DISCOVERY OF THE ALKALOIDAL AFFINITIES OF HYDROUS ALUMINUM SILICATE.*

BY JOHN URI LLOYD, PHAR.M.

In the discursive paper following, which has, of necessity, been written in the first person, I have attempted to answer many questions that have been continuously asked of me during the past two years. I have also aimed to record many incidents, seemingly irrelevant, but which seem to me of sufficient interest to be authoritatively established. The usual exasperating scarcity of authoritative records in the direction of the early history of long-established drugs and remedial agents, leads me to feel that not alone in the present, but in the future, some one may desire to obtain the details embraced in the following narrative account.

History.—In the winter of 1910, calling to my experimental laboratory Mr. Wm. J. Miller, foreman of the technical laboratory that takes my special care, I said:

" Make a mixture of five parts berberine sulphate, with ninety-five parts fullers' earth. Bring it to a putty-like condition with water, working it well in a Wedgwood mortar to a complete and thorough admixture, then dry the product, powder it, and bring me a sample."

Within a reasonable time, a powder having the bright yellow color of berberine was brought to my desk. It was practically odorless, and seemed to be an intimately incorporated mixture of the two substances. Placing some of it upon my tongue, I found it tasteless! Sending for Mr. Miller, I asked:

" Are you sure that this mixture is as I directed, sulphate of berberine and fullers' earth only? "

" Exactly as directed," he replied.

Taking a small amount of the mixture, I digested it with diluted sulphuric acid, and filtered it. The filtrate was colorless, and gave no alkaloidal reaction. The residue on the filter paper retained its full berberine yellow color, but was tasteless.

" Send for a sample of the berberine sulphate used in the mixture." It came, and I found it to be true to name.

" Send for a sample of the fullers' earth used." It also came, and then I took the subject in hand.[1]

I made a mixture of berberine sulphate and fullers' earth, in the proportions aforenamed, added the same to distilled water, agitated the mixture well, and filtered. Behold! the filtrate passed colorless and devoid of alkaloid. I placed some of the residue upon the filter paper, on my tongue. It was tasteless. This mixture likewise, when digested with diluted acid and filtered, gave no evidence of an alkaloid being present.

Next I took, successively, other alkaloidal salts, such as those of morphine, quinine, cocaine, etc., submitted them to the same manipulation, and found that *all alkaloids experimented with* produced insoluble compounds, and that all (brucine excepted) were practically tasteless. I also discovered that the reaction was nearly instantaneous.

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* Read before Scientific Section, A. Ph. A., San Francisco Meeting, 1916.

[1] Readers of this communication may recall the experiment made in 1885 by Professor Thomas H. Norton, who, at my suggestion, studied the combinations that could be made between hydrastine and calcium. These, however, were altogether different from the compounds now under discussion.

Search of Literature.—I now turned to literature on the subject of alkaloidal reagents, for I had no recollection of this material being applied to alkaloidal manipulation. The shelves of the Lloyd Library gave me no references. Nor could any authorities I consulted give me any information in this direction. I accepted, therefore, that this phase of the problem was new.

Search for the Active Constituent.—I next attempted to establish the constituent of fullers' earth that produced this phenomenon.[2] Naturally, I thought of the possible influence of organic contaminations. To establish this point, I digested fullers' earth with nitric acid, and afterwards washed the residue with water. It carried the full alkaloidal qualities of the original material, even when the nitric acid was heated in contact with the fullers' earth. Other methods and agents (such as sulphuric acid), that would have destroyed any organic structures, gave like results.

I next removed all possible amounts of iron, by the oxidizing action of nitro-hydrochloric acid, and subsequent washings with diluted hydrochloric acid. The residue retained its alkaloidal affinities. Digestion with dilute acids to the total removal of calcium and magnesium carbonates and salts, left the product active.

