

PARTS I AND II. A CONTINUED STUDY IN ADSORPTION.*

Illustrated by Experiments.

PART III. KRYPTONINE.

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PART I.

With unusual interest and satisfaction have I studied the paper contributed by Professor Wilbur L. Scoville, of Detroit, to the 1915 meeting of the American Pharmaceutical Association, titled, *Some Experiments in Filtration*. This experimentation concerns the influences of such insoluble, amorphous materials as paper pulp, purified talc, infusorial earth and fullers' earth, the elective affinities of these materials being accurately described in connection with the following alkaloids and alkaloidal salts: Quinine Hydrochloride, Strychnine Sulphate, Caffeine, Morphine Sulphate, Atropine Sulphate, and Acetanilid.²

Need it be said that this paper was to me of exceeding interest, by reason of the fact that many radiating phases of the problem presented by Professor Scoville have, as is known to our older members, taken much of my thought and care for the past four decades. And in this connection it is well to bear in mind that most insoluble substances, such as gums, resins, plant tissues, jellies, etc., possess in themselves marked adhesive affinities for elective materials, this attraction being often very pronounced when in contact with the proper elective substances.

The present paper should in my opinion be considered as a continuation of a series of contributions, five in number, offered by me to this Association, 1879-1885, under the title, *Precipitates in Fluid Extracts*, connecting therewith the recent results of Professor Scoville. In the papers named, thought was constantly directed to physical phenomena and colloidal influences, such as adsorption, adhesion, capillarity, and the attributes of so-called "inert" substances, employed in, or produced by, pharmaceutical manipulations. Thus were included phenomena connected with menstrua, solvents, materials dissolved and materials precipitated, the effort being to specialize some of the actions of structureless bodies that apparently lie outside the domain of atomic chemistry, and which involve physical adhesions, as well as structural rearrangements, often very complicated and not explainable by established chemical processes.

The title of that series of papers (suspended in 1885, although experimentation in connected lines has never been by me relaxed) did not fully comprise their contents, but yet it granted me the privilege of intruding into pure pharmacy a line of investigations that otherwise, in part at least, might seem to have a more congenial home elsewhere.³

* Contributed to the American Pharmaceutical Association, 1916.¹

¹ Continued from *Proceedings of the American Pharmaceutical Association Meeting at Pittsburgh, Pennsylvania, in 1885*.

² At the 1915 meeting of this Association in San Francisco, Professor Scoville's paper led to the adoption of a motion asking "That the Scientific Section take the matter of adsorption in filtration under consideration, and solicit papers on the subject."

³ While no hostility towards these studies was exhibited by any one, it became evident to me that further publication of my apparently fruitless explorations would be an imposition

As perhaps the majority of our members present are unfamiliar with those contributions of the olden time, and may not have access to the *Proceedings* carrying them, a brief summary of the topics then considered, connecting them with the present subject, is proper as an introduction to what I wish to present to-day.⁴

The first paper of that series, 1879, concerns phenomena connected with the art of percolation, the underlying thought being the study of *contact action*, whereby so-called "solution" of plant textures takes place. This includes such phases of the phenomena of solution as the influence of currents, temperature, maceration, maceration with expression, maceration in connection with percolation, influence of the percolator's diameter, the mathematical laws governing the process, the effect of temperature on percolation, and *practical application versus theoretical deductions*. The paper was illustrated with tables and figures.

The next, 1881, considers the precipitates that form in such percolates as fluidextracts, the thought being carried more directly toward what I then denominated "mass action." Let us quote:

The result of my observations and study of precipitates has convinced me that the larger part of the permanent sediments that form in most of our fluidextracts arises from a cause heretofore unconsidered. They are the result of neither a decrease of temperature, of oxidation, nor of chemical change. They follow physical rather than chemical laws. To investigate them, we must depart from the exclusive department of the chemist and pharmacist, and consider such forces as diffusion, the motions of currents, and the influence of various solvents. Perhaps the remarks I shall now venture to record, may open to others a new line of thought, a subject worthy of research.

This paper considers the problems of oxidation, change of solvent power of menstruum due to evaporation, precipitation caused by change of temperature, and the often overlooked influence of light and physical conditions. It led to the announcement that a plant percolate is *not a simple solution* but a *complex structure*, in which certain substances are dissolved to the point of saturation, and that separations of both liquids and content follows from various causes, the solvent power of the mother solution being altered as such precipitates or separates are successively formed. Thus, a percolate being an intercollection of interlocked solutions, the separation from it, of any dissolved material whatever, alters its solvent power, the change being followed by a resulting strain upon some other substance that, separating as a precipitate, changes the solvent power of the new

on the Society. This, too, notwithstanding the urgent request for their continuation by Dr. Charles Rice, who in discussion, in 1884, said: "I think Mr. Lloyd is on the track of some new discoveries in science that will prove to be of importance and in the end will explain phenomena hitherto little understood. I am sure this is not the end. He seems to have crept over into other channels, and I hope he will give us these, next year." Professor Maisch remarked: "Perhaps every one of us has noticed some of these little things, but our minds were not inquisitive enough to endeavor to solve the problem." To me, this line of research became increasingly interesting, and my experiments were never relinquished, although the results were intruded only on personal friends, who honored my laboratory with their visits. To this I will add that my opinion is now, as then, that pharmaceutical manipulations are dominated by *mass actions*, colloidal phenomena, and such border-land force exhibitions as must take the thought of physicists in the future. In pharmacy, as I have long argued, lies a great, rich field, as yet undeveloped.

⁴When it is considered that the entire subject concerned phenomena and experiments covering many phases of manipulative experiments that required nearly one hundred pages of text for description, it will be seen that this Summary is but a restricted fragment.

menstruum, and may thus produce other precipitates. In like manner new solvents are produced. Twelve illustrative experiments were introduced.

