stantial agreement for the ash content of Lupulin, but are not in accordance with actual commercial conditions, which are nearly twice as high as pharmacopœial standards.

Observations relating to ash content, in order to be of practical value, must cover hundreds of thousands of samples, be carried over a series of years and made by a number of observers.

In the Digest of Criticisms of the Hygienic Laboratory an effort had been made to compile ash determinations recorded by different individuals, and also the work done in European laboratories in connection with spices. For the majority of vegetable drugs he thought it necessary to be content with ash determinations, permitting rather wide limitations for drugs in the powdered form.

THE COMPOSITION OF GELSEMININE.

L. E. SAYRE.

The alkaloids of Gelsemium have been investigated at intervals since 1869, by Wormley, Gerrard, Robbins, Sonnenschein, Thompson and others. These valuable contributions have been referred to in previous papers, published in the proceedings of this association since 1907.

It was not until 1887 that F. A. Thompson announced the existence of a second alkaloid in the root which he named Gelseminine. The study of this second principle was left by Thompson for others who might in the future have the time and the inclination to do it. The result of my study of this principle seems to indicate, as stated in former papers, that the Gelseminine of Thompson is not a definite and simple body. Recent study confirms this opinion. Other confirmation, than my own work, has been given by a recent analyst, Charles Watson Moore, whose paper was published in the Jour. Chem. Soc'ty, Nov., 1910, No. LXXVII, p. 2223. This author, after mentioning the less important principles of the alcoholic extract states:

"The portion of the alcoholic extract soluble in water from which the resin has been removed contained scopoletin (a monomethyl ether of esculetin) which was present in a free state and also a glucoside, together with some sugar. It also yielded three alkaloidal products, one of which was obtained in a pure crystalline form corresponding to Gelsemine. The other two were amorphous and non-crystalline, the one to which the name Gelseminine has been given being more basic than the other."

This unexpected confirmation of my observations, previously made, is especially gratifying.

In the April issue of the Bulletin of the A. Ph. A. an article appears by Kimberly, Roberts and Vanderkleed, in which a suitable assay of Gelsemium is discussed. These men state that the activity of the drug depends primarily upon the so-called alkaloid Gelseminine, and only secondarily upon the more readily obtained Gelsemine, which exists in much larger proportion. These investigators fail to recognize the presence of three alkaloids, but this does not detract from their valuable contribution. The existence of three alkaloids, however, makes the assay of the drug still more complicated. A chemical assay can be made reliable only when we *know* the principles we have to consider.

During the past year a further study of this non-crystalline alkaloid, gelseminine, has been attempted. For this investigation, crude products were furnished by Chas. E. Vanderkleed, of the Mulford Laboratory. These products consisted of the crude alkaloids from 50 pounds of the drug, as follows:

Gelsemine, 0.44 gm.; Gelseminine, 6.4 gm.

Special attention was given to the latter. The process for the separation of these, although given in former papers, may be briefly outlined. The concentrated alcoholic extract is treated with acidulated water. The resulting acidulated aqueous solution is thoroughly washed until all of the so-called gelsemic acid is removed. The aqueous solution is then made alkaline and all of the alkaloid removed by repeated shaking with ether-chloroform. After removal of the solvent by evaporation of the ether-chloroform solutions, the residue (crude alkaloids) is separated into crystalline and non-crystalline alkaloidal portions by repeated solution in alcohol and careful evaporation in vacuo., thus allowing the crystalline gelsemine to slowly deposit. The mother liquor contains the gelseminine.

This latter alkaloid, gelseminine, is capable of further separation, I have found. If after all of the gelsemine is entirely removed—which is a tedious operation—it is redissolved in acidulated water and again precipitated with weak solution of ammonia and the precipitate continuously washed with ammonia water it is found to yield alkaloid to that solvent until there is left behind an insoluble portion, this latter portion may be designated Gelseminine. The portion soluble in ammonia, on concentration by means of a hot air blast produces, in thin layer, a reddish yellow scale, strongly alkaloidal, but contains a considerable amount of crystals of ammonium chloride. This contamination is removed by redissolving the scales in water, adding to the solution calcium hydrate. The solution is fanned to a solid concentrate and the solid residue is dissolved in alcohol and filtered. The alcoholic solution is treated with just sufficient sulphuric acid to remove the lime. On filtering and evaporating, the alkaloidal salt remains. For the name of this third alkaloid I would suggest the name of Gelsemoidine.