Next, a portion of the fullers' earth was heated in a crucible, until all the water of combination was expelled. The brick-dust red residue had no alkaloidal affinities whatever! The same paralysis of alkaloidal affinity occurred with calcined specimens free from iron and organic contaminations. All these observations were subsequently confirmed in a short paper[3] by Dr. Sigmund Waldbott, of the Ohio Mechanics' Institute, Cincinnati, Ohio. Heating the material to about 130° did not destroy its peculiar activity, but red heat expelled an additional quantity of water, rendering the reagent inert. I therefore accepted that the alkaloidal affinities did not depend upon either organic structures, iron compounds, adhering calcium or magnesium salts, or water-free aluminum silicate. The reaction was, unquestionably, a function of *hydrous* aluminum silicate.

Physical Condition of the Reagent.—The *physical* form of the reagent was next investigated. It was found that clay free from the "soapy" or "sticky" qualities, as commonly expressed, was likely to run very low in alkaloidal attraction. On the other hand, the sticky, blue clay of the hills of our neighborhood was but slightly active, and this rule was therefore not inflexible. Dr. Waldbott (previously quoted) states as follows:

> The thought suggested itself that water-deposited clay might show the same action; indeed it was found by the writer last summer, that the fine blue clay so abundant in the hills of Cincinnati, after treatment with hydrochloric acid, had the same effect upon alkaloidal salts, rather faintly, as may be expected, yet very distinctly.

Thirty grammes of dry fullers' earth, capable of taking up 3¾ grammes of quinine bisulphate, slowly stirred into 240 grammes of sulphuric acid, resulted in an immediate increase of temperature, due, unquestionably, to the abstraction of water from the hydrous aluminum silicate. The mixture was digested for an hour on a water-bath, cooled, and poured into a gallon of water. The subsided

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[2] Literature consulted gave me little information concerning the exact composition (physical included) of the material known as "fullers' earth." Subsequent experiences have taught me that this is readily explained by the fact that the term "fullers' earth" is a blanket name, covering a multitude of different earth substances, of widely different composition. See Table IV.

[3] Journal of the American Chemical Society, June, 1913.

precipitate took up 2½ grammes of quinine bisulphate. This demonstrated that even a great excess of sulphuric acid did not, by abstraction of water, destroy the alkaloidal affinity of the earth.

Inasmuch as natural fullers' earths are inclined to a slight acid reaction,[4] I attempted to neutralize the acid by alkalies, in order to see if the product could thus be paralyzed. A portion of the reagent was digested for twenty-four hours with dilute ammonia water, then collected on a filter, dried and powdered. It proved to carry its full alkaloidal adhesiveness, thus showing that the neutralization of free acid, if any were in the reagent, did not destroy the alkaloidal attraction. Experimentation teaches me that hydrous aluminum silicate, natural, may be white, practically free from iron compounds and natural dirt, and of a slight alkaline reaction. Professor Virgil Coblentz, to whom such a specimen was submitted, makes the following report:

> Upon testing the reaction of your sample, I find it to be alkaline to phenolphthalein, iodeosine, Congo-red, and methyl orange.

Different samples of fullers' earth, foreign and domestic, were found to vary markedly in both structural composition and in alkaloidal affinities, and it was shown that these alkaloidal affinities were not dependent upon an exact chemical composition, or the acid qualities of the earth.

An attempt was next made to separate from fullers' earth, by chemical processes, the hydrously active agent, if the activity be from hydration alone, but with indifferent success. I had now accepted that the alkaloidal affinity depended upon the *physical* form, which in turn rested upon, and was closely connected with, the *hydrated* condition of the material. I had also determined to my satisfaction, at that date, that successive degrees of hydration made the aluminum silicate increasingly active, and I also became, somewhat reluctantly, tinctured with the thought that the alkaloidal affinity depended upon the *condition of the water of adhesion, or hydration (possibly both)*, and was distinct from that of water of definite combination, or crystallization.