The 1882 contribution aimed to show that although a *theoretical equilibrium* might in time result in such a liquid, phenomena already considered (1881) in connection with temperature changes rendered impossible in such complexities any permanent equilibrium between solvent and content. The liquid tends even to separate into distinct zones, each segment having an individuality of its own and, as temperature changes, a circulation within itself. This tends to carry liquid substances of the heavy, lower strata upward, and those of the lighter, upper strata downward, each segment holding some substances on the solvent strain, ready to separate as precipitates, almost on vibration.⁵ Thus, at the dividing lines (or planes), separating the various sections of such a solution, precipitation is likely to follow, owing to the complicated solution strains at those points. Precipitates thus formed in one stratum may settle into another stratum having a different solvent action, and may then redissolve. Or, they may continue to descend until, as a sediment, they rest upon the bottom of the container. In like manner, precipitates of oil-bearing bodies lighter than the liquid may start upward and be carried to the surface, forming a skin upon the top of the liquid, or, adhering to the container's side at the surface of the liquid, form a line of deposit. Through such changing influences, the entire content of such a complex liquid structure is resultingly active, and precipitation and resolution may be continuous. Adhesion phenomena accompany all changes wherein such precipitates occur. Let us quote:

Thus we find that from natural causes precipitation in fluidextracts made by percolation may continue indefinitely, that these precipitates may continue to increase or decrease periodically, and that there is little chance for absolute rest.

The 1883 paper considers the surface creeping-deposits, mentioned in 1882, that sometimes form above the top of a liquid. It was also shown, by experimental illustrations, that *mixtures* of soluble salts acted as capillary separators on evaporation of their solvent, even though that solvent be pure water. For example, it is stated that:

A mixture made of several perfectly soluble salts may be dissolved and then evaporated, when it will often be found that each salt has selected a location for itself, there being a fair line of demarcation between the zones.

The summary is as follows:

Hence we find that by a process which may be compared with *dialysis without a membrane*, the bromide of ammonium had purified itself from the chloride of sodium, until only about two-thirds of one percent of the latter salt remained.

The 1884 contribution, continuing these studies, is devoted entirely to capillary phenomena. By illustrations it is shown that soluble crystalline salts, as well as colloidal substances, can be thus separated from their solvents, bibulous paper possessing the power of producing separations difficult to explain other than by physics. Inasmuch as the writer was at that time deeply engaged in the study of structureless bodies, now known as colloidal, and was constantly meeting problems that must soon become the subject of general thought, namely, *the*

⁵ The influence of an electrical vibrator on colloidal solutions and precipitating processes was investigated by me in 1914.—J. U. L.

separation of uncrystallizable substances from each other, the following sentence is pertinent:

Perhaps the analytical chemist will find some food for consideration, as it seems reasonable to suppose that the principle involved may be of practical value in the separation of certain colloidal bodies one from another. Then, too, it may be found advisable to *evade the process of filtration*, if possible, where accurate results are desired.

Many experiments were made to illustrate the action of bibulous paper, these being summarized as follows:

In looking at the phenomena as presented, it will be seen that we may sum the matter up as follows:

1. The bibulous paper absorbs the liquid and carries it to a certain height, about as it exists in the vessel.
2. At a point above the surface of the liquid, determined by the texture of the paper and concentration of the solution, the iron salt ceases to pass upward^a as rapidly as the water or other substances held in solution by the water.
3. The liquids then separate, and the *colorless* liquid is then drawn (or thrust), through the solution of iron, without carrying a trace of ferric sulphate beyond the line of division.

No attempt was made in that paper to argue theoretically concerning the phenomenon, as shown by the following sentence:

We do not design in this paper to enter into a theoretical argument regarding the *causes* for the phenomenon herein presented, the aim being simply to present the experiments.

The result of the investigation is summed up as follows:

The facts, then, to be presented in this paper are:

1. Liquids can be separated from solids held in solution, without evaporating the liquid, or precipitating the solid in an insoluble condition.
2. Liquids can be separated from each other.
3. Chemical combinations, even, can be broken without calling upon such recognized dissociating powers as high or low temperatures, or the action of reagents.
4. This dissociating force has been overlooked in many places where, perhaps, it might be useful. It may be an unknown factor, leading to discrepancies in delicate analytical work that involves frequent filtration. There are other points of interest that we hope to consider in the future.

The 1885 contribution directly concerns the adsorptive powers of *selected, inert substances*, on associated constituents in liquids containing mixed principles in solution, as obtained from plants, for example, alkaloidal solutions and their associates. It is introduced as follows:

The influence of capillarity upon certain solutions during their passage through bibulous paper having been illustrated in the immediately preceding portion of this communication (presented in 1884), I am led in continuation to introduce another phase of the subject.

The dominating idea of the problem thus presented is indicated as follows:

Paper Pulp Will Absorb Plant Constituents and Separate Them from Solutions. In reviewing the phenomena presented in that paper (1884), the following query presents itself: Admitting that the passing of a solution through a column of fibrous paper by capillarity will separate many substances from the liquid in the *beginning* of its passage, will this effect follow the *saturation* of a passive capillary body, submerged in a solution?

This was illustrated by a number of experiments with alkaloids and alkaloidal salts, the results being not altogether in accord. The following summary was offered:

^a We use the term "upward" to correspond with this line of experiments. The same phenomenon is presented when the paper is horizontal, or inclined, if capillary attraction, only, carries the liquid forward.

1. The dipping of substances like filter paper into such solutions as are here considered may be attended by a separation of dissolved matters.

2. Liquids expressed from such materials do not necessarily contain the proportion of dissolved matter that was held by the original solution.

3. Like amounts of the expressed liquid may vary greatly in composition.

It was further shown that:

Hydro-alcoholic plant preparations allowed to stand undisturbed are prone to alterations that increase the alcoholic content of the surface, as contrasted with the bottom. This phenomenon is due to a complication of causes, connected with the physical action of insoluble materials and the action of circulating media, as previously cited.