Permit me to call attention in passing to the confusion which exists at present in commerce, particularly, concerning the alkaloid gelseminine. Under this name is supplied, not the article in question, but the crystalline alkaloid gelsemine. The Germans appear to be responsible for this confusion as gelseminine appears to be their name for the crystalline alkaloid. My own orders for gelseminine have brought me, from abroad, gelsemine. In a recent issue of a publication on Newer Remedies, gelseminine is described as a crystalline body, and the description given answers to the alkaloid Gelsemine. In the presence of such confusion I would suggest the name of Sempervrine in place of gelseminine, or some other word which will tend to remove the unhappy confusion that now exists.

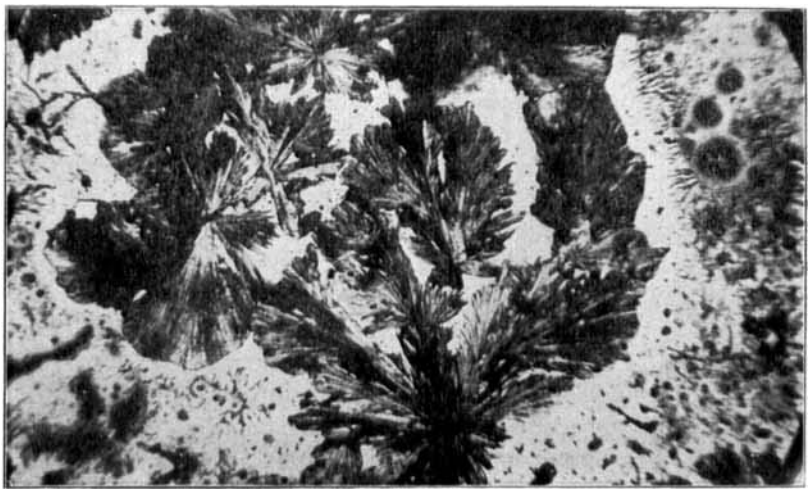
The following color reactions distinguish Gelsemoidine from the other two alkaloids: manganic oxide and sulphuric acid produce with gelsemoidine, first a deep purple. Changing finally to a deep blue. Gelseminine, with the same reagent produces a brown, changing to a brownish pink and finally to a yellow color. Gelsemine produces a crimson, changing to green and finally yellow.

The non-crystalline alkaloids may be further distinguished by their solubility. An aqueous solution of the gelsemoidine hydrochloride, when treated with ammonia water in slight excess will be, after first precipitating, redissolved in the alkaline fluid. Gelseminine when treated in the same manner remains undissolved. Gelsemine hydrochloride when treated similarly goes into solution very slowly but is hastened by warming. Not so with gelseminine hydrochloride.

Many attempts have been made to produce crystalline salts from these two amorphous alkaloids but without success. Gelsemoidine hydrochloride can be obtained in reddish yellow scales which are exceedingly hygroscopic. Gelseminine hydrochloride is on the other hand quite permanent.

PHYSIOLOGICAL RELATION OF THE ALKALOIDS.

Pharmacological experiments have shown that the amorphous alkaloids are many more times toxic than the crystalline gelsemine. It takes 10 milligrams of the gelsemine hydrochloride to cause slight tremors and convulsive movements in



Photograph of Crystals of Gelsemine Hydrochloride. By spontaneous evaporation of alcoholic solution

a guinea pig of medium weight (450 gm.), in 45 minutes, while 3 milligrams of gelseminine hydrochloride will prove fatal to this animal, of same weight in 30 minutes. It has pronounced action on the voluntary muscles, loss of coördination and a paralytic action on the respiration.

1.5 mgs. of gelsemoidine hydrochloride proved fatal to a guinea pig weighing 425 gm. in one and one-half hours, the most pronounced action being upon the voluntary muscles and the respiration. Severe muscular spasms (not tetanic like strychnine) were brought on within 30 minutes. This same alkaloidal salt produced a pronounced stupor on a dog weighing 29 pounds in 45 milligram dose. The action was gradual but rapid.

In all of the physiological experiments it was noted that the two non-crystalline alkaloids in small therapeutic doses had an hypnotic and sedative action.