Artificial Colloids Not Active.—Thus I was led to attempt to make artificially hydrated aluminum silicate, silicic acid, as well as gelatinous alumina and silica. For this purpose I used such processes as are employed for the preparation of hydrous alumina by the reaction between sulphate of aluminum and sodium carbonate. These products, however, whether made by cold or hot water, carried but feeble alkaloidal affinities, although the cold water product was typically gelatinous. Likewise, compounds precipitated as gelatinous forms from sodium silicate, by acids, proved to be practically inert. Then I reluctantly returned to the original, impure, natural material (fullers' earth), accepting that it carried a peculiar colloidal structure, embracing alumina, silica and water, which, in its native form, possessed the qualities of an alkaloidal precipitant.

Standardizing the Reagent.—Turning to the original material, fullers' earth, I now attempted through physical processes to separate, in its greatest degree of

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[4] Fullers' Earth, by Charles L. Parsons: "The shades of color of fullers' earth are fully as great as those of other kinds of clay. Most of the earths on the market are light brown, gray, buff, or cream color, and a few are almost white. All fullers' earths which have been found valuable for bleaching purposes show a distinct so-called acid reaction. If a sample is touched to neutral litmus paper the paper will turn red; if the clay is suspended in water and phenolphthalein is added, a quantity of alkali, which varies widely with different earths, can be added before the red color appears. This property is no indication of true acidity, for the earth contains no acid."

purity, the substance, whatever it might be, that produced the alkaloidal reaction.[5]

Admixture with much water established that a certain part of the fullers' earth quickly settled, whereas another part slowly separated from the water solution. Decanting the overlying water and again adding water established that, in the second washing, a longer time was required for the subsidence of this overlying, gelatinous float. Again decanting the water and adding fresh water was followed by a further retardation (suspension) of the overlying light precipitate, until finally it was discovered that a colloidal, overlying material formed, as a translucent mud or gelatinous float, over the part that quickly settled. This colloidal fluid could be decanted as a liquid, and then allowed, by long time, to settle, separating it, thus, quite free from the heavier body.[6] It was gelatinous and, when collected on a strainer and dried, it formed a tough, hard, colloidal stone that, on being powdered, was found to possess, as contrasted with the original earth, markedly *increased* alkaloidal affinities.

It may be stated that some of the natural forms of hydrous aluminum silicate, mixed with water and agitated occasionally for some days and then permitted to rest, resolve themselves into different structural layers that subside, strata-like, the topmost layer being surmounted by a milky liquid that approaches a colloidal solution. The topmost layer of this sediment is a slime, resembling protoplasm, and is indeed nearly a fluid. Over this rests the milky liquid aforenamed, which is in turn a series of zone-compounds that, on filtration, are found to consist of a colloidal substance, part of which is so attenuated as to pass freely through the filter paper,[7] leaving on the filter a gelatinous, jelly-like material. This jelly reminds one of what the entomologist now calls "plankton," the invisible and transparent organizations that are found, suspended, in all natural waters, and that serve as the long-mysterious food of minnows.

From a fullers' earth, fifteen parts of which are capable of precipitating one part of quinine bisulphate, an increased alkaloidal affinity was thus made possible, only *eight* parts being required to precipitate one part quinine bisulphate. This improvement in quality of the dried colloid from ordinary fullers' earth, being sufficiently energetic, as well as feasible in practical manipulation, was taken as a preliminary standard, and this standard is yet retained, although, by the process to be next named, the alkaloidal affinity of the material can be increased much beyond this point.

Second Process.—In the early course of my experiments it was demonstrated that, with the quality of earth used, with each manipulation of an alkaloid, the colorless wash-water contained a substance that, on evaporation, would crystallize colorless and permanent, if the alkaloidal salt were a sulphate; but that it was hygroscopic if the alkaloidal salt were a chloride. For example, sulphate of morphine and sulphate of quinine, each, on evaporating the washings, furnished a crop of permanent, colorless crystals, whereas the chlorides of these alkaloids furnished a hygroscopic salt. Reasoning from this, I concluded that each

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[5] That this reaction was due to a something in the fullers' earth not yet understood was evidenced by the fact that no two qualities of fullers' earth were identical in their alkaloidal adsorption qualities, some possessing this in a marked degree, while others were very feeble, as shown by Table IV.