To this was added:

These investigations are purely artificial, and I am led to them from disturbing results obtained in practical manipulation. They were made to aid me to study out certain inconsistencies in my work, that could not be accounted for under generally accepted theories regarding the exhaustion of drugs by percolation, or maceration and expression. In the act of exhausting most plants, we have soluble bodies to separate from wood fibre and other substances that resemble filter paper and wood pulp, as well as insoluble mineral principles. We also have to consider in the liquid product the *physical* or *mass* attraction that may exist between chemically inert matters precipitated from solutions, and active constituents of the liquid. It is also true that, as pharmacists, we often use filter paper, paper pulp, felt, phosphate of calcium, carbonate of magnesium, and perhaps other *presumably passive bodies*, to aid in filtration or the clarification of liquids. I hope soon to bring before you a phase of this subject, illustrating the influences apparently passive plant constituents exert on each other.¹

In the discussion of this paper, Professor Prescott's remarks well illustrate his views of the importance of the phenomena presented in the direction of exact chemical analyses, as he saw the problem thirty-one years ago. Let us reproduce these:

MR. PRESCOTT: I wish to say a word on this subject. I think this series of papers has been of great value. This is, I believe, the fifth year in which the Association has received a paper from Professor Lloyd on this subject. I think it is a notable example of the fact that true research is reported from the field of applied science, as well as that of pure science. The reflection is often cast upon us by those engaged in "pure science," that we appropriate the results of investigations made in pure science, giving little credit for them, unless they bear upon the industries of life. The public at large reap the benefits, they say, while those engaged in the investigations get little reward. While that is true, it is equally true that those who are engaged upon investigations in pure science often fail to give credit for the benefits directly due to the workers in applied sciences. Now, it is not true that those who serve the public in technical pursuits contribute nothing to the advance of science in general. As an example, Professor Lloyd says he commenced his investigations in order to avoid certain difficulties in practical work, and he has opened up a field which is of the utmost importance in pure molecular science. It has been asked whether we should refer Professor Lloyd's results to chemical action within molecules, or to those forces between molecules which may be classed under physical action. Now, we do not know a great deal about these two modes of force, or their essential nature; but I think we know this much, that there is no sharp line of demarcation between the *chemical* action *within* the molecules and the *physical* action *between* the molecules. They grade off into each other. We must look out for the interference of *adhesion* in a great many operations called chemical. The interference of adhesion is a cause of error, very many times, when we do not look for it. Now take the matter of opium assay. We use a stated quantity of the filtrate as an aliquot part of the

¹ The footnote under the heading of this paper explains why these contributions were not made. With much regret does the author admit that these studies in directions that might have been useful were unpublished.

entire liquid. If the adhesive power of the filter is sufficient to absorb and hold certain dissolved substances of the liquid, then your filtrate may not fairly represent the entire liquid, or the entire material which has been in the liquid form. The question should arise in every similar operation, whether a separation of materials may occur by *adhesion*.

We very often have to wash three or four times more than we should need to do, if there were no adhesions, and we had only to attain the requisite dilution of the salts of the filtrate. I am glad to know that this series of investigations is attracting the attention of men devoted to physical science, as well as of pharmacists, and is bringing attention to phenomena that have been passed by with too little attention.

PART II.

With this introduction, which seems to me to be essential to what follows, I come to the paper of Professor Scoville (1915), in which, as already stated, four insoluble substances—paper pulp, purified talc, infusorial earth and fullers' earth—were employed with neutral aqueous, acid aqueous, and alcoholic solutions of five plant alkaloids. Professor Scoville sums up, to the effect that paper pulp, as shown by careful analysis, is as a rule less adsorbent of the alkaloids and alkaloidal salts used, than any of the other substances employed. He also demonstrates that in aqueous neutral solution, strychnine sulphate, morphine sulphate, and atropine sulphate were adsorbed, in different amounts, whilst for quinine hydrochloride and citrate of caffeine, the paper lacked adhesion qualities.

Theorizing from Professor Scoville's results, as well as from those recorded three decades ago with other materials, we may rationally conclude that if a solution of mixed quinine hydrochloride, strychnine sulphate, citrated caffeine, morphine sulphate and atropine sulphate be filtered, the adhesion quality of the paper should exert itself differently on these different alkaloidal salts. The filtrate should, theoretically, *not* carry the proportions of the original mixture. Let us here attempt, by a lecture-room experiment, to illustrate both the adsorptive power of paper on alkaloidal salts, and its elective affinities.⁸

If the adsorption qualities of filter paper likewise vary, when colored alkaloidal salts and those colorless are dissolved together, should the affinity of the paper be greater for the colored salts than for those destitute of color, a mixture of solutions of colorless and colored alkaloidal salts should present, on filtration, a visible illustration of the adsorptive power of paper, if the paper elects the colored salt.⁹

Fortunately, the salts of two known alkaloids are *colored*, namely, berberine and sanguinarine; these I shall introduce. In addition, I shall present a highly colored, colloidal, vegetable structure of marked alkaloidal qualities, aiming, in my experiments, to make visible the result of the adhesion qualities existing between these and the filter paper. I also introduce another substance, hitherto neglected, "*Kryptonine*," because, in my opinion, the isolation and purification of vegetable colloids, in which direction I have long taken pleasure, must soon become a feature of recognized pharmaceutical manipulation.

Let me first introduce an experiment with colored alkaloidal salts, paralleling my bibulous paper siphon experiments of 1884, when, by capillarity, such substances

⁸ The adsorptive powers of different makes of filter paper vary greatly. That used in the present experiments is the Whatman, English filter paper, as supplied by the Arthur H. Thomas Company, Philadelphia. In this connection, Wittstein (*Practical Pharmaceutical Chemistry*, 1853, Darby edition) makes the following precise statement: "This is German printing paper, which is far more porous than English."