I am indebted to V. H. Moon of the Pharmacological Laboratory for the following statement as regards the action of the non-crystalline alkaloids of Gelsemium:

"The toxic action of the two alkaloids is almost identical. The muscles become paralyzed and the body limp and relaxed. The respiration is slowed, becomes jerky, labored and irregular and finally ceases apparently from paralysis of the motor endings in the respiratory muscles. The heart's action is slowed and in the later stages, often irregular but continues strong until after respiration ceases. The constrictor urethrae muscles are also paralyzed, causing frequent urination and dribbling. The smallest lethal dose for a 35 gm. frog was .003 gramme and the largest dose which was followed by recovery was .004 grammes. For the 340 gramme guinea pig, the smallest fatal dose was .001 gramme and the largest dose followed by recovery was .002 gramme.

"The medicinal effect of gelsemoidine in no way resembles the toxic effect, but consists of a quieting, sedative action, followed by a hypnotic effect if continued. The following typical example illustrates: A 13 kgm. dog was given a subcutaneous injection of .015 grammes gelsemoidine. Almost immediately the dog became less restless and was disposed to lie prone with head resting on paws; he was apparently normal otherwise and was attentive when spoken to. The respiration rate dropped from 42 to 22 and the heart rate from 137 to 114. This effect was partly due to the fact that the animal was less active. Within an hour the hypnotic effect was evidenced, the animal slept continuously and when roused would lie down immediately and go to sleep again unless prevented. A second injection of .015 grammes one hour later made the hypnotic effect more profound and reduced the heart rate from 114 to 41. Respiration from 22 to 20. A third injection of .015 grammes was given forty-five minutes later, after which the dog immediately went into profound sleep. When roused, he was attentive and wagged the tail as usual but was slightly unsteady on the feet. Twenty minutes after this dose the respiration was 20 per minute and somewhat labored. The heart rate raised to 50. When walking or standing the fore feet would suddenly collapse causing the animal to fall on its face. Muscular control would be regained only to be lost again in a moment. This was accompanied by loss of urethral control. The condition of partial paralysis continued several hours but the dog was apparently normal twenty-four hours later. No attempt was made in these experiments to record the blood pressure nor to determine definitely the exact location of the effect on the nervous system. Only the general physiological effects were sought, but these would indicate that both the cerebrum and the motor endings were affected. As a sedative and hypnotic the new alkaloid Gelsemoidine gives unusual promise, and the therapeutic and physiological effects should be worked out in further detail.

"Some experiments were tried with Gelsemine which is described as *inactive* by some authorities. We secured very decided muscular and nervous effects in guinea pigs from subcutaneous injection of .010 grammes, but these were not carried far enough to state definitely what the physiological effects are. Judgment

should be suspended on this remedy until more definite statements can be made as to its action."

My thanks to Mr. Paul Carl for his valuable assistance in this work is hereby acknowledged.

UNIVERSITY OF KANSAS.

COMPARISON OF THE SENSITIVENESS OF THE FEHLING, THE NYLANDER AND THE PHENYL-HYDRAZINE TESTS FOR THE DETECTION OF DEXTROSE IN URINE.

G. H. MEEKER, PH. D., LL. D.

Preparation of the Dextrose.—The highest purity dextrose prepared by Merck & Co. was used in these experiments.

Owing to the presence of moisture in the dextrose, which would affect the weight of the dextrose when used for the purpose of making percentage solutions, the dextrose was dried to constant weight under a pressure of 125 mm., over calcium chloride, in a vacuum desiccator placed in a thermostat at a constant temperature of 37.5° C. The absorption of water during weighings was prevented by having the dextrose in a glass stoppered weighing bottle.

Date.	Weight.
October 5	26.0951 gms.
October 12	26.0894 "
October 19	26.0868 "
October 20	26.0865 "
October 26	26.0865 "
October 27	26.0866 "
November 2	26.0865 "
November 3	26.0865 "

This table shows that, under the conditions of our experiments, constant weight was reached at the end of fifteen days' drying. Although drying was continued during another fifteen days, there was no further loss in weight.

Preparation of the Dextrose Solutions.—The dextrose solutions were prepared as needed by dissolving weighed quantities of our dried dextrose in the proper quantities of distilled water.

Nylander's Reagent used in these experiments was made as follows:

Bismuth Subnitrate	2 gm.
Sodium Hydroxide	8 gm.
Rochelle Salt	4 gm.
Distilled Water to make	100 cc.

Two kinds of Fehling's Solutions were used in these experiments, as follows:

1. (a) *Copper Solution:*

Cupric Sulphate	34.639 gm.
Distilled Water to make	500.000 cc.

(b) *Alkaline Solution:*

Sodium Hydroxide	175 gm.
Rochelle Salt	60 gm.
Distilled Water to make	500 cc.