[6] The successive washings depleted the substance of its inherent soluble salts, which have a tendency to granulate gelatinous hydrates.

[7] I have not as yet applied the ultra-microscope to this filtrate. In my opinion, it will be shown to carry dispersed colloids, and it may prove to be a very sensitive reagent in alkaloidal research.

alkaloidal manipulation threw out extraneous earths, in the form of sulphates and chlorides of calcium (and possibly aluminum), from the fullers' earth, this indeed proving to be a fact. Dr. Waldbott demonstrated that the reagent had the power of even liberating free sulphuric acid, where no magnesium or calcium carbonates were present.[8]

My endeavor at this period was, however, not to determine the nature of the *side* products, but to increase the alkaloidal affinities of the hydrous aluminum silicate, by the successive alkaloidal recombinations and exhaustions that successively threw out portions of the earth compound. Table I gives an experiment with this object, and illustrates that 8½ grammes of the standardized reagent, having qualities capable of precipitating 1 gramme of quinine bisulphate, continuously decreased in weight by the repeated use of 0.5 gramme quinine bisulphate, and yet carried its revivified alkaloidal adhesive qualities through twelve manipulations, the final result showing that 3.2 grammes of this successively refined reagent were, as regards alkaloidal adsorption quality, as active as the entire amount first employed.[9]

Process.—One gramme of quinine bisulphate was dissolved in 80 Cc. water, to which was added 8.5 Lloyd's reagent (*purified, colloidal, hydrous aluminum silicate*). The mixture was well shaken and filtered, the filtrate showing no alkaloidal reaction with Mayer's test. The precipitate was washed with water, the total aqueous washings being evaporated to dryness, yielding colorless, non-alkaloidal crystals (mainly calcium sulphate). The alkaloidal precipitate on the filter was dried, powdered, and extracted by successive treatments with ammoniacal chloroform (100 Cc., in fractions, for each experiment), until the alkaloid had been practically eliminated. The exhausted reagent was then dried and powdered. It weighed 7.5 grammes. This was used as the material for subsequent manipulations, the foregoing process being eleven times repeated, making twelve manipulations in all. As noted before, after the first exhaustion of the alkaloid, but 0.5 gramme of quinine bisulphate [9] was employed.

TABLE I.

Amount of reagent employed.		Quinine bisulphate employed.		Dried residue.
8.5 Gm.	plus	1.0 Gm.	gave	7.5 Gm.
7.5 Gm.	plus	0.5 Gm.	gave	6.7 Gm.
6.7 Gm.	plus	0.5 Gm.	gave	6.2 Gm.
6.2 Gm.	plus	0.5 Gm.	gave	5.5 Gm.
5.5 Gm.	plus	0.5 Gm.	gave	5.5 Gm.
5.5 Gm.	plus	0.5 Gm.	gave	5.0 Gm.
5.0 Gm.	plus	0.5 Gm.	gave	4.7 Gm.
4.7 Gm.	plus	0.5 Gm.	gave	4.7 Gm.
4.7 Gm.	plus	0.5 Gm.	gave	4.1 Gm.
4.1 Gm.	plus	0.5 Gm.	gave	4.0 Gm.
4.0 Gm.	plus	0.5 Gm.	gave	3.7 Gm.
3.7 Gm.	plus	0.5 Gm.	gave	3.2 Gm.

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[8] Science, July 3, 1914, p. 35.

[9] A question here arises as to whether this increase is due, altogether, to the exclusion of inert constituents of natural fullers' earth. I do not, in these preliminary remarks, exclude the supposition that there may be also a *molecular* change, which increases the affinity of the residue after the alkaloid is separated, by the aforenamed successive steps. In fact, I am now aiming to give only experiments made in the passing along, to the exclusion of theories. The 0.5 gramme was selected because the chloroformic washings were not sufficient to remove the total 1.0 gramme first employed, which was as much as the reagent could hold.