⁹ We use the term as though the attractive force lay wholly in the paper. In our opinion, the reverse term might as well be used. The attraction is mutual.

as ferrous sulphate, ferric sulphate and cupric sulphate, in mixed solutions; were separated one from another, and it was shown that even a *mixture of sulphuric acid and water* could be in like manner dissociated, the first portions of water passing over intact without even a trace of the sulphuric acid. In the experiment before us we shall see that the salts of berberine and sanguinarine¹⁰ are completely separated by the paper siphon, the capillary filtrate passing alkaloid-free and colorless. (Experimental results are herewith exhibited.)

Let us now pass from a capillary siphon to ordinary filtration processes.

Experiment No. 1.—In this cylinder I place a solution, in distilled water, of a salt of the natural red alkaloid of sanguinaria (di-sanguinarine sulphate), to which has been added a small amount of quinine disulphate. A test portion gives, with Mayer's reagent, a heavy precipitate. (Experiment.)

If time permitted, a striking illustration of the principle of paper adhesion could be given by filtering this solution through *single* filter papers, successively, until the filtrate passes colorless. The coloration of each paper and filtrate would decrease, with each operation, until after about the third filtration, the solution would pass colorless. For lack of time, I shall bunch five filter papers together, and pass the solution through them simultaneously, thus obtaining in one process the adhesion opportunities of the total number. (Experiment.)

It will be seen that the papers turn red, but the resultant filtrate passes colorless. The colored sanguinaria alkaloid is separated from the colorless quinine disulphate, which passes unchanged, the colorless filtrate producing an abundant precipitate with Mayer's test. (Experiment.)

Experiment No. 2.—We have here di-Berberine Sulphate dissolved in water to a yellow color. To this is added quinine disulphate, equal amounts of each being used. An acidulated test portion gives an alkaloidal reaction with Mayer's test.¹¹ (Experiment.)

This solution I now filter as before, through five filter papers. Although before filtration the solution is highly colored, the alkaloidal solution is dilute. This, Professor Scoville's experiments indicate as least likely to lose their alkaloidal content. He states:

Two things are clear in these results. First, that excessive amounts of any filtering medium mean a loss in strength of the solution, and this loss is the greater, the nearer the solution is to its saturation point. Weak solutions may show little or even no loss, while strong solutions show a considerable loss.¹²

Note now that after filtration the paper is colored yellow, but that the filtrate passes colorless, and gives a heavy precipitate with Mayer's test (experiment), thus showing that *by elective affinity of the paper, the two alkaloidal salts have been separated.*

¹⁰ I use the name *Sanguinarine* as a blanket term, because it applied originally to the section of sanguinaria alkaloids that produce red salts, that are practically insoluble in water.

¹¹ Berberine sulphate is better precipitated with ammonium picrate. The precipitate with Mayer's test is more of a translucent coagulation, which separates colloidal but finally coalesces fairly well.

¹² My experiments with solutions of identical salts, in different dilutions (1884), demonstrated that the weaker solutions, first, had, progressively thereafter, lost their content. Illustrations were shown in a series (*Proceedings Amer. Phar. Assn.*, 1884) and explained, the following being a part: "In continuing the study of this phenomenon, we find that the proportion the iron salt bears to the liquid, influences the point at which the separation of the iron solution occurs. If the solution is dilute, the separation takes place just above the surface of the liquid in the vessel. As it increases in strength, the iron passes higher upon the paper, and with officinal, syrupy solution of tersulphate of iron, there will be no separation."

Experiment No. 3.—I hold in my hand a colloidal substance obtained from ipecac, that is possessed of decided alkaloidal qualities, as illustrated in the pages following, descriptive of this material, and the process by which it is obtained from ipecac. This alkaloidal structure is more powerfully tinctorial than are the salts of either berberine or sanguinarine. For lack of a pre-given name or previous recognition, so far as I can determine, I call it, for descriptive purposes, *Kryptonine*. In distilled water, I have herewith dissolved enough "Kryptonine" to color the liquid decidedly yellow. I then add some quinine bisulphate, and test it with Mayer's reagent. (Experiment.) This yellow liquid I now filter through five filter papers. Note that the filtrate passes colorless, but yet, with Mayer's test, it gives an abundant alkaloidal precipitate (experiment), thus showing that the paper has abstracted the kryptonine, but not the quinine bisulphate.

REMARKS.

1. The question might arise as to whether this adsorption power would result, were the filter papers wet before filtration. To this I will answer that the wet papers retain the elected alkaloid *even better* than when dry. This I believe to be due to the fact that, as filters, the dry papers act more unevenly than when they are wet and stuck together.

2. Each paper seems to have a fixed adsorptive power for the alkaloid adsorbed. When this point is reached, the total solution passes through, unaltered. Thus the depleting action of the paper is limited to its saturation quality, and depends on the solution content, which I have not measured in this instance with exactness.

3. The adsorbed material is not collected upon the *surface* of the paper, as would be the case with a colloidal material in marked fibrous or gelatinous suspension. Note that the sides of each sheet of paper are tinged to about the same depth of color. Not until coloration appears at the *filtration tip* of the outer paper will there be any coloration of the filtrate. Then, with further filtration, the colored alkaloid passes, increasingly deeper. This problem and connected radiations concern colloidal or physical dispersion, and cannot be even mentioned herein.¹³

CONCLUSION.

