the effect of the therapeutic dose was examined. The action of the latter upon the functions of the heart, the systole and diastole, was determined, and also its action upon the blood pressure, considering separately the effect of heart muscle and capillaries.

I carried out my experiments on the isolated frog's heart by means of Williams' apparatus, modified by Holste. As a circulating medium defibrinated and filtrated ox-blood was used, which was diluted with physiologic sodium-chloride solution in the proportion one to two. The amount of solution was 50 ccm. The heart was kept moist with the same solution to avoid ill effects of desiccation. The systolic changes were registered upon a kymograph by means of a vertical manometer; the diastolic changes were observed by means of a horizontal manometer.

The experiments were conducted with *Rana temporaria* of an average weight of 30 grams, in the month of April. The animals had passed the winter in the terrarium. They were not subjected to any special preparation except that they were kept cool and provided with an adequate amount of water. Besides the *temporaria* also esculentes were used, which were caught in May, and the experiments carried out immediately. The crystalline hydrochloride salt of Lobelin was used, prepared by the firm C. H. Boehringer Sohn, Nieder-Ingelheim a. Rhein. The experiments were carried out in the Institute of Pharmacology of the University of Jena under the direction of Professor A. Holste. A complete account of the work is given in the writer's Inaugural Dissertation, Jena, 1923.37

I. Determination of the Toxic Dose

The Lobelin was administered in increasing amounts, and the effect registered upon a kymograph by means of the vertical manometer. The result of a typical experiment is shown in Fig. A.



A

Immediately after the injection of 0.000018 grams of Lobelin a diminution of the systolic excursions takes place, after a few seconds, however, an increase follows the decrease. After 6 minutes the amplitude is again normal and after 15 minutes a maximum constant amplitude is reached. The pulse rate had then decreased from 42 to 38. The dose was then increased to 0.000036 g which produced still larger and more energetic contractions and decreased the pulse rate to 30. On raising the dose to 0.000054 g arrhythmia occurred i. e. 3 to 6 successive contractions were followed by a diastolic pause. After a few minutes a decrease in the excursions may be observed. The pulse rate has dropped to 19. The dose 0.000072 g produces a few large dichrotic contractions which develop into large regular pulses. After 5 minutes a decrease is observed. The pulse rate is 16. Administration of the dose 0.000090 g causes an immediate cessation in diastole.

The experiments show that the toxic action of Lobelin, indicated by the appearance of arrhythmia, begins with a dose of

0.00005 g. For man this would correspond to a dose of 1.0 g which is very large compared with the therapeutic dose 0.003 g.

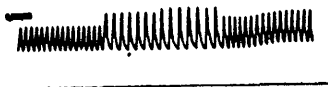
II. Estimation of the Threshold of Action

Decreasing doses were applied until the smallest was reached at which no change in the heart action occurred. This dose proved to be as small as 0.0000002 g.

III. Investigation of the Action of the Therapeutic Dose

To get an approximate determination of the therapeutic dose the total quantity of blood in a frog was calculated in the same manner as for man, allowing 1-12 to 1-13 of the body weight for the quantity of blood present. The therapeutic dose for a man of weight 60 kg is 0.003 to 0.006 g. For a frog of weight 30 g the therapeutic dose will then be 0.000003 g.

(a.) The action of the therapeutic dose is shown by Fig. B. The curve is obtained by the vertical manometer which registers the action upon the internal or systolic heart fibres.



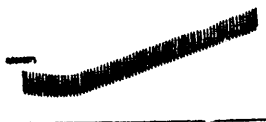
Immediately after the injection of the therapeutic dose the systolic contractions become stronger, and after 3 minutes they attain their maximum amplitude, at which they remain for 20 minutes; then a decrease of the excursions follows, but even after one hour the original amplitude is not reached. The pulse rate decreased from 56 to 46, and when the effect was strongest it was only 26. The curve also shows a slight increase of the blood pressure.

(b.) Experiments with the Horizontal Manometer. The horizontal manometer registers the action upon the external or diastolic heart fibres. The purpose of the experiments with this manometer was to ascertain the relaxation of the external fibres after the stimulating action on the internal fibres was determined. Table I gives the results obtained in two experiments. It is seen that Lobelin has a small effect upon the diastolic fibres of the heart. It is noteworthy that the maximum effect always was obtained with the therapeutic dose.

IV. The Effect Upon the Blood Pressure

The effect upon the blood pressure was studied with the vertical manometer, using hearts of esculentes of an average weight

of 50 g. After the application of the therapeutic dose no change in the pressure was observed. But with an increasing dose a decided increase of the blood pressure was observed as shown by Fig. C.



The effect was found to be strongest with a dose of 0.0000075 g which corresponds to 0.0000045 g for temporaria and to 0.001 for man. This dose is within the limit of the therapeutic dose.

V. Action Upon the Capillaries

The action of Lobelin upon the capillaries was studied on the Trendelenburg preparation. The frog was eviscerated, the renal veins ligated, an afferent canule placed in the aorta and an efferent canule in the abdominal vein. As a circulating medium 125 ccm Ringer solution was used. The Lobelin was injected in the aortic canule. The number of drops flowing from the abdominal vein in a certain time was determined, and the width of the capillaries thus measured. The experiments showed that Lobelin causes the capillaries to contract, the contraction increasing with the dose.

In order to compare the increase in tonus obtained by Lobelin with that produced by Adrenalin, parallel experiments were made with Adrenalin and it was found that the effect with Lobelin on temporariae is only 1-10 of that obtained with Adrenalin. Table II gives the results of one experiment with Lobelin and one with Adrenalin.

All these results taken together prove that Lobelin has, in all respects, a favorable action upon the circulation. It increases the systolic power by increasing the contractility of the systolic muscle fibres, thus promoting the action of the heart. It has a favorable action by enhancing the relaxation of the diastolic fibres, thus permitting a more complete filling of the ventricles. This action is also responsible for the decrease in the pulse rate which, in its turn, causes a strengthening of the heart power. Finally, due to its tonic action Lobelin raises the blood pressure.

Table I.

Dose	Amplitude	
Normal	11 mm.	7 mm
0.000009 g	15 mm.	11 mm
0.000018 g	15 mm.	13 mm
0.000027 g	16 mm.	15 mm
0.000036 g	15 mm.	13 mm
0.000045 g	15 mm.	12 mm

Table II.

Rana temporaria				
A	B	C	D	E
Normal -----	2	40		
	2½	48	19.1	
	2½	46		
	7	134		
0.000009 g Lobelin -----	2½	46		
	2½	46	17.3	
	3	46		
	8	138		1.8
Normal -----	4.25	54		
	4.30	54	12.2	
	4.30	54		
	13 25	162		
0.00000083 g Adrenalin -----	25	54		
	25	54	2.1	
	25	54		
	75	162		10.1

A represents the dose; B the time; C the number of drops; D the average number of drops per minute; and E the difference.

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