From this table it will be observed that there was a steady, but not regular, decrease in the weight of the reagent. It will also be observed that there is much unevenness in the proportion of the dried residue. This can be accounted for by the occlusion of uncertain amounts of water of attraction, not evenly dissipated in the drying; by incomplete washing of some of the precipitates in the successive stages; and by uneven extractions of the alkaloid, as well as by error of manipulation. But this experiment was not intended to be precise in details, or other than a general one, its object being to discover whether or not the reagent decreased in weight during successive manipulations, the trend of the decrease, if any, and also whether the revived reagent resumed its alkaloidal activity after being depleted of alkaloid. This was satisfactorily accomplished, 6.5 Gm. alkaloid having worked 8.5 Gm. of the reagent, which in the manipulation was reduced to 3.2 Gm. The experiment was not repeated to ensure mathematical exactness, this problem being left for those concerned in scientific exactness.[10] I had established that for twelve successive combinations and depletions, the dispossessed natural reagent resumed its alkaloidal vitality, and that, with each experiment, a colorless, inorganic salt was eliminated.[11]

Samples Distributed.—Venturing now to assume that the problem of hydrous aluminum silicate in its relation to alkaloids was of sufficient interest to warrant me in bringing it before the scientific world, I made a considerable supply of the dried and powdered colloidal structure, and placed it, together with stony slabs of the same material and the process by which it was obtained, in the hands of a number of chemists, presumably interested in these directions. None of these parties had ever experienced, or heard of, the alkaloidal affinity of this material, but they received my statements concerning it, most cordially. The fact of an insoluble, therapeutically inactive reagent, that held its alkaloid in the presence of an acid and liberated it in alkaline contact, seemed impossible, but when tested it led to the evolution of a multitude of theoretical possibilities, both technical and therapeutic.

At an early date, as has been stated, Dr. Sigmund Waldbott, of the Ohio Mechanics' Institute, Cincinnati, became interested in the manipulation, as observed by him in my laboratory experimental work. Likewise, Dr. M. I. Wilbert, of Washington, D. C., Dr. H. W. Felter, of Cincinnati, Dr. H. M. Gordin, of Chicago, and Dr. Bernard Fantus, of Chicago, to all of whom I brought the subject, undertook special lines of questioning investigations[12] that lay within their particular provinces. It is not proper for me to print private statements, but I can refer to two public papers that resulted, one by Drs. Gordin and Kaplan, the other by Dr. Bernard Fantus.

Investigations of Drs. Gordin and Kaplan.—Among others to whom specimens of the reagent were forwarded, together with data giving its origin and method of

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[10] Dr. Waldbott's attention was called to this table and to this phase of the problem, at an early date, and he began a series of careful investigations to determine various problems suggested, as well as to establish the composition of the excluded inorganic salt. Dr. H. M. Gordin was also interested in this phase of the investigation, but by reason of the fact that it had been undertaken by Dr. Waldbott, did not, so far as I know, enter into the problem.

[11] On a manufacturing scale, I now use the revived reagent repeatedly, for subsequent batches of the same drug, with as yet no noticeable decrease in affinity. My percolators run, with such drugs as gelsemium and lobelia, from one thousand to two thousand pounds.

[12] I have aimed, in this paper, to avoid intruding on any scientific problem that I know is being investigated by anyone. My aim is to introduce just enough research, or exploration details, to make plain the manner in which the opening problems were met.

preparation, was Dr. H. M. Gordin, of the School of Pharmacy, Northwestern University, Chicago, Illinois. From his very cordial reply (January 15, 1913) I extract one sentence, as follows: " Personally, I would be glad to go more deeply into the subject, and publish the results of my investigations." Much pleased, I supplied Dr. Gordin with an abundance of the reagent aforenamed, together with the process of manipulation, and all I knew concerning its general qualities. His first paper (Gordin and Kaplan), presented at the meeting of the American Pharmaceutical Association in Nashville, 1913, was mainly a study of the adhesive qualities of the reagent, in contrast with other adhesive substances, such as animal charcoal. This paper, printed in full in the JOURNAL OF THE AMERICAN PHARMACEUTICAL ASSOCIATION, 1913, was the first that had been issued in detail concerning the subject. Being widely read and distributed, it called the attention of the chemists of the world to the phenomena connected with hydrous aluminum silicate. It was shown therein that both the rapidity and completeness of the extraction of alkaloids from aqueous solutions by means of " Lloyd's reagent " far excelled that of other " adsorbers," being, in many instances, almost instantaneous.