The adsorptive action of pure filter paper, as indicated in the cited portions of the experiments presented thirty odd years ago, in which Professor Prescott so lucidly pointed to possible analytical variations, seems to me, together with the results tabulated by Professor Scoville, as well as the experiments presented herewith, to demonstrate that filter paper has not only an adsorptive, but a *discriminative* action on both alkaloidal salts and other substances. To this it may be added that colloidal precipitates in different physical conditions, for the separation of which filter paper is used, may, in accordance with their physical structures and alkaloidal affinities, act also as adsorbers for certain substances, thus perhaps accounting for analytical discrepancies where minute amounts of materials are concerned. In this connection, the surface actions of emulsion

¹³ Much of my care in recent years has been devoted to the study of different grades and dilutions of materials. Some substances *seem* to dissolve, but are in dispersion. Others dissolve and next precipitate, often in colloidal suspension or chemical alterations. This mighty subject I aim now to theoretically evade, even by suggestive inference, but I may remark that, in order to establish that the solutions now before us are not *crude* colloidal suspensions, they have been allowed to stand for two weeks, and yet they maintain their transparency. Besides, after a paper is saturated with its elective constituent, the liquid filters freely and unaltered.

films, as well as the presence of finely divided colloids throughout emulsion textures, if neglected in delicate analytical processes may, to use Professor Prescott's words, "adsorb dissolved solids to a very inconvenient extent."

PART III.

KRYPTONINE.¹⁴

Preliminary.—This phase of my contribution is made with the request that it be accepted as an advance offering on a subject that, when further investigated, may lead to conclusions quite different from those now held by the author. If it be thus accepted, an effort will be made to study *Kryptonine* in connection with other alkaloidal slivers derived from the natural ipecac texture. The fact that the substance under consideration is colloidal and not crystalline does not, in the author's estimation, debar it from individuality, although its elaboration is rendered more perplexing. Indeed, as previously remarked, the time must some day arrive, when a study of *natural* plant structures will be a research feature of physicists interested in plant textures. Since they are highly colloidal and amorphous, the isolation of separates will naturally be accomplished by means of neutral liquids of different solvent qualities. Being destitute of crystalline structure, their isolations and descriptions must rest on qualities and attributes that do not govern fixed crystals. Since *Kryptonine* is, as yet, neither crystallizable nor productive of crystalline salts, its nature is herein featured by such attributes as solubility, physical properties, etc., as follows:

Description.—*Kryptonine* is an Ipecac derivative of alkaloidal qualities. Air dried, it contains (*Waldbott*) 9.836 percent moisture, and 0.282 percent ash.¹⁵

Characteristics.—Colloidal, orange-yellow in minute colloidal precipitate, black in mass, scales, deep black in bulk, garnet-red in separates. All forms are destitute of crystalline structure, which also applies to its compounds with acids. Adhesion qualities with pure white filter paper, very pronounced. Not deliquescent.

Taste.—Very bitter. Saliva colored yellow thereby.

Soluble in water, alcohol, chloroform, glycerin, dilute sour acids, and dilute alkalies.

Insoluble in ether and benzol.

Dilute Solution in water and alcohol, *yellow to red*, in accordance with proportions. With alkalies, the yellow solution turns red. Sour acids added to excess, turn the red back to yellow.

Fehling's Test.—No reaction, or very faint.

Test for Tannin.—No reaction with ferric chloride.

Alkaloidal Tests.—Heavy precipitate with Mayer's Test Solution, Picric Acid, Tannin, and other alkaloidal reagents. Supernatant liquid colorless with Mayer's solution.

Chloroform Solution.—Yellow to red, in accordance with proportions. Al-

¹⁴ This substance was isolated by me in 1915, 125 pounds of ipecac yielding two grammes. On establishing its nature, three subsequent lots of ipecac, 125 pounds each, yielded, respectively, 112.4 grammes, 107 grammes, and 120 grammes. From this colloidal, alkaloidal substance, named *Kryptonine* by suggestion of Dr. H. W. Wiley (from "*κρυπτόν*," *the hidden thing*), I have failed in separating anything whatsoever, and believe it to be a non-crystallizable, colloidal alkaloid. Probably heroic chemistry will split it into slivers, some of the fragments being, possibly, crystalline.—*J. U. L.*

¹⁵ This minute amount of ash of adhesion has not been separated by any process as yet applied. It precipitates with *Kryptonine*, and dissolves with it.

kalies turn this solution green. The addition of alcohol turns the green to red. If the solution be more concentrated, the green and red plays of color are more pronounced. On standing, the green of the chloroformic solution gradually fades, red resulting.

Formula (Dr. Sigmund Waldbott).— $C_{29}H_{46}N_2O_9$.

PREPARATION OF KRYPTONINE.

Total Ipecac Alkaloids.—Exhaust ground ipecac with water. Add to the percolate *Lloyd's Reagent*, to ultimate precipitation of the alkaloid. Dry the alkaloid-saturated *Lloyd's Reagent*. This compound carries the total alkaloidal content of the ipecac, in a colloidal form.

Separation of Total Alkaloids.—Powder the saturated reagent, and in a mechanical separator cover it with chloroform. Add carefully 10 percent solution of caustic soda,¹⁶ sufficient to liberate the ipecac alkaloids. Draw off the chloroformic solution into a continuous still, adding fresh chloroform until the reagent is exhausted. The still contents will hold the total alkaloidal content, in chloroformic solution.

Total Alkaloid as Sulphate.—Evaporate the alkaloidal chloroformic solution in the still, to a syrupy consistence, and having previously established its combining strength, add 1 percent sulphuric acid water sufficient to the total extraction of the alkaloidal salt thus produced, distilling the chloroform from beneath. Quickly cool (*with ice*) the solution of total alkaloids (now in the form of sulphates), and then at once dilute with ice water to the bulk of one-third the amount of ipecac used.

Separation of Emetine.—Keeping the liquid ice cold, precipitate the emetine by the addition of dilute solution of caustic soda carefully and slowly added with constant stirring. Filter the magma from the emetine, washing the precipitated emetine with cold, distilled water. Then, in a "knuckle joint," or hydraulic press, gradually applied, squeeze the liquid from the emetine magma, and add it to the previous filtrate. This filtrate contains the "black alkaloid"¹⁷ (Kryptonine) and the *cephaeline*, together with minute amounts of emetine, resins and fat, soluble in that liquid.