Continuing their investigations, Drs. Gordin and Kaplan contributed to the American Pharmaceutical Association, at its Detroit meeting, a report of an attempt to separate the alkaloids morphine and strychnine from their respective combinations (JOURNAL OF THE AMERICAN PHARMACEUTICAL ASSOCIATION, December, 1914). In this, the difficulty in separating the total amount of the alkaloid by the process employed debarred analytical exactness, but reference was made to the fact that Dr. Hugh McGuigan had demonstrated that, in the living digestive apparatus, the union of the alkaloid strychnine and the reagent is readily disrupted, the action of the strychnine resulting. These physiological investigations by Drs. Felter, Gordin and Kaplan, and McGuigan have been given wide publicity.

Disappointment.—My first hope, seemingly well founded, after establishing the energy of this reagent in the presence of acids, was that by the administration of either highly colloidal fullers' earth, or a standardized, colloidal, hydrous aluminum silicate, the professional and scientific world would be able to antidote the action of any alkaloidal poison through its means, and that the reagent would thus prove a great boon to humanity.[13] I hoped that the reagent would grasp an alkaloid in the stomach and hold it to final elimination, thus preventing its assimilation. In order to determine this phase of the subject, Dr. H. W. Felter, Cincinnati, in 1911 made for me a physiological experiment, the record of which is as follows:[14]

TABLE II.

Report by Professor H. W. Felter, M.D.

Cincinnati, December 27, 1911.

9.15 A.M.	Administered to small dog, one year old, weighing 30 pounds, ¾ of one powder (1½ to 1¾ grains strychnine sulphate).
9.23 A.M.	No appreciable effects; followed at
9.24 A.M.	By tremulous whining; dog very alert; locomotion good.
9.31 A.M.	Locomotion slightly impaired; great uneasiness.
9.32 A.M.	Lay down as if very tired; got up in half minute, still whining.
9.33 A.M.	Gets on haunches frequently, and is very restless (or rather uneasy).

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[13] See Eclectic Medical Journal, Cincinnati, October, 1913, pp. 540–542.

[14] My mind naturally reverted to the " Clay Eaters " of the South, concerning whom I have been attempting to collect evidence, together with specimens of the clay thus employed. The result may yet be useful.

9.34 A.M. Locomotion is impaired in hind quarters, with contracted appearance; gets up and lies down at intervals of fifteen seconds.
9.35 A.M. *First convulsive start;* in half minute, another.
9.36 A.M. Convulsive starts frequent.
9.37 A.M. Ataxic or incoördinate gait.
9.38 A.M. Paralysis of hind quarters.
9.39 A.M. Sudden convulsive start, with tremors.
9.40 A.M. *First general convulsion,* in three convulsive movements.
9.41 A.M. While still in tetanic convulsion, administered a very little chloroform; but dog was dead before this could act.

(Signed) H. W. FELTER, M.D.

Next, Dr. Bernard Fantus made a like investigation, concerning which he reports as follows:

TABLE III.

Report by Dr. Bernard Fantus, Chicago, Ill.

Chicago, August 1, 1913.

10.30 A.M. Female dog, weighing 25 pounds, whose stomach was empty, was given by stomach tube 25 grains of alcresta strychnine sulphate (6 percent), representing 1½ grains strychnine sulphate (1.167 grains strychnine).
10.45 A.M. Up to this time animal was resting quietly.
10.46 A.M. Got up and walked; hind legs rigid. Animal is now restless, gets up and lies down, hind limbs rigid, until
11.00 A.M. Mild convulsion occurs.
11.01 A.M. Violent convulsion.
11.03 A.M. Violent convulsion.
11.06 A.M. to 11.10. Animal standing; limbs stiff; occasional convulsive starts; frequently rubs its nose against floor of cage.
11.10 A.M. to 11.13. Walking about; front as well as hind legs rigid.
11.14 A.M. Convulsion, more violent than any preceding, lasting several minutes, leaving animal prostrated, with gasping and irregular respirations, frequent convulsive starts and tremors.
11.34 A.M. Convulsive starts becoming more severe.
11.36 A.M. Violent and prolonged convulsion.
11.38 A.M. Another severe and prolonged convulsion.
11.40 A.M. Death.