Separation of Cephaeline.—Extract the liquid by repeated agitations with chloroformic fractions, which abstracts the cephaeline and kryptonine, contaminated with traces of emetine and resins. Distil the chloroform to a thin syrup and, slowly, with constant stirring, pour into an excessive amount of sulphuric ether. Most of the cephaeline and emetine remain in solution. *The Kryptonine separates as a friable, orange-yellow, amorphous precipitate.*

To Purify Kryptonine.—Decant the ether, and wash the precipitate with successive amounts of cold ether, until all the chloroform is removed, the orange-yellow precipitate being practically thus freed from traces of adhering cephaeline and emetine.¹⁸ Add now an excess of ether, and (*gradually*) small amounts of distilled water, shaking well together. The yellow precipitate immediately coalesces into a material, black and tar-like. This frees the kryptonine from appreciable amounts of cephaeline and emetine, which, if present at all, remain

¹⁶ This was used in this experiment, to determine if Kryptonine is an ammonia decomposition product, ammonia having been used in preceding processes that gave the same substance. One hundred and twenty-five pounds of ipecac were used.

¹⁷ Following the old name, "Black Tar," I first gave to this alkaloidal substance the title, "Black Alkaloid." (See footnote 19.)

¹⁸ The adhesion powers of alkaloidal precipitates for soluble alkaloidal salts of other alkaloids, even in the presence of strong solvents, is often most pronounced.

in the ether. Now decant all the ether, which leaves the kryptonine in mass practically pure, the contaminations being mainly small amounts of resinous materials.

Separation of Traces of Adhering Resinous Materials.—Dissolve the kryptonine¹⁹ in distilled water to a very thin, syrupy condition, and allow it to stand twenty-four hours, thus separating the resinous material. Filter the dark-red, almost black, aqueous solution, and in order to catch any remaining resin or foreign alkaloid, if any there be, again wash it thoroughly in a rotater, by means of sulphuric ether, in which the kryptonine is insoluble. This final ether washing will remove all traces of fat, resin, and any possible contamination with cephaeline and emetine, the ruby-red aqueous liquid carrying the kryptonine in a physically pure condition.²⁰ Evaporate to a syrupy condition, spread on glass, and dry.

SUMMARY.

The process may be summarized as follows:

1. Total extraction of the ipecac alkaloids soluble in water, or 1 percent aqueous sulphuric acid.
2. Total precipitation in adhesion, by means of Lloyd's Reagent.
3. Extraction of total alkaloid from Lloyd's Reagent by liberation with 10 percent solution of caustic soda (or other alkali), in contact with chloroform.
4. Transferring of total alkaloid from the chloroform to the estimated amount of diluted sulphuric acid.
5. Separation of emetine by precipitation with solution of caustic soda. (Other alkalies answer the same purpose.)
6. Extraction of mixed cephaeline and kryptonine by agitation of the filtrate with chloroform fractions.
7. Precipitation of kryptonine by pouring slowly, in thin stream, the mixed chloroformic solution (evaporated to syrupy condition), with constant stirring, into an excess of ether.
8. Purification, by precipitation and washing with proper solvents. (See process. Kryptonine, being colloidal by this process, is not capable of crystallization.)
9. Drying of the "black alkaloid," *Kryptonine*.

The ultimate analysis of Kryptonine, by Dr. Sigmund Waldbott, reached me just before this session convened. I take great pleasure in extending to Dr. Waldbott, herewith, my personal thanks for his painstaking care, and append the detailed results obtained by him, in the following report:

ULTIMATE ANALYSIS OF JOHN URI LLOYD'S IPECAC ALKALOID "KRYPTONINE."

BY DR. SIGMUND WALDBOTT.

Water.—Upon drying between 105° and 110° C., the substance lost 9.836 percent H₂O.

Ash.—Upon incineration, the substance left 0.282 percent of ash.

Combustion.—(a) 0.2939 Gm. of original substance, corresponding to 0.26416 Gm. of ash-free, anhydrous substance, yielded: H₂O, 0.1693 Gm. or $H = 0.0189$

¹⁹ More than thirty years ago, in working ipecac on a large scale, I obtained a substance of alkaloidal qualities, which at that time was to me a perplexing disturber. I then applied the term "black tar" in referring to it, ascribing its alkaloidal qualities to *adhering emetine*.—*J. U. L.*

²⁰ The overlying ether will be colored yellowish. It is scarcely necessary to record that the water taken by the ether carries enough kryptonine to color the mixture. In pure ether, kryptonine is insoluble.

Gm. = 7.15 percent (referred to ash-free, anhydrous alkaloid). CO_2 , 0.5991 Gm. or $C = 0.16339$ Gm. = 61.85 percent (referred to ash-free, anhydrous alkaloid). (b) 0.3235 Gm. of original substance, corresponding to 0.29077 Gm. of ash-free, anhydrous substance, yielded: N gas, 13.2 Cc. at 755 mm. barometric pressure and 24.5°C . $N = 0.01459$ Gm. = 5.02 percent.

From these data, the molecular formula, $\text{C}_{29}\text{H}_{40}\text{N}_2\text{O}_9$, is deduced for the ash-free, anhydrous alkaloid. The water content of the hydrous substance corresponds to about 3.5 molecules.

| Percentages found, as above, for ash-free, anhydrous alkaloid | Percentage calculated from $\text{C}_{29}\text{H}_{40}\text{N}_2\text{O}_9$ |
|--|--|
| Carbon..... 61.85 percent | 62.11 percent |
| Hydrogen.... 7.15 percent | 7.14 percent |
| Nitrogen..... 5.02 percent | 5.00 percent |
| Oxygen..... 25.98 percent (by difference) | 25.71 percent |
| Water..... 9.864 percent (referred to ash-free substance) | 10.11 (calculated from $\text{H}_{20}\text{H}_{10}$ N_2O_9 . 3.5 H_2O) |

CONCLUSION

The process outlined should be conducted, from beginning to end, with *cold* liquids, wherever manipulation connected with precipitation is concerned.

So far as I can determine, the substance herein described under the term "Kryptonine," has been, till now, overlooked, unless it be the "third alkaloid" mentioned in the investigations of Paul and Cownley (*Ph. J. and Trans.*, Feb. 16, 1895), which seems improbable, by reason of the fact that they obtained it *in crystals, from an ether solution*. They state:

The quantity obtained as yet was too small to admit of complete examination, but the physical characters of this alkaloid distinguish it in a very definite manner. It is a crystallizable substance obtainable by slow evaporation of an ether solution in well-defined transparent prisms of a pale lemon-yellow color.

With reluctance do I affix a name to this substance, but to do so is a necessity. Even though the term "Kryptonine" be subsequently found to apply to a colloidal body not altogether alkaloidal, its qualities seem to me to be pronounced enough to individualize it as a non-crystallizable structure, capable, by its characteristics, of standing alone.

Considering this present contribution to be but a preliminary announcement, I would ask that this colloidal substance, and its relationship to the ipecac texture that yields it, as well as other ipecac alkaloids, be awarded me for further consideration.

DISCUSSION.

H. H. RUSBY: I want to ask Professor Lloyd a question that is of fundamental importance. I would like to ask him which one of the three varieties of ipecac was used in these tests, how it was received, whether ground or not, and what steps were taken to ascertain whether there were any impurities—whether there were any stems present, and, if so, were they attached to the root or separated from it? Was each piece examined separately to be sure it was ipecac and of the particular species used?

Now, if anyone thinks these things are unimportant, I am going to make a few statements which will convince them that they are important.

During the last two years there has been several times as much adulteration and substitution of ipecac as has ever been known before, some intentional and some unintentional. The presence of stems in ipecac not attached to the stems is exceedingly dangerous, because some of these stems may belong to other plants growing with the ipecac, and they resemble it so closely that it is almost impossible to discriminate between them. Some of the impurities of a vegetable character in ipecac have been so like it that we people who have examined

the ipecac did not detect them for a long time, but I know that we found in the Cartagena ipecac as much as fifty percent of a stem which resembles the underground rhizome of the Cartagena ipecac. These were so much like the rhizomes of the Cartagena variety that they had to be examined microscopically to be sure which was which.

If anyone is going to examine a drug in the splendid manner in which this was investigated, I hold that no efforts can be too painstaking to determine beforehand that the substance is pure.

On one occasion I made some investigations of Scopolia and Belladonna which involved one hundred pounds of each and I took every single piece and examined it, and I was then able to swear there was not one single piece that went into the substance examined that was not the genuine.

I do not know what steps Dr. Lloyd took to determine whether or not there was a certain amount of impurities. The Pharmacopœia admits a certain amount of impurity. If there is any present we are bound to admit it. That is the law. But, that small amount, that may have been present, may also have been the substance which contained this alkaloid.

I want to tell you that the importance of this has never been properly appreciated. If every step is not taken with such care that the existence of any impurity is impossible, the whole positiveness of the chemical results is destroyed.

J. U. LLOYD: That was really ipecac as nearly as I could determine. As nearly as I could tell it was pure. I will be extremely glad, however, if you will furnish a lot that carries your name as authority. I am sure, however, there was not enough foreign material in the ipecac to produce the kryptonine obtained.

GEO. M. BERINGER: I was very much impressed with the paper just presented, and with its far-reaching importance. It seems to me that there is hardly a line of scientific research on which the substance of this paper is not going to have an influence. All the way through this paper has a bearing on the work in every line of physical and chemical science. I can see the importance of publishing these papers and the influence they are going to have on general science and scientific investigation.

C. P. WIMMER: I have also listened with a great deal of interest to Professor Lloyd's paper. I believe he has really discovered a new substance in ipecac. Look at it from a colloid standpoint. The colloidal chemists say that when a substance changes from one state to another state, it will pass through a colloidal state before it will assume a crystallized state. Professor Weymouth goes so far as to say that gases are colloidal, but this is far-fetched and perhaps difficult to prove.

Let us apply this to the plant. The alkaloid in a plant is supposed to be excretum. That is, the metabolism of the plant will have no use for certain substances—nitrogenous, carbonaceous, and these will be formed, first, into colloidal substances and then into alkaloidal crystals.

I believe Professor Lloyd has discovered a colloidal alkaloidal plant substance and has shown us the way to find many new alkaloids. Take alone the point of the solubility of that alkaloid. That may be of the utmost importance in pharmaceutical work.

I have listened to this paper with a great deal of interest, and I think it is of the utmost importance to research workers.

VIRGIL COBLENTZ: A few years ago I had occasion to work up some experiments, and I was exceedingly annoyed by the presence of this substance. Every time I used ether or benzol I would get this substance. I assumed it was a resin substance carrying some of the alkaloidal matter. I tried to crystallize it in all possible solvents but it was simply impossible to do so, and I laid it aside for future reference. I now find that Professor Lloyd has gone ahead and named it.

J. U. LLOYD: There is no question about it being there. The peculiar yellow color is simply indicative of it.

VIRGIL COBLENTZ: In your separation of the alkaloids, can you wash your filter paper and still retain the one alkaloid and allow the other to be washed out?

J. U. LLOYD: It reluctantly retains it.

PHILIP ASHER: We can hardly appreciate what Professor Lloyd has done for us. This opens up a great many avenues of research work for us. It is surprising in looking at a

tabulation of analytical results sent out by various committees to see the difference in them, and we can now appreciate why some of these differences may obtain.

The physicist has also a new problem with which to battle, and that is upon what physical laws, upon what conditions do these changes actually take place? Suppose we have a different mixture of alkaloids, if we get this study to an exact science we can say with positiveness that this condition will take place, but to-day we are all at sea. The Pharmacopœia and all other standards have given us certain standards for finished preparations. The pharmacist has been honest and conscientious in making preparations to the best of his ability. But let us see now what it amounts to when we find that simple filtration destroys all our efforts; and if I am in order, when the motion is put, I feel that we should all show our appreciation of Professor Lloyd's efforts by a rising vote.