(Signed) BERNARD FANTUS, M.D.

As already stated by Dr. Gordin, Dr. McGuigan (whose detailed report I have not received) had also established that the strychnine combination possessed, in alkaline contact, its lethal strychnine qualities, the difference between its action and that of the alkaloid alone seeming to be a more or less prolonged influence, before death resulted.

Dr. Fantus's Investigations.—Dr. Bernard Fantus, who is much interested in the subject of pleasant medicines, has recently published a work titled, "Candy Medication." [15] He naturally became concerned in these alkaloidal compounds because, while tasteless, or nearly so, they are yet therapeutically effective. In the year 1912 he obtained from me supplies of different alkaloidal combinations from which, even with strychnine, he made candies that were free from bitterness, his report being contributed to the American Pharmaceutical Association, Nashville, 1913. In 1915,[16] he contributed another and very valuable article, entitled "Fullers'

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[15] Candy Medication, C. V. Mosby Company, St. Louis, 1915.

[16] Journal of the American Medical Association, May 29, 1915.

Earth," on the antidotal value of hydrous aluminum silicate as found in fullers' earth, exemplifying the same with many studies concerning outreaches of the subject, together with a table giving adsorption values of different earths. His table on fullers' earth agrees with my experiences,[17] so far as demonstrating the uncertainty of fullers' earth in alkaloidal manipulation is concerned.

Other Opportunities.—Deeply disappointed in my hope that the reagent would prove to be an antidote in the direction of alkaloidal poisons, I was next led to a consideration of the practical utilization of the discovery for technical purposes. In this direction I had not given the compound any consideration whatever. However, Dr. Wilbert, who visited my laboratory in December, 1911, and Professor A. B. Stevens, of Ann Arbor, who also visited me in August, 1912, were both much interested in its varied problematical outreaches, including its possible practical applications. Each of these gentlemen foresaw clearly that a substance capable of holding an alkaloid intact in the presence of an acid, and of liberating it in the presence of an alkali, might possess advantages in therapeutic directions heretofore unattainable. Dr. Wilbert studied the report of Professor Felter, concerning the experiment just made by him (see Table II), and decided that the strychnine did not commence to exert itself until it passed into the alkaline secretions of the bowels, where it was dissociated from the reagent.[18] In March, 1913, I took the reagent, together with a number of alkaloids, to Washington, and inviting Dr. Lyman Kebler and Dr. H. W. Wiley to my room in the Raleigh Hotel, I illustrated for them its qualities with a line of experiments.[19] I now recall that, during the discussion following, Dr. Wiley referred to the fact that a physician had once come to Washington, enthusiastically advocating the use of fullers' earth as a local application for diphtheritic throat tissues. Some time afterward a private demonstration was made at the Hygienic Laboratory, Washington.

First Public Announcement.—In May, 1913, in a paper read before the Pennsylvania Pharmaceutical Association, Dr. M. I. Wilbert, of Washington, made the first public announcement in a pharmaceutical direction, following which came a communication by Dr. Sigmund Waldbott to the Journal of the American Chemical Society, June, 1913. The first detailed presentation of the adhesion phase of the reagent was made at the meeting of the American Pharmaceutical Association, Nashville, August, 1913, by Dr. H. M. Gordin, of Chicago, and at the same meeting Dr. Bernard Fantus, of Chicago, presented a paper that first introduced the compounds of the reagent in pleasant medication. The first public demonstration of the material and its activities before a body of scientists was made April 8, 1914, at the University of Cincinnati, at the General Meeting of the American Chemical Society. Each step in the precipitation of alkaloids by this reagent was there demonstrated with the able coöperation of my young assistant, Miss Eda

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[17] Table IV.