F. R. ELDRÉD: Dr. Rusby raised a question of the possible impurities in the material used by Dr. Lloyd, and I might add that in having worked up a large number of lots of ipecac, we have accumulated quite a large quantity of the substance which I presume is the same as Professor Lloyd has shown here—insoluble in ether, soluble in water, and it has practically the same qualities as those he has mentioned. It seems to me that that answers the question as to whether the substance is a constituent of the ipecac or an impurity.

L. W. ROWE: It seems to me that Dr. Lloyd is a pioneer in the application of physical chemistry to pharmacy. We know that pharmacy so far is an impractical science. We have a lot of rule-of-thumb methods, which we hope some day will be put on a scientific basis. Physical chemistry has been applied in nearly every science—it is being used in practically every branch of industry, and you will find that physical chemistry is the means of putting rule-of-thumb methods on a scientific basis.

Now, Professor Lloyd is a pioneer in the application of physical chemistry to pharmacy. Not long ago, some correspondence which I had with Professor Bancroft, at Cornell, shows that he is very much impressed with the wonderful field there is to place pharmacy on a scientific basis—the vegetable extracts, etc., which Professor Lloyd has taken up. We certainly have to take off our hats to Dr. Lloyd for starting this new field of physical chemistry and we hope his work will be a stimulus to younger men in continuing the work he has begun.

W. H. ZEIGLER: I would like to ask if any thing has been done from a pharmacological standpoint with this new substance, and if it has any therapeutic action at all.

J. L. TURNER: What impressed me most in Professor Lloyd's paper is his wonderful power of observation, combined with his ability to doubt authorities given us in literature. Everyone of us would have seen this substance, but we would not have gone on with it as he has. We are used to working with crystalline substances. Nevertheless, Professor Lloyd was not satisfied. Instead of calling this substance an impurity, he went further into the subject and did more than anyone of us would have done—he investigated the substance, and this shows the necessity of going deeper into the subject we are investigating, far deeper than we usually do, and especially to develop that ability of doubting the authorities that Professor Lloyd possesses.

I would like to ask Professor Lloyd if any attempt was made to prepare the various salts of Kryptonine, such as sulphates, picrates, hydrochlorides, etc.

J. U. LLOYD: I will try and answer the various questions, to the best of my ability, but I would like to ask you to comprehend that I too am only a questioner, so that I shrink from venturing into the subject that is extending outside of my line so remarkably. I think the first question was as to the material employed. Old-fashioned ipecac, which was unquestionably true to name was used. Second. All the salts of Kryptonine with the sour acids are colloidal. All alkaloidal reagent precipitates are likewise amorphous, or colloidal.

I come now to the colloidal composition of drug structures. May I go a little further than you have gone?

Excluding opium, of which I have made no systematic study, I have as yet to find an alkaloidal drug that does not contain a water-soluble alkaloid, if it contains an insoluble one.

My studies of plants have also led me to believe that alkaloids existing in plants are,—*in the plants*,—colloidal. In the plant structure they are not crystals, and when they become crystalline, through an artificial process, such alkaloidal salts, are, *in themselves*, valuable or

otherwise, regardless of the conditions in which they exist in the mother structure of the drug which yields them.

Another question was asked me as to the physiological aspect of Kryptonine. I do not place as much dependence on the physiological action of a drug on a creature in health, or its disturbance of a normal life function as proving its total therapeutic value, as some people do. But this is an invaluable method for establishing certain qualities (activities) of the drug, even if it does not always apply in diseased conditions. Kryptonine has been put into the hands of a well-known pharmacologist, but I have not as yet received his report.

Let me say in conclusion that I have not answered all the questions that have been asked me, because of my hesitancy in directions in which I feel myself quite inadequate. The whole colloidal problem is to me full of questionings. The ultra-microscope will be a mighty factor, in my opinion, in determining the answers to many of the questions that have come to me, as well as to many others, as yet unuttered.

SOLID AND POWDERED EXTRACTS.

BY E. L. MAINES.

The U. S. P. Ninth Revision states that "Pilular Extracts are solid or semi-solid products prepared by exhausting drugs with appropriate solvents and carefully evaporating the solutions to the proper consistence."

It also further states that, Pilular Extracts are extensively used in pill masses and in ointments and, to facilitate their use in these preparations, the degree of concentration is commonly directed to be that of a "pilular consistence."

The Pharmacopœia tells us that for the convenience of the prescriber, the standards of strength for the extracts have been adjusted, wherever possible, so that each bears a definite relation to that of the respective drug of average strength, and a statement of the standard precedes the formula.

This is certainly a step in the right direction.

For some time the writer has endeavored to procure definite standards for non-alkaloidal solid and powdered extracts, this work being taken up by the Scientific Section of the American Association of Pharmaceutical Chemists.

The term "pilular consistence" is indefinite and questionable. Solid extracts may be of "pilular consistence" and yet be adulterated with fifty percent or more of glucose.

Powdered extracts are even more liable to "filling" with starch, magnesia, powdered marc, kieselguhr, etc., than solid extracts.

Unofficial non-alkaloidal powdered extracts may be made to almost any standard and yet pass undetected.

This is decidedly unfair in a commercial way to say nothing of its practice as a menace in a therapeutic way.

The physician must depend upon reliable, uniform and potent remedies in order to obtain satisfactory results.

In a commercial way it is of utmost importance that extracts be of some definite strength. One firm quotes upon a 1 to 3 extract while another quotes on a 1 to 5 product. What is the result? The consumer thinks one party is taking an unfair advantage of him or he could quote a lower price.

Much of this could be eliminated by proper regulation of standards.

I would suggest that the next Revision Committee consider the advisability of adopting a uniform and definite relation of drug to extract for every commercial crude drug and that this list of standards be included in the text of the next Pharmacopœia for both solid and powdered extracts.