[18] I am not in a position to do justice to these compounds in a commercial sense. I am intensely interested in research directions that concern plant problems, and this work would necessarily have been disturbed, or perhaps even abandoned, had I taken upon myself the making and distributing of a new line of medicaments. Therefore arrangements were made with my friend, Mr. J. K. Lilly, in accordance with which the commercial problem was transferred to the establishment of Eli Lilly & Company, Indianapolis. In this arrangement I am much gratified and consider myself very fortunate.

[19] As yet I had made no printed reference to this subject, which was, indeed, but one phase of my laboratory research, and which, until this date, had seemed to me to need no conspicuity.

Van Guelpen, to the satisfaction of the audience. This demonstration was prefaced with a brief paper by Dr. Sigmund Waldbott, who made known the liberation of free sulphuric acid from quinine bisulphate by means of Lloyd's reagent, previously freed from its calcium content.[20]

Concerning Hydrous Aluminum Silicate.[21]—This historical sketch would be incomplete without some reference to the substance, hydrous aluminum silicate, itself. It will be noted that the standard established as being readily attainable was that of a powder capable of precipitating one gramme quinine bisulphate, by means of eight grammes of hydrous aluminum silicate. All my inquiries for references proving futile, for the reason that literature was absolutely devoid of any reference to the use of this material as an alkaloidal precipitant, a series of studies of the alkaloidal adhesion phases of various clays became necessary, with the object of obtaining a satisfactory commercial source. This search demonstrated that no two specimens seemed to possess the same alkaloidal affinity (see Table IV). Chemical methods did not avail to establish a standard, while lixiviation produced, from the same earth, various products of discordant alkaloidal affinities. Standardization proved thus to be most perplexing. Some clays that seemingly should have classed high ran very low; whilst others less promising were decidedly active. After an exhaustive study of many native American fullers' earths, as well as from England [22] and Japan, together with two Turkish clays that Mrs. Lloyd had found in use among the Turkish ladies for washing the hair, I determined to my own satisfaction that the degree of alkaloidal affinity depended upon an undetermined, but yet hydrous, *colloidal* condition of the silicate, which, under other forms, may be devoid of alkaloidal affinity. Whilst engaged in this very perplexing but most interesting study, Dr. Charles L. Parsons,[23] of the Department of the Interior, Washington, issued his bulletin [24] on fullers' earth, carrying the most comprehensive study of the subject I have yet obtained. This bulletin, however, is mainly technical, and being devoted to the use of fuller's earth as a clarifying agent with oils and as a decolorizer, it carries no reference to its alkaloidal affinities. However, a personal visit from Dr. Parsons led to the placing in my hands of a very complete line of American fullers' earths, from which I determined the alkaloidal affinities of all the specimens. These, tabulated as follows, exhibit the great unevenness of natural fullers' earths, the standard for comparison being " Lloyd's reagent," *eight grammes of which* are capable of taking up one gramme of quinine bisulphate.

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[20] These personal references are designed simply to establish, chronologically, the various contributions that were early made in this direction. They also enable me to express my thanks and obligation to the various friends herein named, whose encouragement was much needed, and who have my most grateful thanks. For years I had refrained from appearing publicly in connection with this problem, so many phases of which were, and still are, to me so mysterious.

[21] This material, as supplied by Eli Lilly & Company, is now known as " Lloyd's Reagent."

[22] English earths run better than most others, but are very dark and much contaminated with foreign materials that are difficult to eliminate.

[23] Dr. Parsons discovered that an application of heat to redness did not altogether destroy the decolorizing qualities of the earth. I have as yet, however, found no specimen in which the elimination of all its water by the act of calcination does not at the same time annihilate the alkaloidal attraction.

[24] Bulletin No. 71 Mineral Technology 3, Department of the Interior. Fullers' Earth, by Charles L. Parsons, 1913.

(To be continued.)